TIRF REMS FENTANYL CITRATE ANDA	BATES RANGE
77312 – Teva/PAR	11332 - 12264
78907 - Mallinckrodt/SPECGX	12265 - 12651
79075 - Watson	12652 - 13149
207338 – Actavis	13150 - 13376

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312

REMS NOTIFICATION

Teva Pharmaceuticals USA
400 Chestnut Ridge Road
Woodcliff Lake, NJ 07677

Attention: Robert Vincent
Director, Regulatory Affairs

Dear Mr. Vincent:

Please refer to your abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Fentanyl Citrate to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.

We further refer to the meeting held on October 28, 2010, at the FDA White Oak Campus, at which we discussed that in the interest of public health and to reduce the burden on the healthcare system of having multiple unique REMS programs, we have determined that a single, shared system should be used to implement the REMS for all members of the class. The necessary REMS elements should be implemented across the class of transmucosal immediate release fentanyl (TIRF) products to address the serious risks described above.

At the October 28, 2010 meeting we informed the sponsors of the TIRF products of our development of standardized REMS materials that could be used in the development of a single shared system to implement the REMS for all TIRF products. At that meeting, we told sponsors that we intend to move rapidly to review and approve REMS for each of the TIRF products that include the standardized program, and we encouraged sponsors to work together to implement a single shared system to reduce the burden on the healthcare system of individual programs. This letter is a follow up to that meeting discussion.

Attachment 1 contains a REMS program that can be implemented as a single shared system across all TIRF products, and we recommend that your proposed REMS conform to this program. The program includes standardized elements and enrollment forms that can be used by all sponsors of TIRF products and can be implemented using existing pharmacy systems.

Your proposed REMS must include the following:

Medication Guide: FDA previously approved a Medication Guide for distribution with Fentanyl Citrate in accordance with 21 CFR Part 208. The Medication Guide must be revised to incorporate information about the above-described risks. Under 21 CFR Part 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fentanyl Citrate.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions, including a plan to ensure that a Child Safety Kit will be available to patients within 48 hours of filling the initial Fentanyl Citrate prescription, and that this kit contains an interim container for incompletely used Fentanyl Citrate units, a locking fanny pack, and a cabinet/drawer lock.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include all elements listed in Attachment 1.

In accordance with section 505-1, within 120 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

This submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that includes information that we believe is pertinent across the class of TIRF products (see Attachment 1). Additionally, all relevant proposed REMS materials including: enrollment forms, educational, and communication materials should be appended to the proposed REMS. These appended

documents should also be standardized across the class of TIRF products, with the exception of the product-specific information that will be included in the training program for prescribers and information about the Child Safety Kit. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Attachment 2).

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT**." To facilitate review of your submission, please provide labeling in Final Printed Labeling (FPL) and Microsoft Word format.

If you have any questions, please contact Melaine Shin, Labeling Reviewer, at melaine.shin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA #
Drug Name and Dosage Form
Opioid Analgesic
[SPONSOR].
[ADDRESS]
[PHONE]
[FAX]

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the Fentanyl Citrate REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing Fentanyl Citrate only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Fentanyl Citrate prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe Fentanyl Citrate for <u>outpatient</u> use are specially certified.

a. Teva will ensure that healthcare providers who prescribe Fentanyl Citrate for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe Fentanyl Citrate, prescribers will be required to enroll in the Fentanyl Citrate REMS program. Prescribers must complete the following requirements to be enrolled:

i. Review the Fentanyl Citrate REMS prescriber educational materials (*Prescriber Education Program*), including the Full Prescribing Information, and successfully complete the knowledge assessment (*Prescriber Knowledge*

Assessment).

ii. Complete and sign the *Prescriber Enrollment Form*. In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I understand the responsible use conditions for Fentanyl Citrate and the risks and benefits of chronic opioid therapy.

b) I understand that Fentanyl Citrate can be abused, and that this risk should be considered when prescribing or dispensing Fentanyl Citrate in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that Fentanyl Citrate is indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that Fentanyl Citrate must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.

f) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose, and that patients must be titrated individually.

g) I understand that Fentanyl Citrate is not bioequivalent with any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to Fentanyl Citrate must not be converted on a microgram-per-microgram basis.

h) I will complete and sign a Fentanyl Citrate REMS *Patient-Prescriber Agreement* with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.

In signing the *Patient-Prescriber Agreement*, the prescriber documents the following:

1) Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.

2) Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral

oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) The Fentanyl Citrate Medication Guide has been provided to and reviewed with the patient or their caregiver

4) The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of Fentanyl Citrate including communication of the following safety messages:

   A. If patients stop taking their around-the-clock opioid medication, they must stop taking Fentanyl Citrate.

   B. NEVER share Fentanyl Citrate

   C. Giving Fentanyl Citrate to someone for whom it has not been prescribed can result in a fatal overdose.

   D. Fentanyl Citrate can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

In signing the *Patient-Prescriber Agreement*, the patient and/or their caregiver document the following:

1) My prescriber has given me a copy of the Fentanyl Citrate Medication Guide and has reviewed it with me.

2) I understand that before I can take Fentanyl Citrate, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking Fentanyl Citrate.

4) I understand how I should take Fentanyl Citrate, including how much I can take, and how often I can take it.

5) I understand that Fentanyl Citrate can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take Fentanyl Citrate <u>exactly</u> as my prescriber has directed me to take it.

6) I agree to contact my prescriber if Fentanyl Citrate does not relieve my pain. I will not change my dose of Fentanyl Citrate myself or take Fentanyl Citrate more often than my prescriber has directed.

7) I agree that I will never give Fentanyl Citrate to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store Fentanyl Citrate in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of unused and remaining Fentanyl Citrate and will dispose of Fentanyl Citrate as soon as I no longer need it.

10) I understand that selling or giving away Fentanyl Citrate is against the law.

11) I have asked my prescriber all the questions I have about Fentanyl Citrate. If I have any additional questions or concerns in the future about my treatment with Fentanyl Citrate, I will contact my prescriber.

12) [placeholder for sponsor to add HIPAA/privacy statement language]

i) I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the Fentanyl Citrate REMS program (by fax, scan and e-mail, mail or through the Fentanyl Citrate REMS website) within ten (10) working days.

j) At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.

k) I understand that Fentanyl Citrate is only available through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for prescribers.

b. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new *Patient-Prescriber Agreement* at least every two (2) years.

c. Teva will:

i. Ensure that prescriber enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, prescribers receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Prescriber Education Program*
- *Prescriber Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement*

iii. Ensure that prescribers have successfully completed the knowledge assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the Fentanyl Citrate REMS program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, are certified to prescribe Fentanyl Citrate.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

2. Fentanyl Citrate will only be dispensed by pharmacies that are specially certified.

a. Teva will ensure that Fentanyl Citrate will only be dispensed by certified pharmacies. To become certified to dispense Fentanyl Citrate, each pharmacy must be enrolled in the Fentanyl Citrate REMS program.

b. Each pharmacy will be required to designate an authorized pharmacist to complete enrollment on behalf of the pharmacy.

c. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals, hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to enroll their **outpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program)* and successfully complete the *Pharmacy Knowledge Assessment*.

ii. Ensure the pharmacy enables their pharmacy management system to support communication with the Fentanyl Citrate REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I understand the risks and benefits associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing Fentanyl Citrate have been educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program*. This training should be documented and is subject to audit.

c) I understand that Fentanyl Citrate is not bioequivalent with other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for <u>all</u> patients is the lowest dose.

f) I understand the importance of discussing the risks and benefits of Fentanyl Citrate with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the Fentanyl Citrate Medication Guide must be given to the patient or their caregiver each time Fentanyl Citrate is dispensed.

h) I understand that Fentanyl Citrate will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL Fentanyl Citrate prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the Fentanyl Citrate REMS program to dispense Fentanyl Citrate.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program and successfully complete the enrollment requirements every two (2) years.

n) I understand that Fentanyl Citrate is only available through the REMS program. I understand that the pharmacy must comply with the Fentanyl Citrate REMS program requirements for outpatient pharmacies.

e. ***Inpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program*) and successfully complete the *Pharmacy Knowledge Assessment*

ii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form* the authorized pharmacist is required to acknowledge the following:

a) I understand the benefits and risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program*.

c) I understand that Fentanyl Citrate is not bioequivalent to other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the Fentanyl Citrate REMS program to dispense Fentanyl Citrate to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy is not to dispense Fentanyl Citrate for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with an Fentanyl Citrate prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the REMS program, as described in section B.1 of this REMS.

i) I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the Fentanyl Citrate REMS.

j) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program every two (2) years.

m) I understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years

g. Teva will:

i. Ensure that pharmacy enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, pharmacies receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Pharmacy Education Program*
- *Pharmacy Enrollment Form*
- *Pharmacy Knowledge Assessment*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the knowledge assessment before activating a pharmacy's enrollment in the Fentanyl Citrate REMS program. For outpatient pharmacies only, Teva will also ensure that the upgrades to the pharmacy management system have been validated before enrolling a pharmacy in the Fentanyl Citrate REMS program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, certified to dispense Fentanyl Citrate.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

3. Fentanyl Citrate will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. Teva will ensure that Fentanyl Citrate will only be dispensed for outpatient use if there is documentation in the Fentanyl Citrate REMS system that the dispensing pharmacy, prescriber, and patient are all enrolled and active in the Fentanyl Citrate REMS program.

b. Patients are passively enrolled in the Fentanyl Citrate REMS program when their first Fentanyl Citrate prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the Fentanyl Citrate REMS system. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2.a-d, respectively.

c. Prior to dispensing Fentanyl Citrate, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the Fentanyl Citrate prescription through their pharmacy management system.

i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient

ii. If one or more of the required enrollments can not be verified, the Fentanyl Citrate REMS system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

i. The patient has not filled a prescription for more than six (6) months

ii. The patient receives prescriptions for Fentanyl Citrate from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the Fentanyl Citrate REMS program cannot fill the prescription for Fentanyl Citrate until the new prescriber is active in the Fentanyl Citrate REMS program.

f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for Fentanyl Citrate are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. Teva will ensure that wholesalers/distributors who distribute Fentanyl Citrate are enrolled in the Fentanyl Citrate REMS program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving Fentanyl Citrate inventory for distribution:

a. Review the distributor Fentanyl Citrate REMS program materials

b. Complete and sign the *Distributor Enrollment Form* and send it to the Teva (by fax, scan and e-mail, mail or through the TIRF website). In signing the *Distributor Enrollment Form*, each distributor is required to indicate they understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program and that they must comply with program requirements, and acknowledge that:

i. I will ensure that relevant staff are trained on the Fentanyl Citrate REMS program procedures and will follow the requirements of the Fentanyl Citrate REMS program.

ii. I will ensure that Fentanyl Citrate is only distributed to pharmacies whose enrollment has been validated in the Fentanyl Citrate REMS program.

iii. I will provide data to the Fentanyl Citrate REMS program including information on shipment to enrolled pharmacies.

iv. I will cooperate with periodic audits or non-compliance investigations to ensure that Fentanyl Citrate is distributed in accordance with the program requirements.

c. Teva will ensure that all forms are complete, prior to enrolling a distributor in the Fentanyl Citrate REMS program.

d. Teva will notify distributors when they are enrolled in the Fentanyl Citrate REMS program, and therefore, able to distribute Fentanyl Citrate.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the Fentanyl Citrate REMS program every two (2) years.

g. The following distributor materials are part of the Fentanyl Citrate REMS program and are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*

2. Teva will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the Fentanyl Citrate REMS requirements.

3. Teva will develop a REMS system that uses existing pharmacy management systems that allow for the transmission of REMS information using established telecommunication standards. The REMS system should incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the REMS requirements, if deemed necessary in the future.

4. Teva will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing Fentanyl Citrate. Additionally, Teva will monitor to ensure that Fentanyl Citrate is only being dispensed for outpatient use to actively enrolled patients of actively enrolled

prescribers. Corrective action or inactivation will be instituted by Teva if non-compliance is found.

5. Teva will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement* with each Fentanyl Citrate patient, and to submit it to the REMS program within ten (10) business days. This will be accomplished through patient surveys and by reconciling the *Patient-Prescriber Agreements* submitted to the REMS program with patient enrollment data captured through the pharmacy management system.

6. Teva will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the Fentanyl Citrate REMS program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

7. Prostraken will evaluate enrolled inpatient pharmacies' compliance with REMS requirements through surveys.

8. Teva will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the Fentanyl Citrate REMS program.

9. Teva will ensure that all materials listed in or appended to the Fentanyl Citrate REMS will be available through the Fentanyl Citrate website www. Fentanyl CitrateREMS.com or by calling the Fentanyl Citrate REMS call center at XXX-XXX-XXXX.

10. Teva will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the REMS program. Notifications for patients will be sent to the patient's prescriber.

11. If there are substantive changes to the Fentanyl Citrate REMS Program, Teva will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the Fentanyl Citrate REMS program are defined as:

    a. Significant changes to the operation of the Fentanyl Citrate REMS program for outpatient pharmacies.

    b. Changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of Fentanyl Citrate.

12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, Teva will take reasonable steps to improve implementation of these elements and to maintain compliance with the Fentanyl Citrate REMS program requirements, as applicable.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System

4. Information Needed for Assessments

5. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

11/12/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

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Submitted to FDA via ESG

December 5, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

SUPPLEMENT – PROPOSED REMS

RE: ANDA 077312
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Webber:

Reference is made to the Fentanyl Citrate risk management program for Oral Transmucosal Fentanyl Citrate as required by the approval of ANDA 077312.

Reference is also made to the transfer of ownership of this ANDA from Barr Laboratories, Inc. (an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA) to Par Pharmaceutical, Inc., effective October 14, 2011.

The Agency has determined that transmucosal immediate release fentanyl drug products are required to have a Risk Evaluation and Migitigation Strategy (REMS) to ensure that their benefits continue to outweigh their risks. Collectively, these products are referred to as "TIRF (Transmucosal Immediate Release Fentanyl) products".

The NDA/ANDA holders of these products have formed a consortium to develop this REMS at the request of the Agency. Collectively, these companies are referred to as the "TRIG", or TIRF REMS Industry Group.

As a sponsor participating in the TIRF REMS program, Par hereby submits the proposed REMS program to the subject ANDA, utilizing guidance from the Agency for the requirements for this submission. Since Par is not yet filing submissions in an eCTD format, the information for the REMS program, as dictated by the Agency, is provided in Module 1, in a single folder named "REMS".

Further reference is made to the telephone conversation today between Carrie Lemley, FDA, OGD, and Krista Richardson, Par Pharmaceuticals, Inc., in which Ms. Lemley requested that the draft labeling for the REMS (PI, Medication Guide and carton), which was submitted to the Agency via e-mail correspondence on November 30, 2011, also be provided in this submission. The requested labeling is

provided in Module 1.14. Par has provided marked-up versions of the PI, Medication Guide and carton, as well as clean versions of the PI and Medication Guide for ease of review.

Please note that the revised labelling provided does not represent the currently approved PI and Medication Guide for the application. The RLD (Actiq) was updated by Cephalon in July 2011 to implement REMS/safety information. Teva did not implement the updates, as they were not part of an approved REMS program at that time. With the current initiative underway (TIRF REMS ACCESS program), Par has revised the subject labelling to be in compliance with the current RLD labelling, and is representative of what will be implemented upon approval of the REMS program.

This is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Krista Richardson

Digita ly signed by Krista Richardson
DN: o=Ver Sign Inc ou=VeriSign Trust Network
ou=www veris gn com/repository/RPA Incorp by Ref LIAB LTD(c)98
ou=Persona Not Validated ou=D gital ID Class 1 Microsoft Fu l Service
cn=Kr sta Richardson email=kr sta richardson@parpharm com
Date: 2011 12 05 15 18:55 05 00

Krista Richardson
Senior Manager, Regulatory Affairs

Transmucosal Immediate Release Fentanyl (TIRF)

Sponsors:

TIRF REMS Industry Group (TRIG) of Companies

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) SUPPORTING DOCUMENT

1. TABLE OF CONTENTS

2. BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended release and immediate release products. Extended release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic [Biedrzycki et al, 2009]. Secondary effects of fentanyl on central nervous system, respiratory and gastro-intestinal functions are typical of opioid analgesics and are considered to be an effect [Simpson et al, 2007].

TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, BTP). All the TIRF medicines as such, are short acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and on occasion fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

In order to mitigate these risks, TIRF Sponsors will implement a Risk Evaluation and Mitigation Strategy (REMS) for the transmucosal immediate release fentanyl products (or "TIRF medicines"), intended for use in breakthrough pain (BTP) in patients with cancer, while ensuring treatment access for patients who would benefit from this therapy.

The TIRF medicines which are the subject of this proposed TIRF REMS are shown in Table 1 below. Table 1 shows the products and dosage forms. These products are currently used for the treatment of BTP in adult patients with cancer who are already receiving, and are tolerant to, around-the-clock (ATC) routine opioid therapy. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

Table 1: TIRF Medicines

Product Name (active ingredient)/formulation	Applicant/Sponsor	Availability	Initial Dose
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg	100 mcg
ACTIQ® (fentanyl citrate) oral transmucosal lozenge*	Cephalon, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg 200 mcg 400 mcg 600 mcg 800 mcg	100 mcg**
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg 400 mcg	100 mcg
ONSOLIS® (fentanyl), buccal soluble film	Meda Pharmaceuticals	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg

Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Mallinckrodt Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg

*Can be used in patients aged 16 and older
**Unless substituting from an Actiq dose of 600 mcg or greater. Please see full prescribing information.

The TIRF REMS Access proposal presented here addresses the current requirements set forth by the FDA provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

A. Clinical Features of BTP

BTP is a transient exacerbation of pain of moderate to severe intensity that occurs on a background of otherwise stable pain in a patient receiving regular, continuous opioids. It is characterized by rapid onset, with pain reaching maximal intensity within 3 minutes and lasting approximately 30 minutes [Laverty, 2007]. Often classified by its relationship to specific events or spontaneous onset, BTP arises as a consequence of the cancer, the anticancer treatment or a concomitant illness. BTP can affect up to two-thirds of patients with cancer, and can have a significant impact on patient quality of life [Breivik et al., 2009]. Moreover, a number of patients remain inadequately treated for their BTP or feel dissatisfied with their pain control [Fishbain, 2008]. There is therefore a need for effective pharmacologic treatments that will help relieve and control the symptoms of BTP. An ideal treatment for BTP is an analgesic with good efficacy, rapid onset and short duration of action, with minimal adverse effects in appropriately selected patients, and is easy and quick for a patient or caregiver to administer.

B. Assessment of Key Risks of TIRF Medicines

The TIRF REMS Access program will address the primary risks of overdose, misuse, abuse, addiction and serious complications due to medication errors. These are broad risks relating to the distribution, sale, use and misuse of opioids in the US and are not unique to TIRF medicines. However, TIRF medicines are absorbed transmucosally and partially bypass gastrointestinal absorption and first-pass metabolism, resulting in rapid onset of analgesic effect, and potentially, adverse effects. The key acute risk for any individual exposed to TIRF medicines is excessive respiratory depression which can be fatal if untreated. This risk is highest in opioid non-tolerant patients. Therefore, TIRF medicines must not be used by opioid non-tolerant patients. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

By restricting the use of TIRF medicines to opioid tolerant patients the risk of serious outcomes such as severe respiratory depression should be minimized. Opioid addiction arising in palliative care patients is rare [Hojsted et al, 2007**].**

3. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

4. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors will execute the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program including patients, prescribers, pharmacists and distributors will be enrolled in the TIRF program, educated on the requirements of the program and required to document that they understand and will abide by the "elements to assure safe use."

Program materials will be provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program will contain both TIRF medicine class and product-specific components. Enrollment forms, the Patient-Prescriber Agreement Form (PPAF), stakeholder letters and overview documents containing program information will be provided to stakeholders as TIRF medicine materials. In addition, the Medication Guides will be provided to stakeholders in product-specific material format unique to the respective TIRF medicine being prescribed / dispensed.

The program procedures will be monitored for adherence and will be modified as necessary to ensure optimal effectiveness. The TIRF Sponsors will conduct ongoing and retrospective analysis as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

A. Additional Potential Elements

a. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF medicine prescription. Every TIRF medicine will have a unique Medication Guide. There will be sufficient copies distributed by each Sponsor to ensure that every patient receives a copy with each prescription. Medication Guides will be available through individual TIRF Sponsors, the TIRF REMS Access website, and the TIRF REMS Access call center.

The Medication Guide contains FDA approved language including an explanation of the risks associated with the use or misuse of TIRF medicines, augmented with information on precautions for safe use of the product, a brief explanation of essential elements of the TIRF REMS Access program, and contact information for customer assistance (i.e., call center with toll-free number and website). The TIRF medicine Medication Guides are developed to enhance patient awareness and understanding of the potential serious risks associated with the use of TIRF medicines with the intent of increasing the patients' appropriate use of TIRF medicines. The Medication Guides include critical information that every patient and caregiver should know about TIRF medicines including, but not limited to:

- Patients should not use a TIRF medicine unless they are regularly using another opioid pain medicine around-the-clock for their constant cancer pain and their body is used to these medicines (opioid tolerant).
- TIRF medicines must be kept in a safe place away from children.
- If a child, or an adult who is not already taking opioids regularly, takes a TIRF medicine, this is a medical emergency and can cause death. Get emergency help right away.

A copy of each product specific Medication Guide is distributed with every TIRF medicine.

TIRF Sponsors will supply all enrolled prescribers and pharmacies with sufficient copies of the Medication Guides to ensure that every patient who is prescribed and dispensed a prescription will have access to the specific TIRF medicine Medication Guide each time it is prescribed or dispensed.

The Medication Guide will be available through the TIRF REMS Access website, www.TIRFREMSaccess.com. Copies can also be obtained by calling the TIRF REMS Access program at **1-866-822-1483**.

b. Other Information Materials for Patients

The prescriber will discuss the benefits and risks of TIRF medicines as outlined in the Medication Guide with the patient, including proper dosing and administration, appropriate use and handling and storage of TIRF medicines.

The prescriber will discuss enrollment in the TIRF REMS Access program. The prescriber and the patient will review and sign the TIRF REMS Access program Patient-Prescriber Agreement Form (not required for inpatients) and a copy will be provided to the patient or caregiver. The prescriber will also provide the patient or caregiver with a copy of the Medication Guide.

The patient or caregiver will be offered counseling on the specific TIRF medicine by the dispensing pharmacist on appropriate use, storage and disposal, and receive an additional copy of the Medication Guide each time a TIRF medicine is dispensed.

The prescriber will have access to the TIRF REMS Access Program: An Overview for Patients and Caregivers to utilize with patients during discussions regarding the use of TIRF medicines. In patient-friendly language, the materials will focus on a description of the TIRF REMS Access program, including enrollment details and contact information (call center with toll-free telephone number and website address). This overview will also be available for download on www.TIRFREMSaccess.com.

c. Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS is not required. However, TIRF Sponsors will send Dear Healthcare Professional letters to targeted stakeholders to support implementation of the TIRF REMS Access program. These communications will include Dear Healthcare Provider and Dear Pharmacy letters, and will inform prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means of reporting adverse events.

TIRF Sponsors will send letters to healthcare professionals approximately 2 weeks prior to first availability of TIRF REMS Access program.

The target audience for the *Dear Healthcare Provider* letter will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

Additional materials will be available via the TIRF REMS Access program website or through the TIRF REMS Access program toll-free number.

B. Elements to Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This can be achieved by prescriber's enrollment through a review of the TIRF REMS Access Education Program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the enrollment form.

TIRF medicines will only be available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies will be enrolled into the TIRF REMS Access program. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals that dispense for inpatient use only). For Long-Term Care (LTC) and Hospice patients whose prescriptions are obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access program.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to undergo enrollment through review of the *TIRF REMS Access Education Program* and successful completion of the *Knowledge Assessment* on behalf of the pharmacy. The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transactions to validate the system enhancements and submit a completed and signed TIRF REMS Access enrollment form. The authorized pharmacist will be responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training must be documented and is subject to audit. At a minimum this documentation should include the store name, the store number, the pharmacist/pharmacy staff member's name, and the date training was completed.

For inpatient pharmacy enrollment, the authorized pharmacist must undergo the *TIRF REMS Access Education Program*, successfully complete the *Knowledge Assessment*, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist must also acknowledge that they understand that outpatient pharmacies within their facility must be separately enrolled.

For chain pharmacies, an authorized chain pharmacy representative must complete enrollment. The authorized chain pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program

requirements by submitting a completed and signed enrollment form. Pharmacy sites that have been trained may be updated by the authorized chain pharmacy representative using an online dashboard.

Pharmacies will not be able to successfully order TIRF medicines from distributors unless they are enrolled in the TIRF REMS Access program.

All patients (excluding inpatients) must complete and sign a Patient-Prescriber Agreement Form (PPAF) with their healthcare provider, documenting safe-use conditions. Their healthcare provider will submit a copy of the PPAF to the TIRF REMS Access program via the website at www.TIRFREMSaccess.com, fax at 1-866-822-1487, or regular mail at (Address: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038). Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program. A completed *Patient-Prescriber Agreement Form* needs to be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

a. Prescriber Education and Enrollment

The TIRF REMS Access program education materials are the primary tool for educating prescribers about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The *Education Program* also includes information for prescribers on the requirement to complete a *Patient-Prescriber Agreement Form* before writing the first prescription for a TIRF medicine (not required for inpatients). For inpatient administration of TIRF medicines prescriber enrollment in the TIRF REMS Access program is not required.

The *TIRF REMS Access Educational Program* for prescribers comprises the Education Program and *Knowledge Assessment* that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available on the TIRF REMS Access website (www.TIRFREMSaccess.com):

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

If the prescriber does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded on the TIRF REMS Access website, or requested as a hardcopy from the TIRF REMS Access program call center.

Review of the Knowledge Assessment

Following review of the TIRF REMS Access Education Program, the program Knowledge Assessment must be successfully completed. A description of the process followed in reviewing the Knowledge Assessments is presented below, and this description applies equally to prescribers and pharmacists.

Manual Knowledge Assessment Review (i.e. on receipt of printed materials)

The prescriber should review the *TIRF REMS Access Education Program*, complete the paper *Knowledge Assessment* and return it by fax to the TIRF REMS Access program.

Upon receipt of a manual program *Knowledge Assessment*, a TIRF REMS specialist will review the assessment and determine the stakeholder type.

The TIRF REMS specialist will enter each answer to the assessment question in the validated TIRF REMS Access database.

If the answers are correct (the user has passed the assessment with a score of 100%) and all other enrollment criteria have been met, the user will be enrolled in the program by notice through email or fax.

If answers are incorrect a *Knowledge Assessment* feedback fax will be generated and sent to the enrolling user that only addresses the incorrect questions received. If answers are missing an "Incomplete" fax is generated and sent to the user advising them to resend a completed *Knowledge Assessment* to allow for successful processing of the assessment.

Website Knowledge Assessment Review (web-based materials)

Upon completion of the review of the *Education Program*, the user is required to successfully complete the *Knowledge Assessment* prior to enrolling in the program.

The user is presented with one question at a time and required to provide an answer.

Upon completion of all program assessment questions, the system calculates a score. The score is presented to the user.

If the score is 100%, then the user has passed the program assessment.

If the user's score is less than 100%, they will be presented with the incorrectly answered question that they will be required to retake, in addition to further feedback on the incorrect answer.

The Knowledge Assessment (manual or website) may be attempted up to three times. If a score of 100% is not achieved after three attempts, the TIRF REMS Access Education Program must be reviewed again before retaking the *Knowledge Assessment*. Having performed the training again, a further three unsuccessful attempts at the *Knowledge Assessment* are permitted before enrollment is denied.

Successful completion of the *Knowledge Assessment* is required in order for the prescriber to enroll in the TIRF REMS Access program. Prescribers may enroll online or by paper by completing the TIRF REMS Access Prescriber Enrollment Form.

Verification of prescribers having successfully enrolled will be recorded in the TIRF REMS Access program and will allow them to access the full TIRF REMS Access program and to prescribe TIRF medicines. Prescribers will receive a user ID and password as part of the enrollment process. In addition, these forms will also be available as printed materials and can be downloaded from the website for stakeholders that prefer not to enroll electronically. These forms along with the *Knowledge Assessment* may be completed on paper and faxed to the TIRF REMS Access call center at 1-866-822-1487.

Manual Enrollment

Upon receipt of a paper enrollment form, a TIRF REMS specialist will review the form for completeness and determine the enrolling stakeholder type (i.e., prescriber or pharmacy). The TIRF REMS specialist will enter all data on the form into the TIRF REMS Access database.

Required for successful enrollment form:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation
4. The program Knowledge Assessment has been passed successfully.
5. All enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation is sent to the stakeholder via the preferred method of communication (fax or email) that is indicated on the enrollment form.

An enrollment form is considered incomplete where:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

If the enrollment form is incomplete, a fax is generated clearly listing all incomplete fields and a description of the action required to resolve the issue. The fax is sent to the fax number provided by the enrolling user on the enrollment form (email or phone can be used to send/discuss the incomplete form if the fax number is not available). The enrolling user must provide the incomplete information and return it to the TIRF REMS Access program for reprocessing. The enrollment is not considered complete until all required fields have been received and validated.

Web-based Enrollment

The enrolling user will be required to review the TIRF REMS Access Education Program, complete the *Knowledge Assessment* with a score of 100%, and complete the appropriate enrollment form.

Required for successful enrollment:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.

3. Successful Identifier Authentication Validation.
4. The enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation and completed enrollment form are sent via the indicated preferred method of communication (fax or email) provided by the enrolling user on the enrollment form. In the case that email is not available, a fax confirmation will be sent. Enrollment confirmation is also provided via the website.

An enrollment form is considered incomplete when:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

Unsuccessful Enrollment: The field edit messages are displayed back to the enrolling user. The enrolling user cannot progress further with the enrollment process until errors are corrected. Only the user's initial registration information will be retained; no enrollment data are saved to the TIRF REMS Access database.

TIRF Sponsors will maintain a database containing a list of all enrolled prescribers and their status (i.e. active or inactive). Upon initial activation, prescribers remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate prescribers for non-compliance reasons.

If a previously active prescriber becomes inactive, the prescriber will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment form in its entirety.

While a prescriber is inactive, prescriptions from that prescriber can no longer be filled under the TIRF REMS Access program. If the prescriber is providing care for patients using TIRF medicines at the time of prescriber inactivation, it is the prescriber's responsibility to ensure that the patients continue to receive appropriate pain medication via referral to another prescriber in the TIRF REMS Access program.

Prescribers are re-educated and re-enrolled in the TIRF REMS Access program every two years. TIRF Sponsors will notify prescribers of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify prescribers of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of TIRF medicines.

All communication methods utilized by the TIRF REMS Access program will provide information on how to report any suspected adverse events, including reports of misuse and abuse to TIRF Sponsors.

b. Outpatient Pharmacy Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating pharmacists about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines.

The TIRF REMS Access education for pharmacists comprises the *TIRF REMS Access Education Program* and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

If the pharmacy does not want to perform the *Education Prog*ram and *Knowledge Assessment* online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested from the TIRF REMS Access program call center.

The *Education Program* will cover information regarding how to validate prescriptions via the TIRF REMS Access program before they are filled as well as information on appropriate dispensing and use of TIRF medicines. Following review of the *Education Program*, the authorized pharmacist may enroll the pharmacy by successful completion of the *Knowledge Assessment* and the appropriate TIRF REMS Access program pharmacy enrollment form. On receipt of a valid enrollment form, the pharmacy will be sent by fax or email the instruction guide on the test transactions they will be required to run to verify that their pharmacy management system has been configured. If the test transactions have been completed successfully, the pharmacy will be enrolled and confirmation will be sent to the pharmacy. If the test transactions are not completed successfully, the pharmacy will not be enrolled and a message will be sent to contact the call center in order to further explain the need to configure the pharmacy management system.

The authorized pharmacist will be responsible for educating all pharmacy staff that participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training should be documented and is subject to audit.

An authorized chain pharmacy representative may complete the TIRF REMS Access training, *Knowledge Assessment* and enrollment on behalf of all their pharmacies within the chain and then document and manage training of all pharmacy staff by the chains' internal processes. The authorized chain pharmacy representative would also ensure completion of system testing to verify that their pharmacy management system has been configured. Upon completion of enrollment, the authorized chain representative would update trained stores on their chain

pharmacy dashboards or would submit a list to the TIRF REMS Access program for uploading into the database.

Enrolled Pharmacies will be recorded in the system which will allow them access to the TIRF REMS Access program to dispense TIRF medicines. Following web-based enrollment and successful completion of the test transactions, the authorized pharmacist will receive a username and enrollment ID, where the user can then create a password for the TIRF REMS Access website.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the Knowledge Assessment and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled Pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, the pharmacy will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines or dispense TIRF medicines under the TIRF REMS Access program.

Pharmacies are re-educated and re-enrolled every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies, of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any TIRF medicine.

The pharmacist will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

c. Inpatient Pharmacies: Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating inpatient pharmacies about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The Education Program also includes information about the requirements of the TIRF REMS Access program in the inpatient setting.

The TIRF REMS Access education materials for inpatient pharmacies comprise the Educational Program and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

An authorized pharmacist of the inpatient pharmacy is required to undergo the TIRF REMS Access Pharmacy Education Program. If the pharmacist does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested as a hardcopy enrollment from the TIRF REMS Access program call center.

The Education Program will cover information about the requirements of the TIRF REMS Access program. Following review of the Education Program, the authorized pharmacist may enroll the pharmacy by successfully completing of the Knowledge Assessment and the TIRF REMS Access Inpatient Pharmacy Enrollment Form.

Inpatient pharmacy enrollment will be recorded in the system. Upon successful enrollment the inpatient pharmacy will have the ability to order TIRF medicines for inpatient dispensing. Pharmacies will receive a user ID and password as part of the enrollment process.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the *Knowledge Assessment* and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled inpatient pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled inpatient pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, it will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines.

Inpatient pharmacies are re-educated and re-certified every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program.

b. Changes to the Prescribing Information and Medication Guides that affect the benefit-risk profile of any TIRF medicine.

The inpatient pharmacy will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

d. Patient Enrollment and Counseling

Patient enrollment is not required for inpatient use of TIRF medicines.

- Prescribers for outpatients will be provided with copies of a TIRF medicine Medication Guide and materials to use in counseling patients. Medication Guides are product specific and can be accessed from the specific TIRF Sponsor, the TIRF REMS Access website, or the TIRF REMS Access call center. Patients will be counseled on the TIRF REMS product by enrolled prescribers, supported by review of the Medication Guide and the overview of the TIRF REMS Access program for Patients and Caregivers. Patients will also have the opportunity to discuss any questions or concerns they have with their prescriber. Together the prescriber and patient will review and sign the Patient-Prescriber Agreement Form.
- The patient will be counseled by the prescriber and personally sign the *Patient-Prescriber Agreement Form* unless they are unable to act on their own behalf. For incapacitated patients, the patient counseling can be provided to and signed by the patient's legally authorized representative or medical guardian.
- Both the prescriber and patient must complete the *Patient-Prescriber Agreement Form* and the prescriber must provide a completed copy by fax or through the TIRF REMS Access website to the TIRF REMS Access program within 10 working days. Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program.

- The TIRF REMS Access Program: An Overview for Patients and Caregivers will be available for distribution to the patient by the prescriber or through the program website. This overview details the steps the patient must follow. Further information will be available on the TIRF REMS Access program website or at the TIRF REMS Access call center.
- Patients will be offered counseling by the dispensing pharmacist on the responsible use, handling and disposal of TIRF medicines. A copy of a specific TIRF medicine's Medication Guide will be provided by the pharmacist when their prescriptions are dispensed by the pharmacy.
- A database will be maintained containing a list of all enrolled patients and their status (i.e. active or inactive). Upon initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include: a prescription has not been filled for more than 6 months or the patient receives prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, overdose, or addiction.
- If a previously active patient becomes inactive, the patient can become active again by completing the standard patient counseling and re-evaluation by their prescriber (i.e. a complete review of the current TIRF medicine's Medication Guide) and completing a new Patient-Prescriber Agreement Form.
- If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot authorize the prescription for the TIRF medicines to be filled until the new prescriber is active in the TIRF REMS Access program.
- Patients will be re-counseled and required to complete a new *Patient-Prescriber Agreement Form* every 2 years. TIRF Sponsors will notify the patient's prescriber of forthcoming enrollment expiration and the need to complete a new *Patient-Prescriber Agreement Form*.
- If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify the patient's prescriber of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program
    b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any and all TIRF medicines.

e. Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies must verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

TIRF Sponsors will use a model that uses a pharmacy billing claim and engages a switch provider in the validation process. The switch provider provides information to pharmacists at point-of-dispensing via their pharmacy terminals. Their secure connectivity network provides a single point of access between pharmacies and payers so that transactions are routed quickly and reliably, instantly transmitting claims to the appropriate processor and returning the adjudicated response to the pharmacy within seconds.

Patients must complete a Patient-Prescriber Agreement Form (PPAF) prior to being given a prescription for a TIRF medicine. This may be done in two ways – online at www.TIRFREMSaccess.com or paper based. If conducted online, the PPAF will be recognized immediately. Paper based PPAFs must be faxed to the program within 10 working days to complete enrolment.

On receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the pharmacist will enter the prescription details in their pharmacy management systems and send the transaction to the TIRF REMS Access program via the Switch Provider. The TIRF REMS Access program will use this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the REMS database will then be interrogated, via the Switch Provider, in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, a billing request will be sent to the payer by the Switch. Once the payer authorizes payment the switch provider will then authorize the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will reject the claim (prior to the claim being forwarded to the payer) and the pharmacy will receive a rejection notice from the Switch Provider. This automated feedback will indicate the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notify the pharmacist to contact the TIRF REMS Access call center for further information. The current switch authorization process typically takes 3-5 seconds to complete. Interrogation of the TIRF REMS Access program enrollment database should add not more than 1 second to the overall process. This method of verification is designed to integrate into normal pharmacy workflow patterns and therefore minimize burden to the pharmacy while providing a robust control on ability to dispense TIRF medicines outside of the TIRF REMS Access program.

The TIRF REMS Access system communicates an authorization number when the submitted prescription billing request passes all qualification rules and the processor approves the billing request. The switch provider appends the authorization to a message field before delivering the response to the pharmacy practice management system.

If the pharmacy is enrolled and the electronic prescription verification process fails, prescription verification can be facilitated through the call center. The call center representative can enter the required fields necessary to provide prescription verification.

The 'back-up' process/system is not the primary method for verification, and will only be available to enrolled, active pharmacies. All instances where the back-up process is used will be adequately documented, including the specific reason it is being used. A report on back-up system use will be included in the REMS Assessment.

Back-up system utilization will be incorporated into compliance monitoring; if excessive use is observed corrective action will be implemented.

f. The TIRF REMS Access Program Website

- The TIRF REMS Access program website (www.TIRFREMSaccess.com) contains information about the TIRF REMS Access program and serves as one method by which prescribers can receive education and enroll themselves in the TIRF REMS Access program. The prescriber will also be able to complete and submit a Patient-Prescriber Agreement Form via the website.
- Pharmacies can use the website for education and enrollment, including a dashboard functionality to allow chain pharmacies to manage their stores.
- The website includes the TIRF REMS Access Education Program, Knowledge Assessment and enrollment forms that must be reviewed and completed before enrolling. The website is referenced in all TIRF REMS Access program and TIRF medicine related materials.
- Prescribers can use the website to inform patients of enrolled pharmacies that can dispense TIRF medicines.

  The TIRF REMS Access program Website also serves as a resource for:
  - Description of the TIRF REMS Access program
  - Ordering TIRF REMS Access Medication Guides
  - Full Prescribing Information for all TIRF medicines
  - Medication Guides for all TIRF medicines
  - Patient/Caregiver, Prescriber, Pharmacy and Inpatient Pharmacies TIRF REMS Access program overviews in on-screen and printer friendly format
  - TIRF REMS Access program contact information
  - Frequently Asked Questions

g. The Key Elements of this REMS that Mitigate the Risks Associated with the Use of TIRF medicines are:

i. A certified prescriber who has acknowledged and agreed to adhere to the conditions that must be met for the appropriate outpatient use of each TIRF medicines.

- Prescribers will be educated and certified on the risks of inappropriate patient selection, including non-opioid tolerant patients. In order to become enrolled, outpatient prescribers will be required to complete the TIRF REMS Access Education Program and Knowledge Assessment. Enrollment is contingent upon prescribers documenting that they understand the risks of TIRF medicines and agree to the appropriate use of TIRF medicines (See appended Prescriber Enrollment Form).
- Without this enrollment, patients, with prescriptions from outpatient prescribers will be unable to have TIRF medicine prescriptions filled by an enrolled pharmacy.
- The TIRF REMS Access program will maintain a database of all enrolled prescribers.

ii. The certified pharmacy has agreed to send all claims through the system to verify eligibility

- All pharmacies that intend to purchase and dispense TIRF medicines must be enrolled in the TIRF REMS Access program in order to receive product from distributors. Pharmacies will be enrolled only after an authorized pharmacist undergoes *TIRF REMS Access Education Program*, completes a *Knowledge Assessment* and submits an enrollment form.
- Pharmacies that are not enrolled will be unable to obtain supplies of TIRF medicines.
- The TIRF REMS Access program will maintain a database of all certified pharmacies.

Outpatient Pharmacies

- The outpatient pharmacy will ensure that the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- The authorized pharmacist will ensure that all pharmacy staff involved in dispensing TIRF medicines at their pharmacy have been educated on the risks associated with TIRF medicines, maintain auditable training records for pharmacy staff, and adhere to the requirements of the TIRF REMS Access program.
- The pharmacist must ensure that TIRF medicines have been dispensed under the following safe use conditions:
    - The pharmacist has dispensed TIRF medicines only to enrolled patients, based on a valid Schedule II prescription from an enrolled prescriber and receipt of an authorization message from the TIRF REMS Access program.
    - The pharmacist has offered counseling to patients on appropriate TIRF medicine use.
    - The pharmacist has provided each patient with a product specific Medication Guide for every TIRF prescription dispensed, instructed the patient to read it and has answered any questions the patient may have.

- Additionally, all TIRF medicine prescriptions will be tracked based on the following:
    - Prescription validation and dispensing steps performed by enrolled pharmacists;
    - Generation of a prescription authorization number from the TIRF REMS Access database upon confirming enrollment status. This tracking will enable identification of prescriptions, as well as provide utilization information used in the evaluation of the TIRF REMS Access program.

Inpatient Pharmacies

- The authorized pharmacist for an inpatient pharmacy will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program. The authorized inpatient pharmacist acknowledges that Pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
- An inpatient pharmacy is not to dispense TIRF medicines for outpatient use.
- A prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.

iii. An informed outpatient and/or caregiver should understand the inherent risks in the use of opioids and know how to administer TIRF medicines appropriately at home. Therefore, each patient must:

- Sign a TIRF REMS Access program *Patient-Prescriber Agreement Form* that documents appropriate use conditions and opioid tolerance (See appended Patient-Prescriber Agreement Form).
- Deliver the TIRF medicine prescription to an enrolled pharmacy.
- Understand that they must be regularly using another opioid pain medicine for their constant pain.
- Be counseled on responsible use and handling by the pharmacist at each dispensing when they receive an additional copy of the appropriate Medication Guide.
- These requirements do not apply to inpatient use of a TIRF medicine.

C. Implementation System

The Implementation System includes the following:

a. Wholesaler/Distributor Enrollment and Fulfillment

- TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

- For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors will be contacted and will receive a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies. The distributor's authorized representative reviews the distributor program materials. The distributor's authorized representative will complete and sign the *Distributor Enrollment Form* and fax it to the TIRF REMS Access program. TIRF Sponsors will not ship TIRF medicines to any distributor who has not completed and signed the enrollment form; by checking the status of the distributor prior to shipping the drug (See appended Distributor Enrollment Form).
- As part of the TIRF REMS Access program, distributors will need to enroll in the TIRF REMS Access program. Distributors will need to confirm their understanding of the distributor requirements in the TIRF REMS Access program, which includes verifying that pharmacies are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
- The distribution process for TIRF medicines as it relates to drug distributors will consist of:
    - Only those TIRF medicine Sponsor contracted distributors will be eligible for TIRF REMS Access program enrollment.
    - TIRF medicine distributors will be contacted and will receive a communication describing the TIRF REMS Access program.
    - TIRF medicine distributors must acknowledge receipt and understanding of the TIRF REMS communication, by completing the TIRF REMS Access Distributor Enrollment Form, in order to become a customer eligible to receive and/or distribute TIRF medicines from TIRF Sponsors. In addition to the TIRF REMS Access *Distributor Enrollment Form*, the distributor's authorized contact will receive communication on how to verify pharmacies that are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
    - The procedures for the TIRF REMS Access program will include the method for timely communications of newly enrolled as well as inactive pharmacies in the TIRF REMS Access program.
    - The procedures for the TIRF REMS Access program will also include the procedure for reporting and management of non-compliance with the TIRF REMS Access distribution program.
    - Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor

becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

- Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years. TIRF medicine Sponsors will notify distributors (based on contractual relationships in place between Sponsor and distributors) of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.
- If there are substantive changes to the TIRF REMS Access program, impacted TIRF Sponsor or TIRF Sponsor team will update all affected materials and notify distributors of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    i. Significant changes to the operation of the TIRF REMS Access program.
    ii. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of impacted TIRF medicine.

b. The TIRF REMS Access Program Database

- The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive).
- Management of the TIRF REMS Access database will be contracted to an appropriately qualified third party vendor and overseen by the TIRF Sponsors. Data for all users will be updated in the TIRF REMS Access database. This includes data received from both the call center manual process and web-based processes. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing their TIRF medicine. Additionally, TIRF Sponsors will monitor to ensure their TIRF medicine is only being dispensed for outpatient use to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by the TIRF Sponsors if noncompliance is found.
- TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a Patient-Prescriber Agreement Form with each TIRF medicine patient, and to submit it to the REMS program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This will be accomplished by reconciling the *Patient-Prescriber Agreement Forms* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.
- TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.

- TIRF Sponsors will monitor the prescribing and dispensing of TIRF medicines to enrolled patients. If non-compliance is found, TIRF Sponsors will institute corrective actions. Please refer to Section 5(B) for further details.
- TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

Based on monitoring and evaluation of these elements to ensure safe use, TIRF Sponsors will work to improve implementation of these elements and to ensure compliance with the TIRF REMS Access program requirements, as applicable.

c. TIRF REMS Access Program Call Center

The TIRF REMS Access program includes a call center component. The call center will be staffed by qualified and trained specialists, who will provide TIRF REMS Access program support to patients, prescribers, pharmacies and distributors.

The call center specialists' responsibilities will include, but are not limited to, the following:

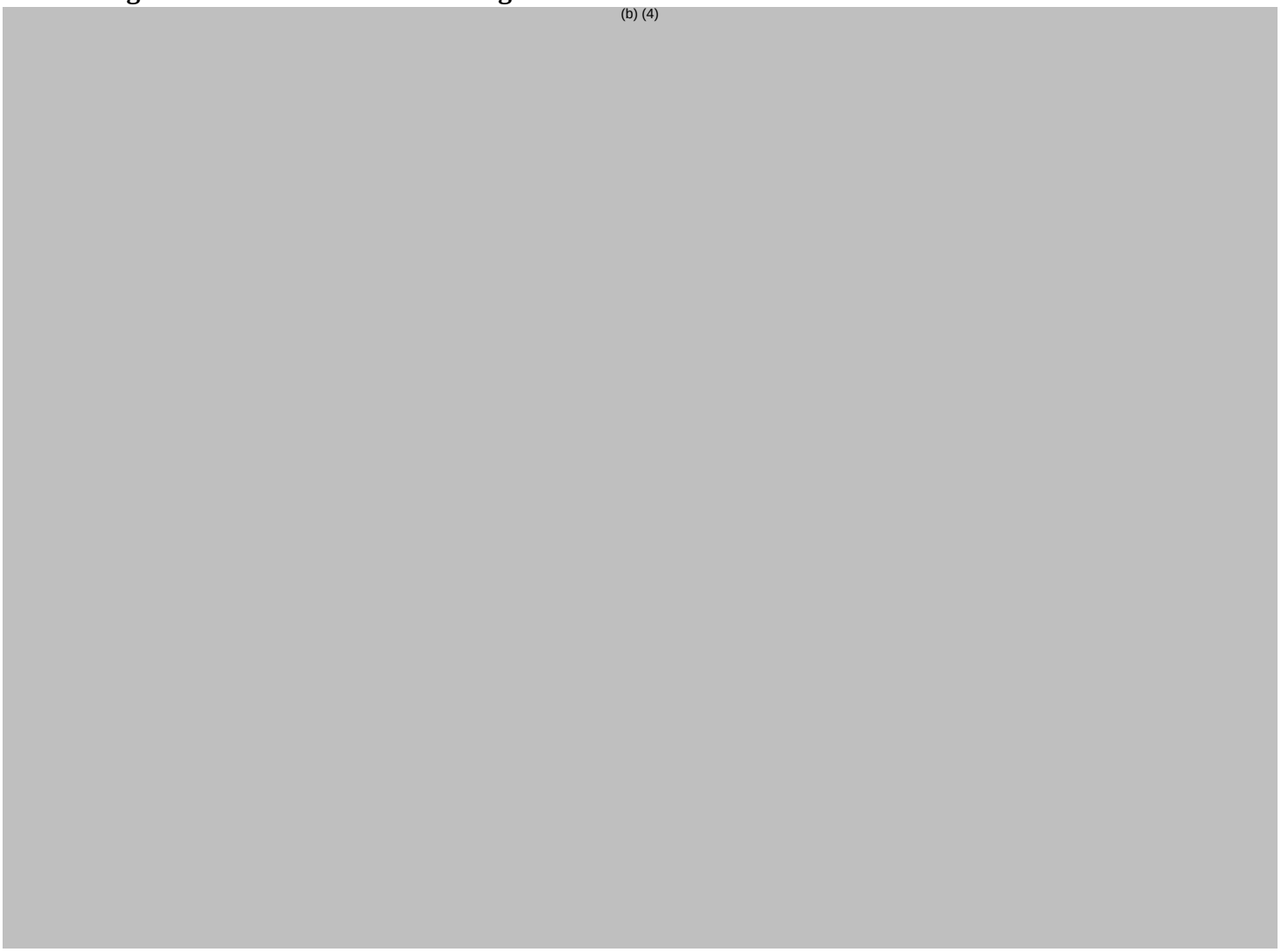
- Provide TIRF REMS Access program enrollment assistance to prescribers, pharmacies, distributors and patients
- Processing of prescriber, pharmacy and distributor enrollments and Knowledge Assessment forms
- Provide stakeholder enrollment verification in the TIRF REMS Access database
- Processing of Patient- Prescriber Agreements Forms
- Assist prescribers or patients in locating enrolled pharmacies
- Identify and transfer product complaints and potential adverse event information to TIRF Sponsors
- Provide general program information and technical assistance to stakeholders interacting with the TIRF REMS Access website

The TIRF REMS Access program call center hours of operation are Monday – Friday, 8:00am to 8:00pm EST. Callers outside of these hours are instructed to leave a message that will be addressed at the beginning of the next business day. TIRF medicine Medication Guides may include the TIRF Sponsor phone number and may be contacted. TIRF Sponsors may refer caller to Emergency Room.

The TIRF REMS Access program call center flow is show below in Figure 6.

Figure 6 TIRF REMS Access Program Call Center Flow

(b) (4)



D. Timetable for Submission of Assessments of the REMS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. The knowledge, attitude, and behavior (KAB) surveys will be submitted at 12 and 24 months from the date of the REMS approval, and as needed thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

5. REMS ASSESSMENT PLAN

The aim of the TIRF REMS Access program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations will be used in an effort to improve the processes, over time, as needed.

A Data Sources

Data will be collected from the following main sources as described in detail below: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program infrastructure and performance, d) safety surveillance, e) periodic surveys of patients, healthcare providers, and pharmacies.

a. The TIRF REMS Access Program Outreach

The following metrics will be tabulated for every reporting period to assess program outreach efforts:

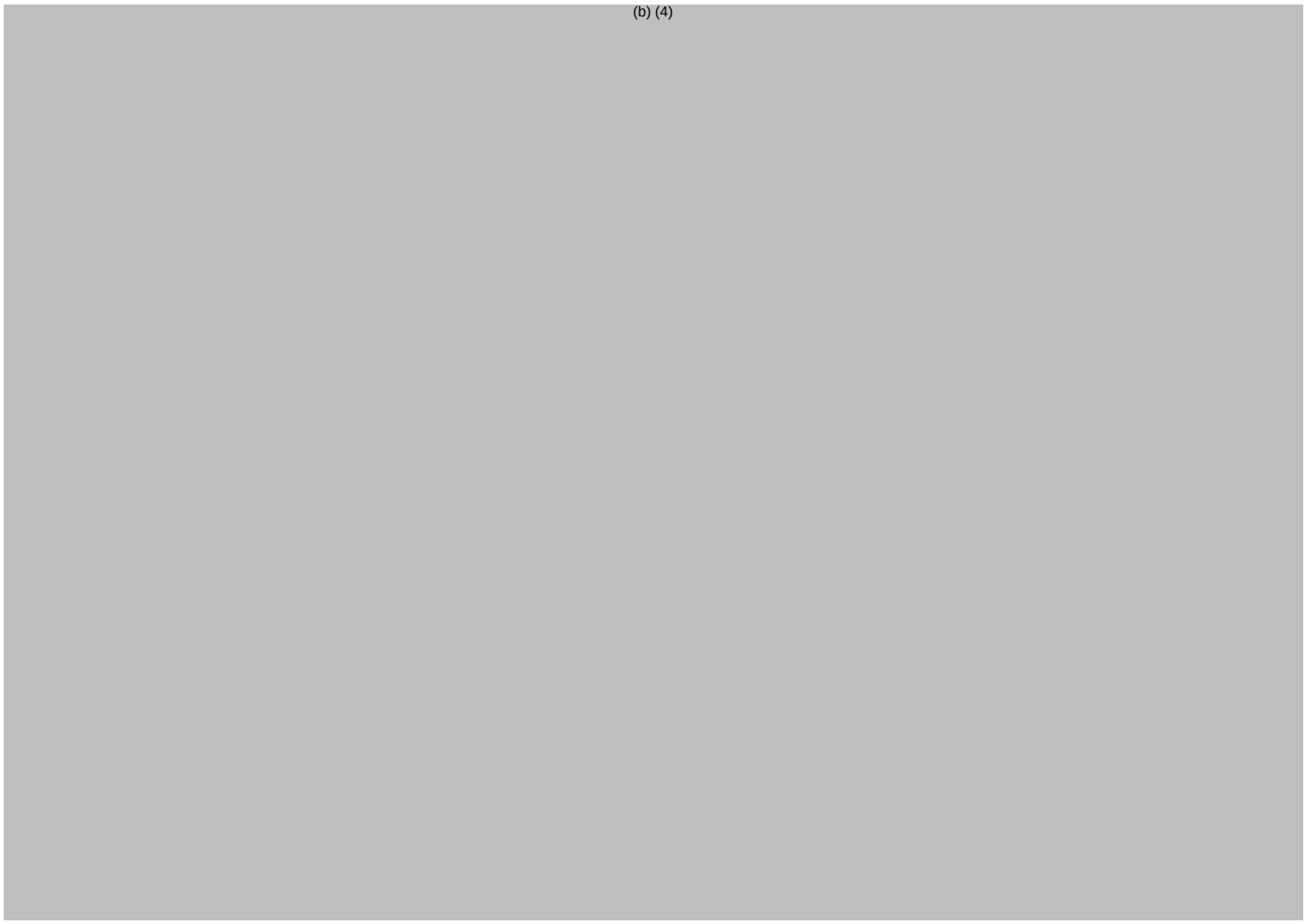
1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

b. The TIRF REMS Access Product and Program Utilization Statistics

The TIRF REMS Access program data flow is show in Figure 7 below.

Figure 7 TIRF REMS Access Program data flow

(b) (4)



For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following data will be tabulated for each reporting period and cumulatively:

5. Number of new patients enrolled by state
6. Number of patients inactivated
7. Number of attempts needed for prescribers to successfully complete Knowledge Assessments
    - Method of completion
8. Number of new prescribers enrolled by state
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
9. Number of prescribers who are inactivated
10. Number of new pharmacies enrolled by type (inpatient or outpatient), by state

- Method of enrollment
- Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

11. Number of pharmacies that are inactivated by type (inpatient or outpatient)
12. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments
13. Dispensing activity for enrolled outpatient pharmacies
    - Total number of prescriptions authorized
    - Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome)
15. Number of wholesalers/distributors inactivated, total
16. Number of new wholesalers/distributors enrolled
    - Method of enrollment
    - Number of incomplete forms
17. Number of days between passive enrollment and receipt of a Patient-Prescriber Agreement Form
    - Method of PPA submission
18. Number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment with and without a PPAF in place.

c. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be tabulated for each reporting period and cumulatively:

19. Assessment of process for pharmacies to upgrade their pharmacy management systems (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems)
20. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem)
21. Call center report
    - Summary of frequently asked questions
    - Problems reported
22. Description of corrective actions taken to address program/system problems.
23. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area
24. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays

The following reports for unintended system interruptions will be provided for each reporting period:

25. Reports identified of inadvertent enrollment deactivations
26. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code)
27. Reports of failure of re-enrollment notifications to reach stakeholders
28. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection.

d. Safety Surveillance

- TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures.
- Surveillance data from the following sources will be included in the REMS Assessment Reports:
    - FDA AERS database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion
    - Other external databases.

e. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Survey results will be reported at 12 months and 24 months after the TIRF REMS Access program approval. TRIG will discuss with the FDA if additional surveys are needed after 24 months. The results from the surveys will be analyzed together with other REMS assessment data, and a report on any corrective actions taken and the outcome of those actions will be provided.

B. TIRF REMS Access Non-Compliance Plan

GOALS & OBJECTIVES

The TIRF REMS Access program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the non-compliance plan is to ensure that TRIG monitors the functioning of TIRF REMS Access and identifies and investigates deviations and non compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program.

TIRF REMS ACCESS NON-COMPLIANCE REVIEW TEAM

A TIRF REMS Access Non-Compliance Review Team will be created. The team will have membership from the companies of the TRIG. A detailed plan for the TIRF REMS Access program will be created and implemented by the team.

The TIRF REMS Access Non-Compliance Review Team's responsibility will be to:

- Evaluate the compliance of patients, healthcare providers, distributors and pharmacies (stakeholders) with the TIRF REMS Access program
- Investigate potential non-compliance activity when events are referred to the team
- Devise corrective measures and issue notices, warnings, suspensions, or deactivations of stakeholders where warranted
- Review need for changes to the TIRF REMS Access program as a result of deviations or non-compliance

The TIRF REMS Access Non-Compliance Review Team will meet regularly.

Any needed program modifications or stakeholder notifications will be approved by TRIG prior to implementation.

SOURCES OF NON-COMPLIANT EVENTS

There are a variety of ways in which the TIRF REMS Access program can detect non compliance. Those potential sources include:

- TIRF REMS Assessment reports
- REMS database activity
- TRIG Member Company Adverse Event Reporting or Medical Information
- TIRF REMS Access Program Call Center
- Data Requests and Audits

TIRF REMS Access Assessment Reports

TIRF REMS Access program data will be collected from the following main sources: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program performance, d) safety surveillance, e) periodic surveys of stakeholders. The TIRF REMS Access Non-Compliance Review Team will regularly review the assessment reports for evidence of non-compliance or deviation from program procedures.

REMS Database Activity

The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive). Data for all users will be updated in the TIRF REMS Access database including data from the call center manual process, web-based processes and the pharmacy network.

The TIRF REMS Access Non-Compliance Review Team will regularly analyze database reports to detect evidence of non-compliance or deviation from program procedures.

TRIG Member Company Adverse Event Reporting or Medical Information

Each company in the TRIG is responsible for the intake, investigation, review and reporting of adverse events and answering medical information queries for their own product. Each TRIG member will review adverse events or medical information queries received by that company and forward events which contain evidence of TIRF REMS Access non-compliance or deviation to the TIRF REMS Access Non-Compliance Review Team for further evaluation. For privacy or commercial confidentiality reasons, this information may be redacted before forwarding, and individual investigation for these events will be referred back to the company that initially received the event.

TIRF REMS Program Call Center

The TIRF REMS Access program will have a call center available for questions about the program, or to process non website enrollments. Enrollments or queries that contain evidence of non-compliance or deviation from program procedures will be referred to the TIRF REMS Access Non-Compliance Review Team.

Data Requests and Audits

TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

The TIRF REMS Access Non-Compliance Review Team will review information received from data requests and audit reports to detect evidence of non-compliance or deviation from program procedures.

EVALUATION PROCESS

Events of suspected non compliance or deviation from TIRF REMS Access program procedures will be evaluated by the TIRF REMS Access Non-Compliance Review Team. Further corrective actions for stakeholders may occur and are described below.

CORRECTIVE ACTION MEASURES

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action in accordance with the TIRF REMS Access non-compliance plan. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access Non-Compliance Review Team according to the severity of the action. The stakeholders in this non-compliance plan include prescribers, patients, distributors, inpatient pharmacies and outpatient pharmacies. The primary elements for corrective action include; notices, warnings, suspension, and deactivation, based on the incidence and outcomes of misuse, abuse, and overdose, in addition to accidental or intentional exposure. If a prescriber or pharmacy is

suspended or deactivated, information will be made available through the program to assist patients in finding alternative prescribers or pharmacies.

Notices

Notices are defined as minor violations that demonstrate a misunderstanding of the program requirements. Notices of non-compliance reinforce the program requirements and are intended to re-educate stakeholders. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

Warnings

Warnings are serious violations that result in an improper patient receiving a TIRF medicine. Warnings may be accompanied by other corrective actions (e.g. retraining) that may be required in order to avoid suspension.

Suspension

Suspension is a temporary deactivation from the program pending the completion of a Corrective Action Plan. Multiple warnings received by a stakeholder within a sixty day time-period will result in a Suspension. Multiple warnings received by a stakeholder over longer periods will accumulate, be logged in reports and may result in a suspension at the discretion of the TIRF REMS Access Non-Compliance Review Team.

A suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension, but may not purchase or acquire additional TIRF medicines until the suspension is removed. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension, and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity (e.g. a Chain Pharmacy or a multi-site distributor), the parent entity will be notified of the non-compliant activity and resultant suspension.

Deactivation

Deactivation is defined as an indefinite deactivation from the program. Deactivation may result from the failure of the stakeholder to implement corrective actions, multiple failures to comply with material program elements, and/or non-compliances where there is no feasible corrective action. Deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

A deactivated stakeholder may request reinstatement in the TIRF REMS Access program. Requests for reinstatement must be in writing (e.g. letter, fax, etc.) and contain sufficient details on corrective actions taken to prevent any future non-compliance with program elements. Patients that have been deactivated will only be reinstated by a request made by the patient's prescriber. Requests for reinstatement will be evaluated by the TIRF REMS Access Non-

Compliance Review Team which will make a recommendation to TRIG. TRIG will make the final determination on reinstatement.

TIRF REMS ACCESS PROGRAM AUDITS

As part of non-compliance monitoring, TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

C. Internal Quality and Compliance

The TIRF medicines REMS program team will be supported by written procedures to define process and will be audited against these for compliance.

6. OTHER RELEVANT INFORMATION

A. The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program, all TIRF medicines in an individual REMS program will be transitioned to the TIRF REMS Access program. The transition for the TIRF REMS Access program will begin upon system availability. From this point onward all *new* stakeholders will be required to enroll in the TIRF REMS Access program.

Upon system availability the individual REMS program websites, call centers, and enrollment forms will be redirected to the TIRF REMS Access program. The TIRF REMS Access program will provide information and direction on why the individual REMS program website is no longer available, in addition to providing an introduction to the new TIRF REMS Access program and resources available to stakeholders. Historical data from all individual REMS programs will be referenced to determine the date of last prescription so that the TIRF REMS can accurately calculate 6 months of no prescription activity.

All pharmacies and prescribers already enrolled in an individual REMS program will be notified (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. They will also be notified in these letters that:

- They must review the Education Program on the TIRF REMS Access program website or request a copy from the call center.
- If the prescriber changes the patient's TIRF medicine at any time the prescriber is required to counsel the patient on the new product and provide the relevant Medication Guide but no new Prescriber-Patient Agreement Form (PPAF) is required.

Prescribers
Enrollment data for each enrolled prescriber will be transferred from the individual REMS program to the TIRF REMS Access program database when it is available. These prescribers will then be able to prescribe any TIRF medicine within the TIRF REMS Access program. Healthcare providers will be guided to review the educational program for the TIRF REMS Access program but will not be tested on these materials. These prescribers will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

Inpatient Pharmacies
Enrollment data for each enrolled inpatient pharmacy will be automatically transferred from the individual REMS program to the TIRF REMS Access program database when it is available. Inpatient pharmacies will then be able to order and dispense any TIRF medicine within the TIRF REMS Access program to inpatients.

Outpatient Pharmacies
All outpatient pharmacies in an individual REMS program will be automatically transitioned to the new TIRF REMS Access program.

However, chain pharmacies will need to execute a TIRF REMS Access program contract with their switch provider before they can order and dispense all TIRF medicines. Chain pharmacies that have not executed a TIRF REMS Access program contract with their switch provider will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If chain pharmacies do not execute a TIRF REMS Access program contract with their switch provider within six months, they will no longer be able to order or dispense any TIRF medicine.

Independent pharmacies will need to agree to the shared program terms and conditions before they can order and dispense all TIRF medicines. Independent pharmacies that have not agreed to the shared program terms and conditions will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If outpatient pharmacies do not sign the new business contracts within six months they will no longer be able to order or dispense any TIRF medicine, and will have to complete an updated contract if they wish to continue to dispense TIRF medicines.

All pharmacies that have been transitioned from an individual REMS program will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their original enrollment in the individual REMS program.

Patients
Enrollment data for patients will be automatically transferred from the individual REMS program to the TIRF REMS Access program database. Patients who have previously been

enrolled in an individual REMS and have completed a PPAF can be prescribed/receive any TIRF medicine within the TIRF REMS Access program. Patients will only be required to complete a new PPAF for the TIRF REMS Access program every 2 years from their last PPAF.

Distributors
Distributors already enrolled in a single product REMS program will be notified of the transition to the TIRF REMS Access program (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. Enrollment data for distributors will be transferred from the individual REMS program to the TIRF REMS Access program database. Distributors will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

B. The TIRF REMS Access Program Steering Committee

A TIRF REMS Access program steering committee will be comprised of representatives from each Sponsor who will provide high level oversight and strategic direction for the TIRF REMS Access program. One voting member from each Sponsor company will be included in the Steering Committee. Significant issues and trends will be reviewed and appropriate recommendations made to the TIRF medicine Operations Team.

C. Abbreviations

The following abbreviations refer to the REMS program descriptors and products.

TIRF Medicines:	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access:	REMS program for TIRF medicines
TIRF Sponsors:	The group of sponsors that are submitting this REMS (please refer to the 'List of TIRF REMS Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.)

7. REFERENCES

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TIRF REMS ACCESS PROGRAM

Risk **E**valuation and **M**itigation **S**trategy

Web Prototype

Date: 11/30/2011

Table of Contents

TIRF REMS Access Web Prototype

NOTE FOR SCREEN CAPTURES

On every screen capture within this document the following 2 items have been eliminated from the web screen captures to reduce number of pages and reduce redundancy in this document. The “For Assistance message”, and the web page footer can be viewed within the next 3 pages, but will not be seen as part of the screen captures through the document even though they will exist on every page.

TIRF CALL CENTER ASSISTANCE MESSAGE:

For assistance, please call the TIRF REMS Access program at 1-866-822-1483.

TIRF REMS Access Web Prototype

IMPORTANT SAFETY INFORMATION

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
Patients considered opioid-tolerant are those who are taking:
- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions
The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting
Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at 1-866-822-1483. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide
It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

You must provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:
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TIRF REMS Access Web Prototype

WEB PAGE FOOTER

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TIRF REMS Access Web Prototype

COMING SOON PAGE

Coming Soon!

The TIRF REMS Access Program website is currently under construction.

For assistance or enrollment inquiries, contact the TIRF REMS Access program at 1-866-822-1483.

Check back soon for program updates.

What is the TIRF REMS Access Program?

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program is an FDA-required program designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are treated to ensure appropriate use of TIRF medicines. The purpose of the TIRF REMS Access program is to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines.

For assistance, please call the TIRF REMS Access program at 1-866-822-1483.

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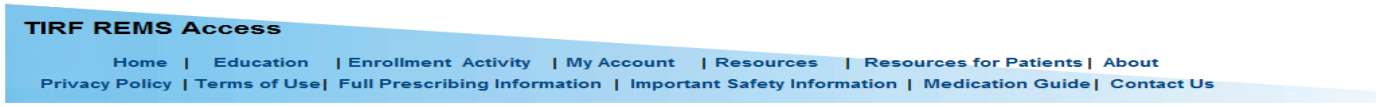
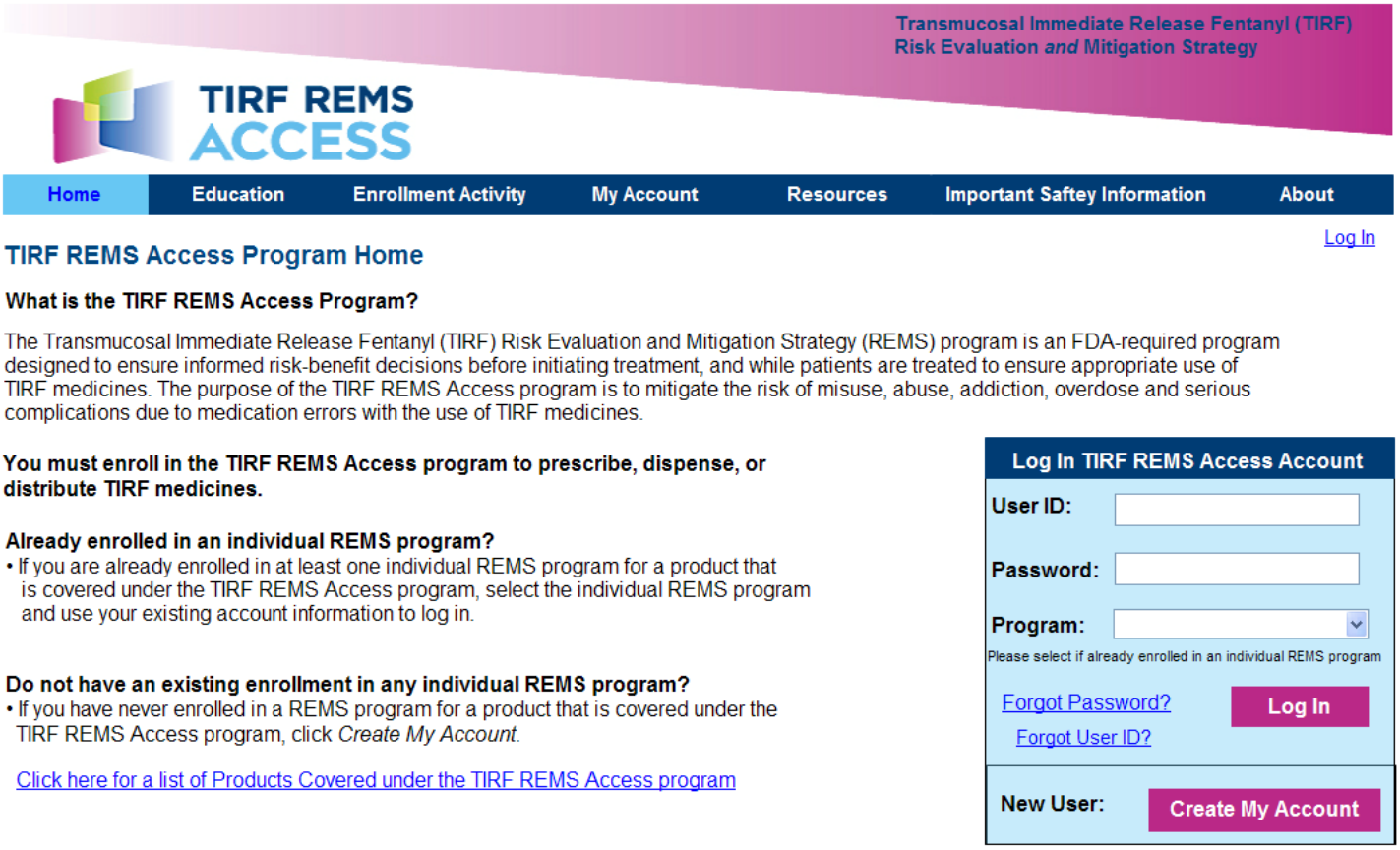


TIRF REMS Access Web Prototype

HOME PAGE



Click here for a list of Products Covered under the TIRF REMS Access program hyper link will open the document in a pdf window

TIRF REMS Access Program

Products covered Under the TIRF REMS Access Program:

- Abstral ® (fentanyl) sublingual tablets
- Actiq ® (fentanyl citrate) oral transmucosal lozenge
- Fentora ® (fentanyl citrate) buccal tablet
- Lazanda ® (fentanyl) nasal spray
- Onsolis ® (fentanyl) sublingual spray
- Approved generic equivalents of these products are also covered under this program

Comprehensive table is also available at the Education section of the website

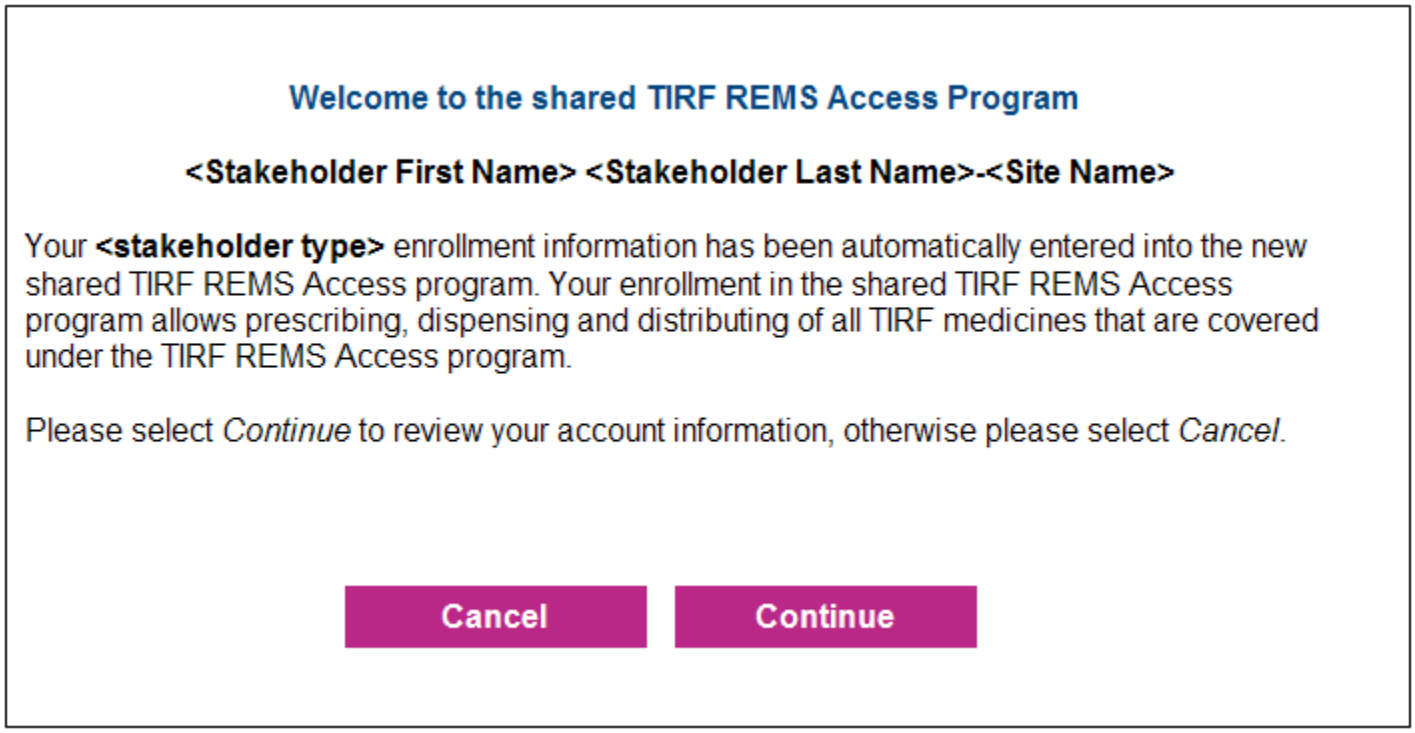
www.TIRFREMSaccess.com

Important Safety Information is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

TRANSITIONING STAKEHOLDERS

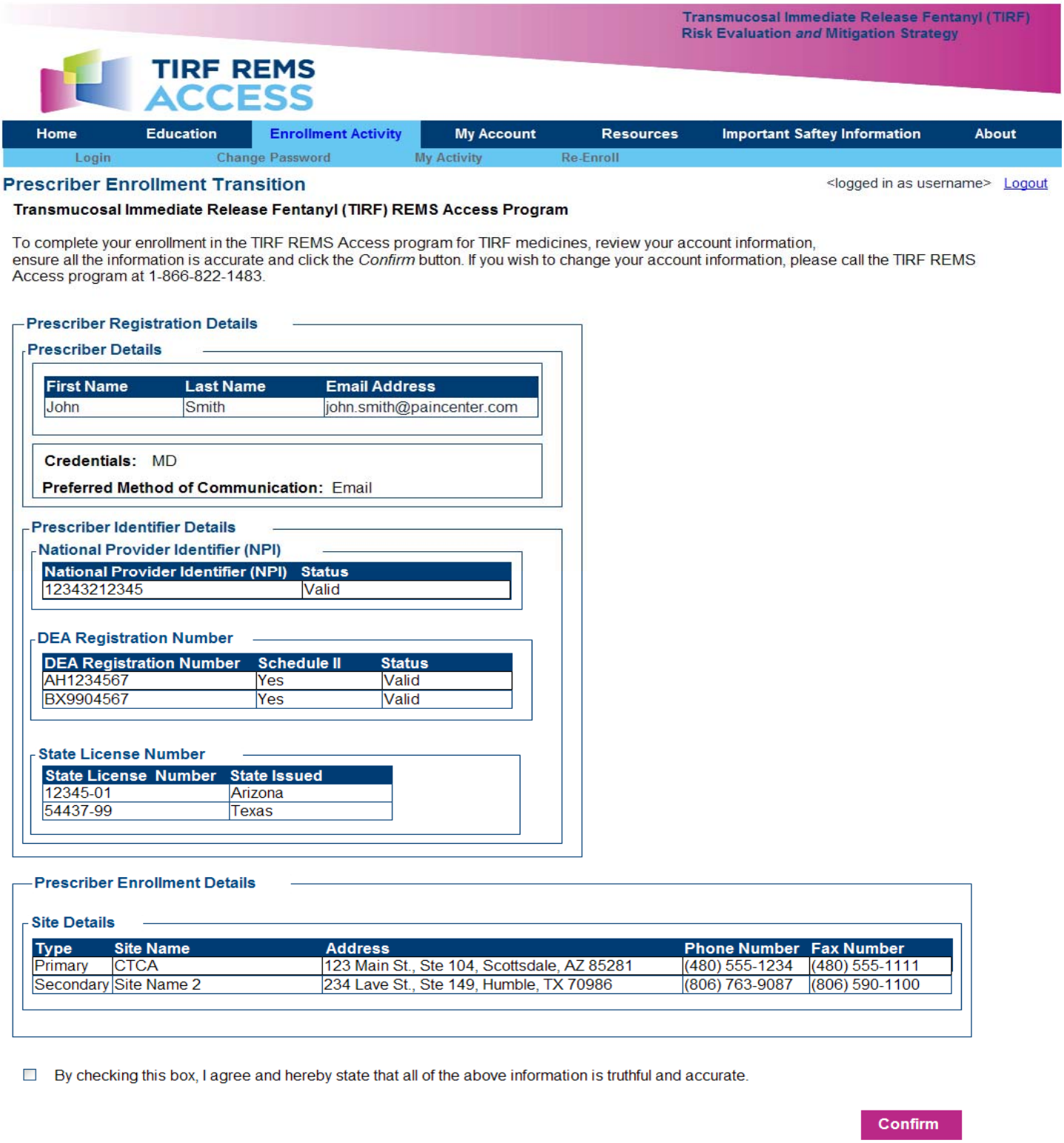
Transitioned Prescriber Enrollment Process

Welcome Message



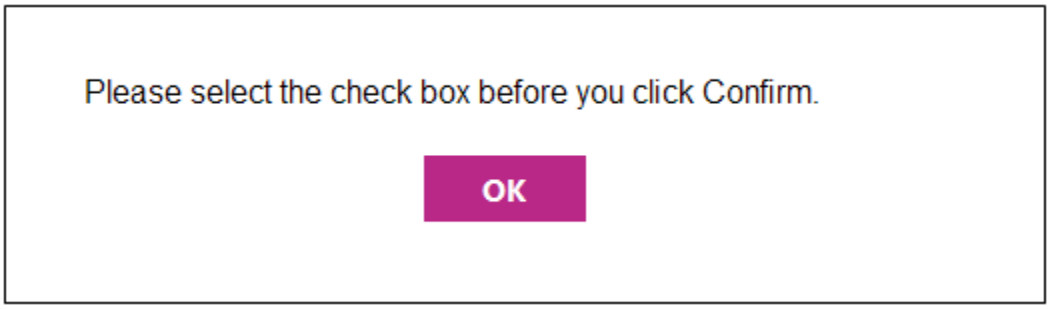
TIRF REMS Access Web Prototype

Prescriber Enrollment Transition



TIRF REMS Access Web Prototype

Error Message – Check Box Not Selected



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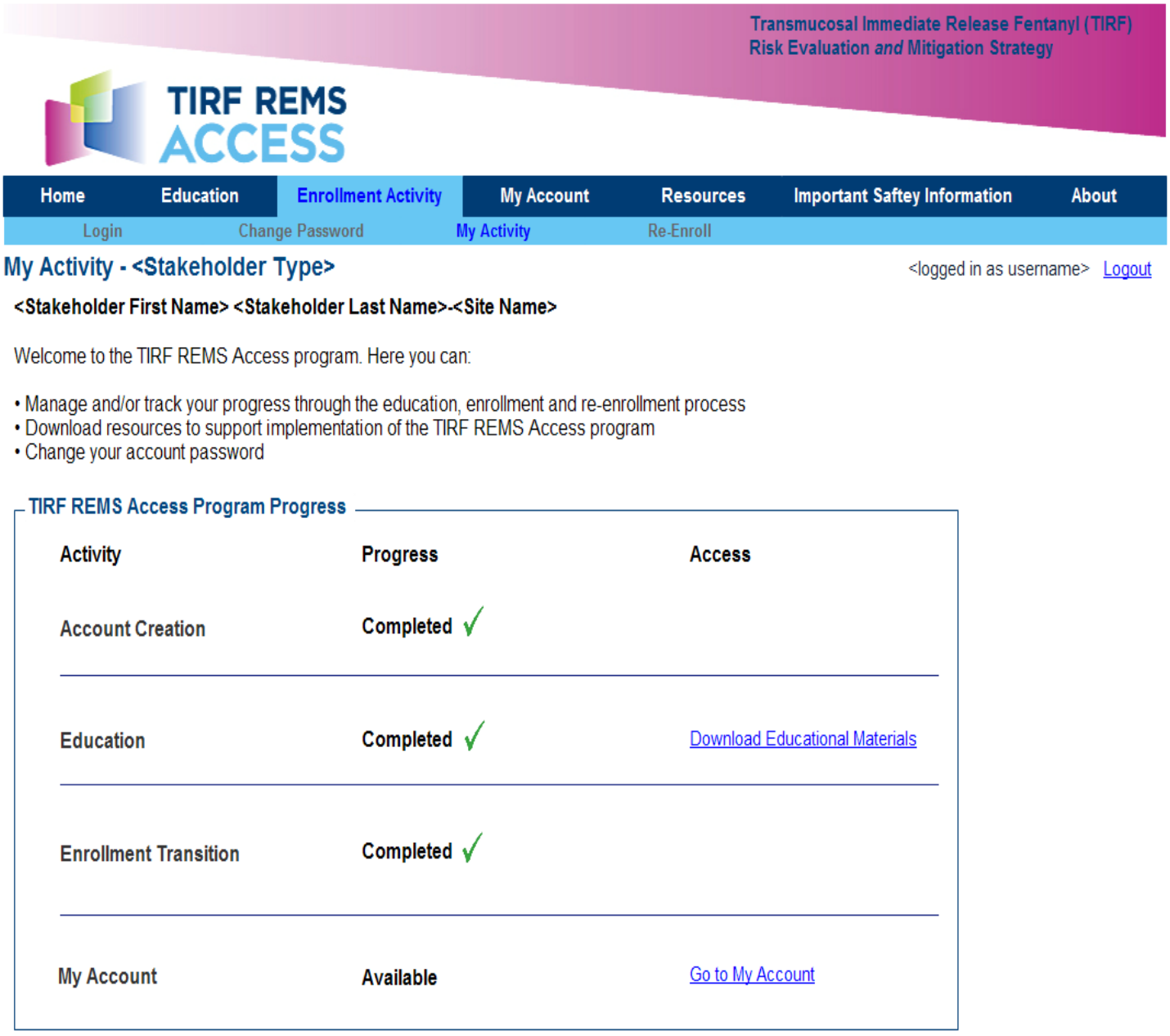
Account Status – Enrollment Transition Complete

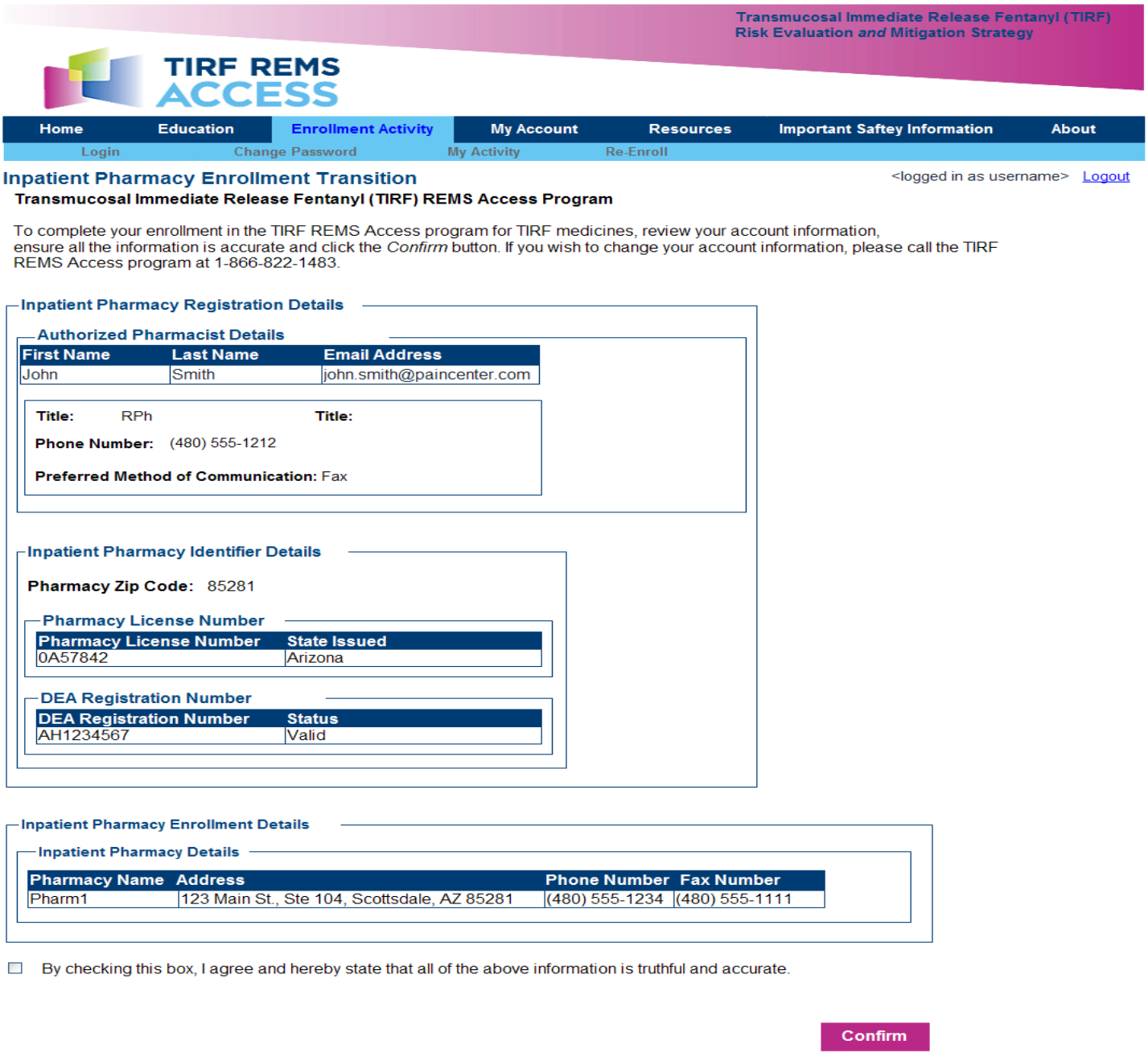


TIRF REMS Access Web Prototype

Transitioned Inpatient Pharmacy Enrollment Process

See Welcome Message page 11

Inpatient Pharmacy Enrollment Transition



→See Error Message – Check Box Not Selected page 13
See Account Status – Enrollment Transition Complete page 14

Transitioned Outpatient Pharmacy Enrollment Process

Welcome Message – Transitioned Outpatient Pharmacy

Welcome to the shared TIRF REMS Access Program

<Stakeholder First Name> <Stakeholder Last Name>

Your **outpatient pharmacy** enrollment information has been automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program.

To complete your enrollment into the TIRF REMS Access program, you must complete the following 2 steps:

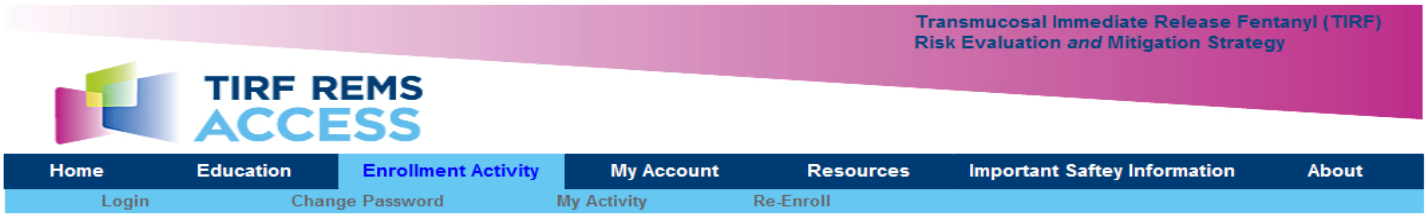
1. **Agree to the TIRF REMS Access program terms and conditions**
2. **Review and confirm your account information**

Please select *Continue* to review your account information, otherwise please select *Cancel*.

Cancel Continue

TIRF REMS Access Web Prototype

Outpatient Pharmacy Enrollment Transition



Outpatient Pharmacy Enrollment Transition

<logged in as username> Logout

Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

To complete your enrollment in the TIRF REMS Access program for TIRF medicines, review your account information, ensure all the information is accurate and click the *Confirm* button. If you wish to change your account information, please call the TIRF REMS Access program at 1-866-822-1483.

Outpatient Pharmacy Registration Details

Authorized Pharmacist Details

First Name	Last Name	Email Address
John	Smith	john.smith@paincenter.com

Title: RPh **Other:**

Phone Number: (480) 555-1212

Preferred Method of Communication: Fax

Outpatient Pharmacy Details

Pharmacy	Address	Phone Number	Fax Number	NPI	NCPDP	DEA	Medicaid ID-State
Pharm1	123 Main St.,Ste 104, Scottsdale, AZ 85281	(480) 555-1234	(480) 555-1111	1234567890	0123456	AZ0098765	1234-09-AZ, 9876-23-CA
Pharm2	400 W Universaity Dr, Tempe, AZ 85281	(480) 663-0098	(480) 663-0009	09876543211	1234567	AZ9908765	1975-09-AZ, 76534-1123-AZ
Pharm3	1500 Mill Ave, Phoenix, AZ 85051	(480) 998-1234	(480) 998-9999	1239874569	9987879	AZ8797654	11234-087-AZ
Pharm4	4343 N Scottsdale Rd., Scottsdale, AZ 85251	(480) 887-1239	(480) 776-7676	1112345678	0987654	AZ9876554	98765-123-AZ 123456-CA 456789-AZ

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

☐ By checking this box, I agree to the Additional Terms and Conditions and hereby state that all of the above information is truthful and accurate.

Confirm

The TIRF REMS Access Program Additional Terms and Conditions

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42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32,63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28, 51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30, 00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30,0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30, 55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30, 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access program to Providers via submission of all billing and reversal request. Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

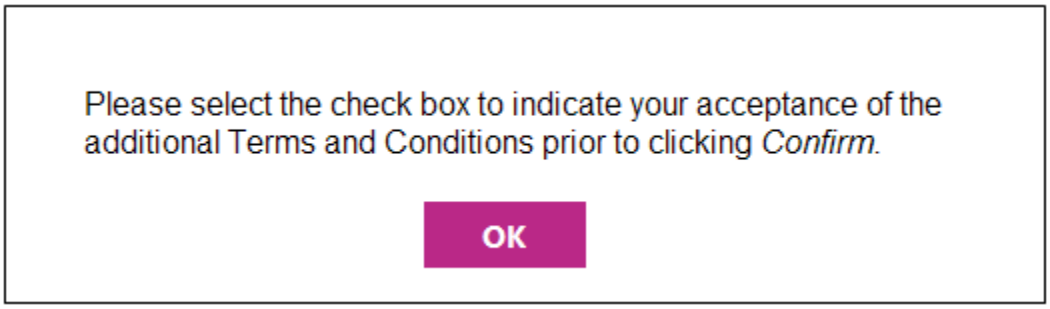
Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Error Message for Outpatient Pharmacy – Check Box Not Selected



See Account Status – Enrollment Transition Complete page 14

TIRF REMS Access Web Prototype

Transitioned Chain Pharmacy Enrollment Process

Welcome Message – Transitioned Chain Pharmacy with No Switch Provider Contract

Welcome to the shared TIRF REMS Access Program

<Stakeholder First Name> <Stakeholder Last Name>-<Site Name>

Your **chain pharmacy** enrollment information has been automatically entered into the new shared TIRF REMS Access program. **Our records indicate that you have not executed a TIRF REMS Access program contract with your switch provider. Please contact your switch provider account manager for a new contract.**

If you do not sign the new TIRF REMS Access program contract within six months, you will no longer be able to order or dispense any TIRF medicine. You will only be able to continue to dispense those TIRF medicines with an individual REMS program, in which you previously enrolled, for up to six months from availability of the TIRF REMS Access program.

To complete your enrollment into the TIRF REMS Access program, you must complete the following 2 steps:

1. Execute a TIRF REMS Access program contract with your switch provider
2. Review and confirm your account information

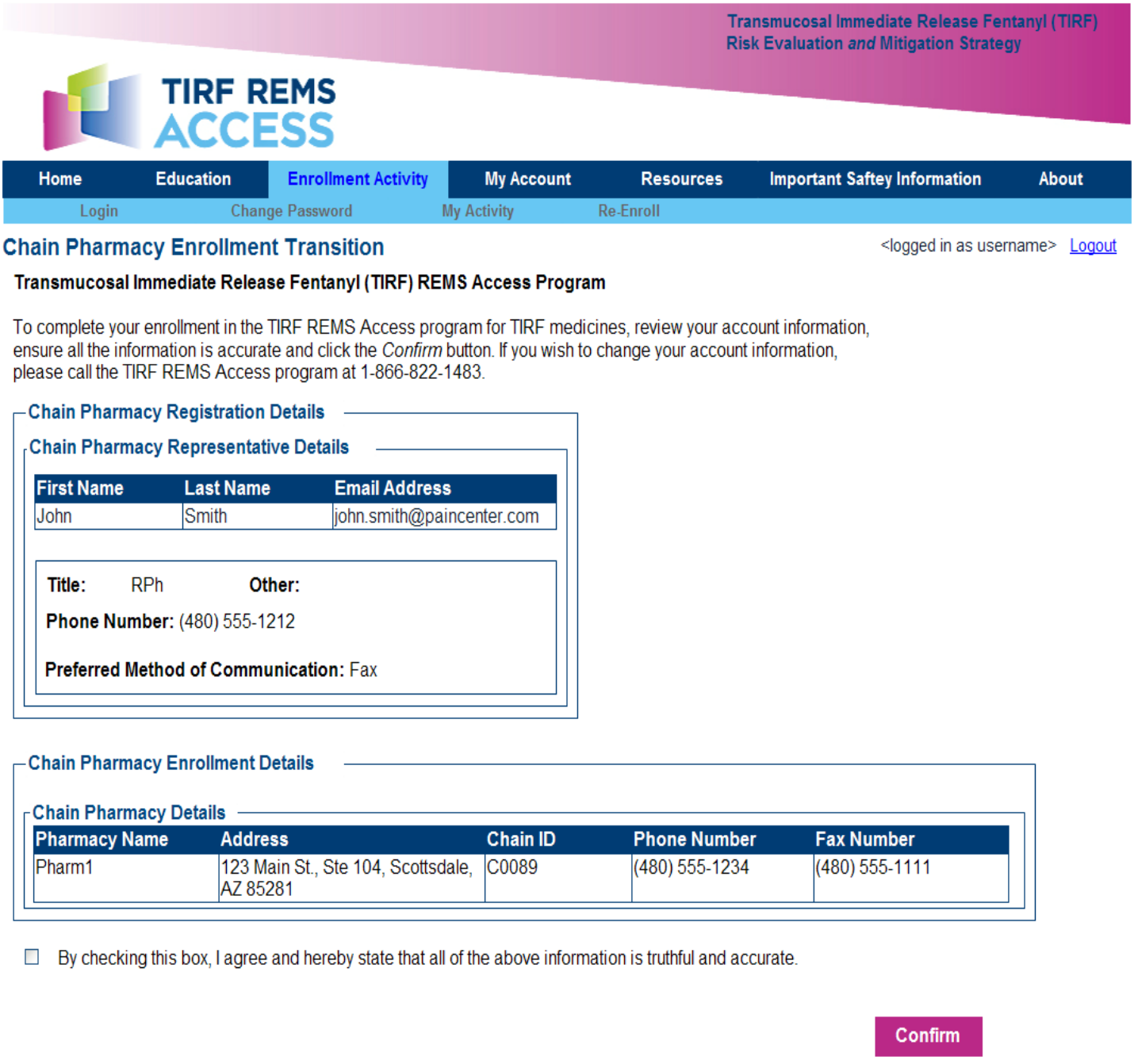
Please select *Continue* to review your account information, otherwise please select *Cancel*.

For assistance, please call the TIRF REMS Access program at 1-866-822-1483.

Cancel Continue

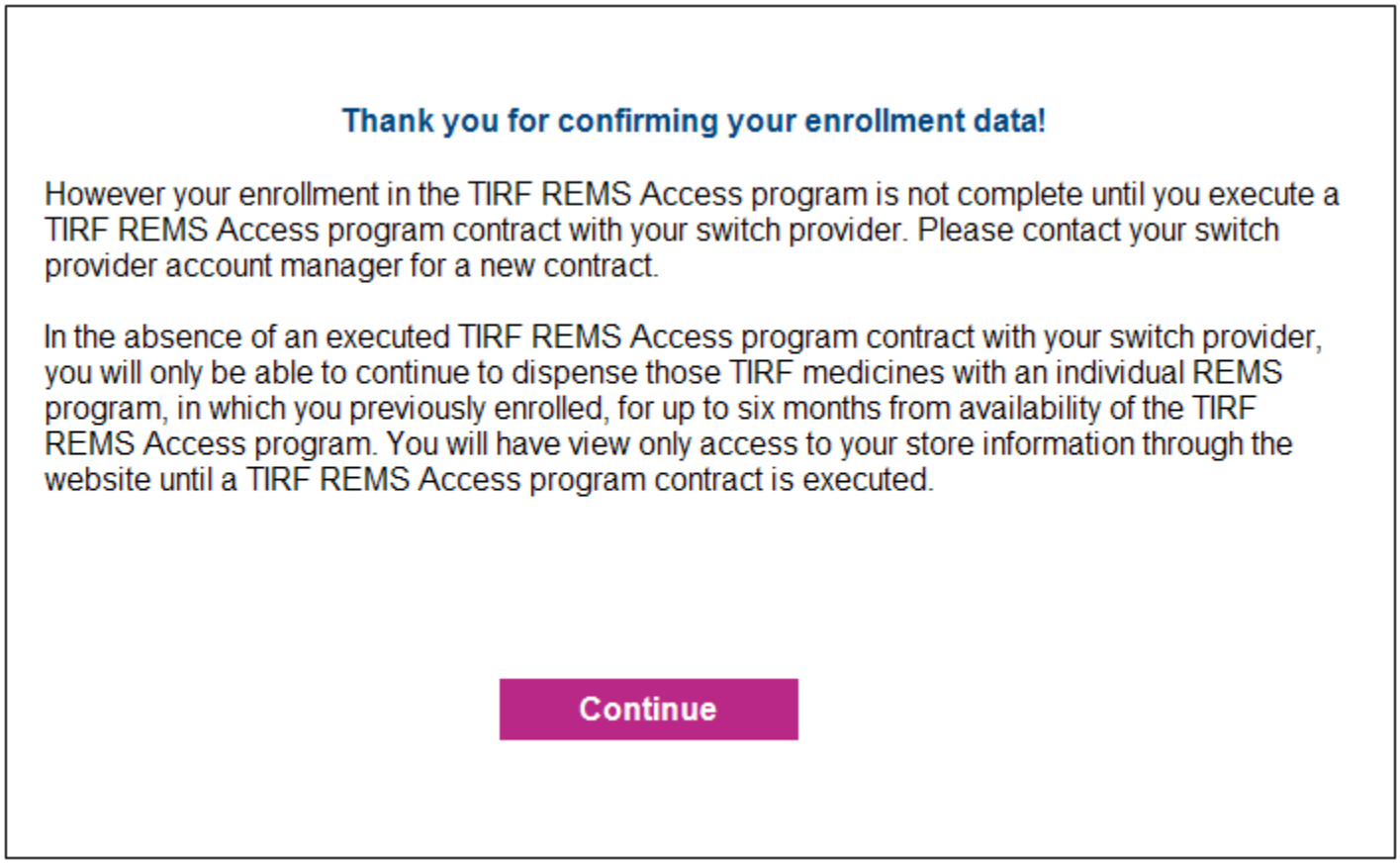
TIRF REMS Access Web Prototype

Chain Pharmacy Enrollment Transition



TIRF REMS Access Web Prototype

Chain Pharmacy Enrollment Transition Message – No Switch Provider Contract

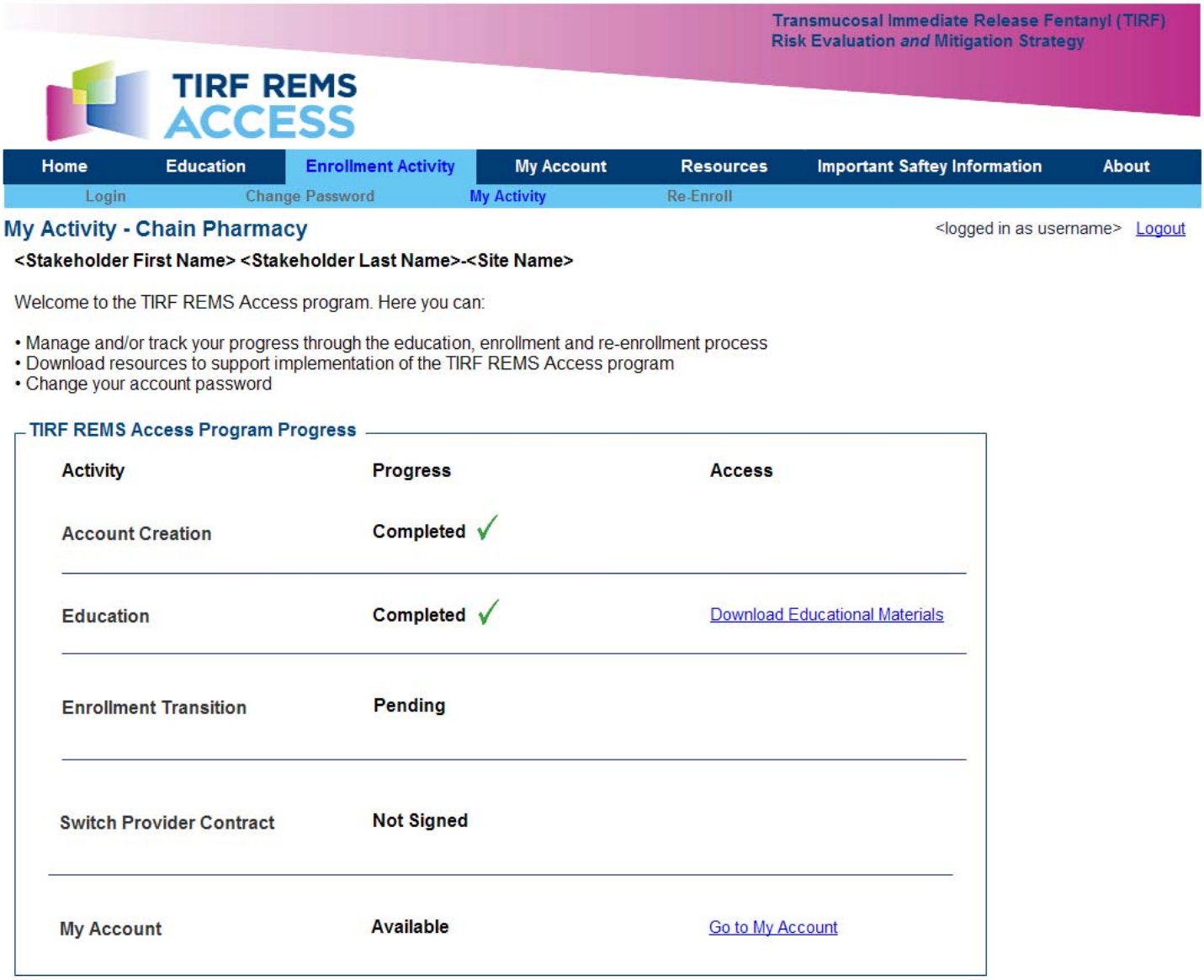


TIRF REMS Access Web Prototype

Chain Pharmacy Enrollment Transition – No Switch Provider Contract

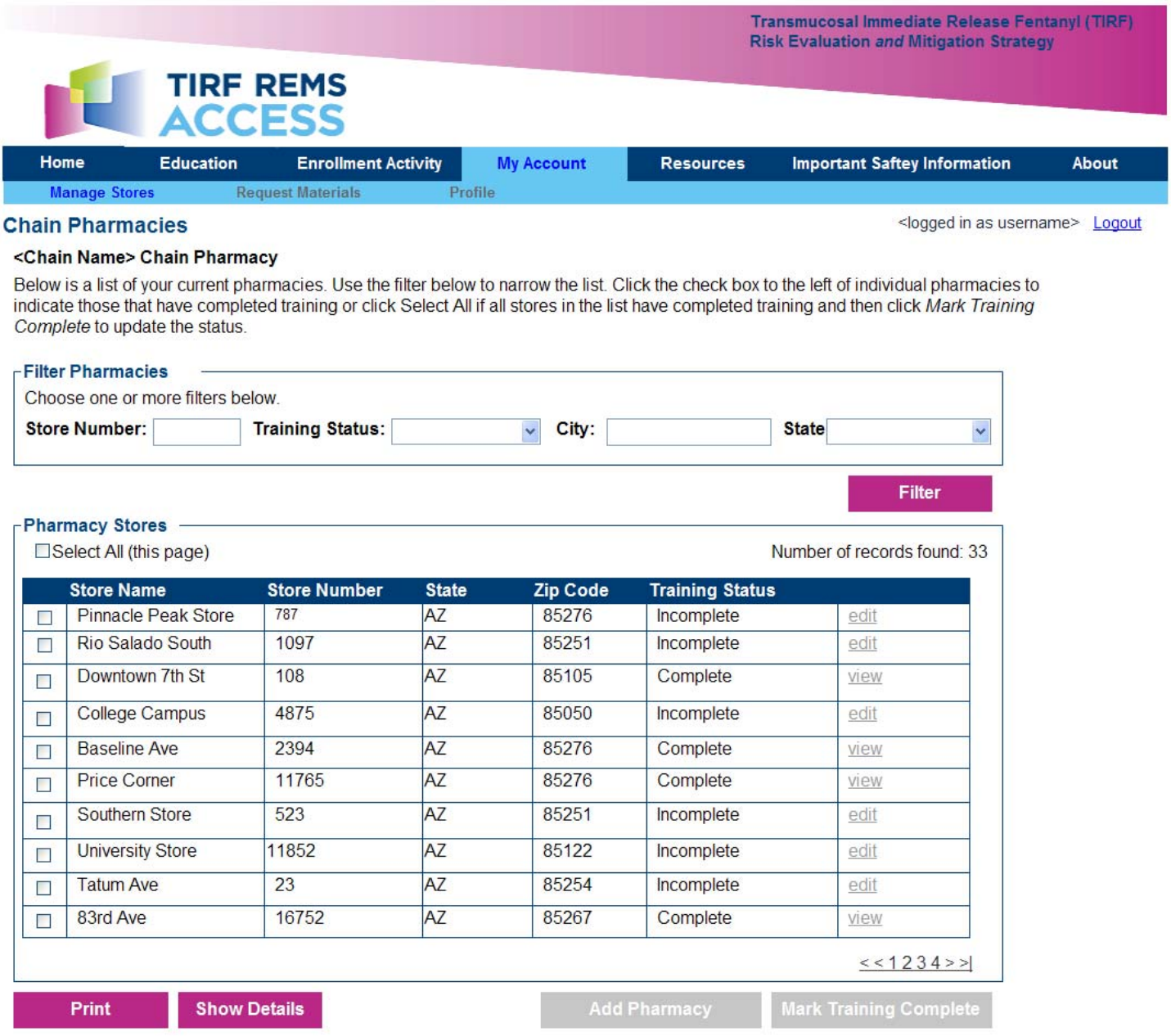
→See Error Message – Check Box Not Selected page 13

Account Status – Enrollment Transition Pending



TIRF REMS Access Web Prototype

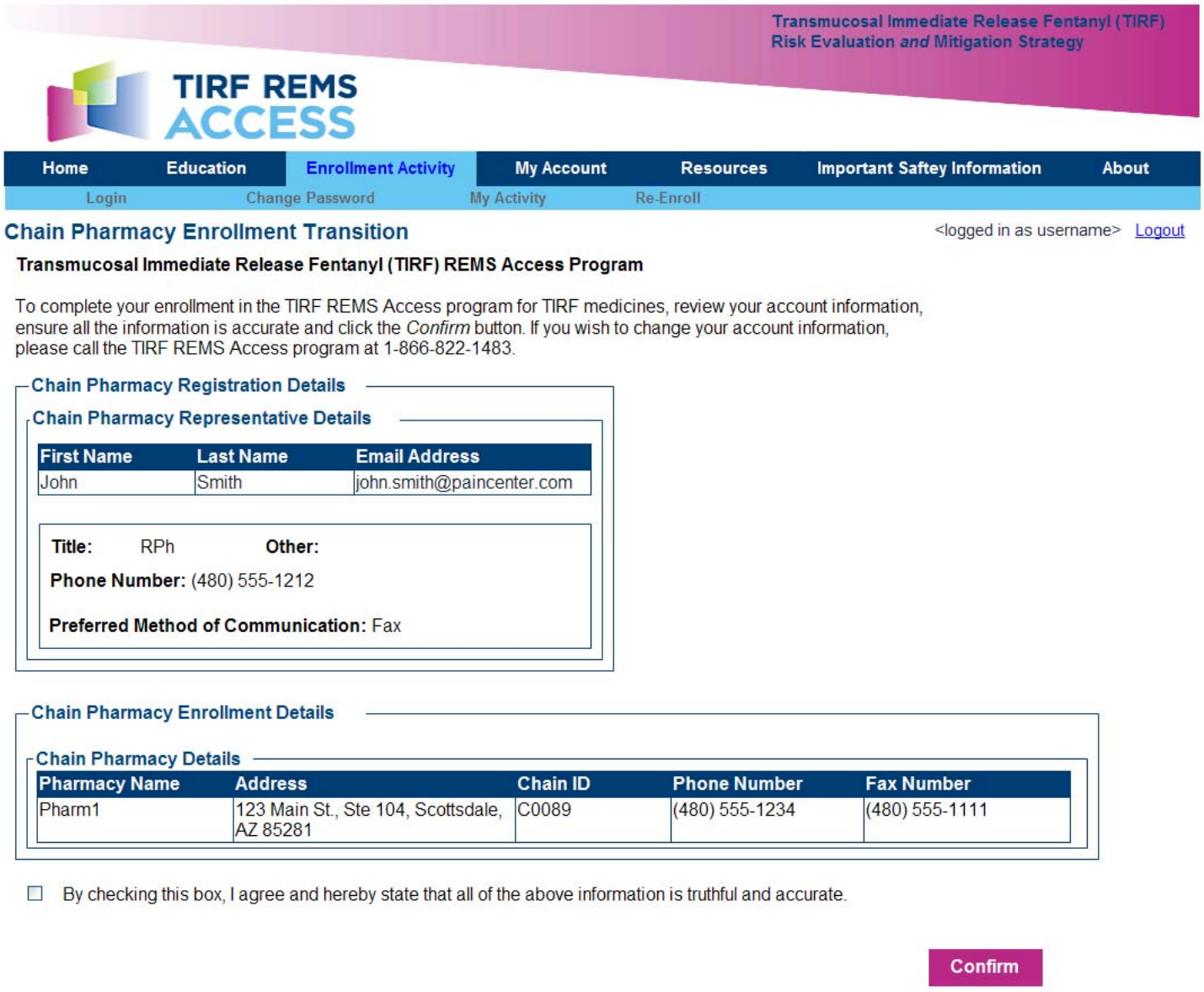
No Switch Provider Contract - Chain Pharmacy Dashboard



Welcome Message – Transitioned Chain Pharmacy with Switch Provider Contract

→See Welcome Message – Transitioned Outpatient Pharmacy on page 16

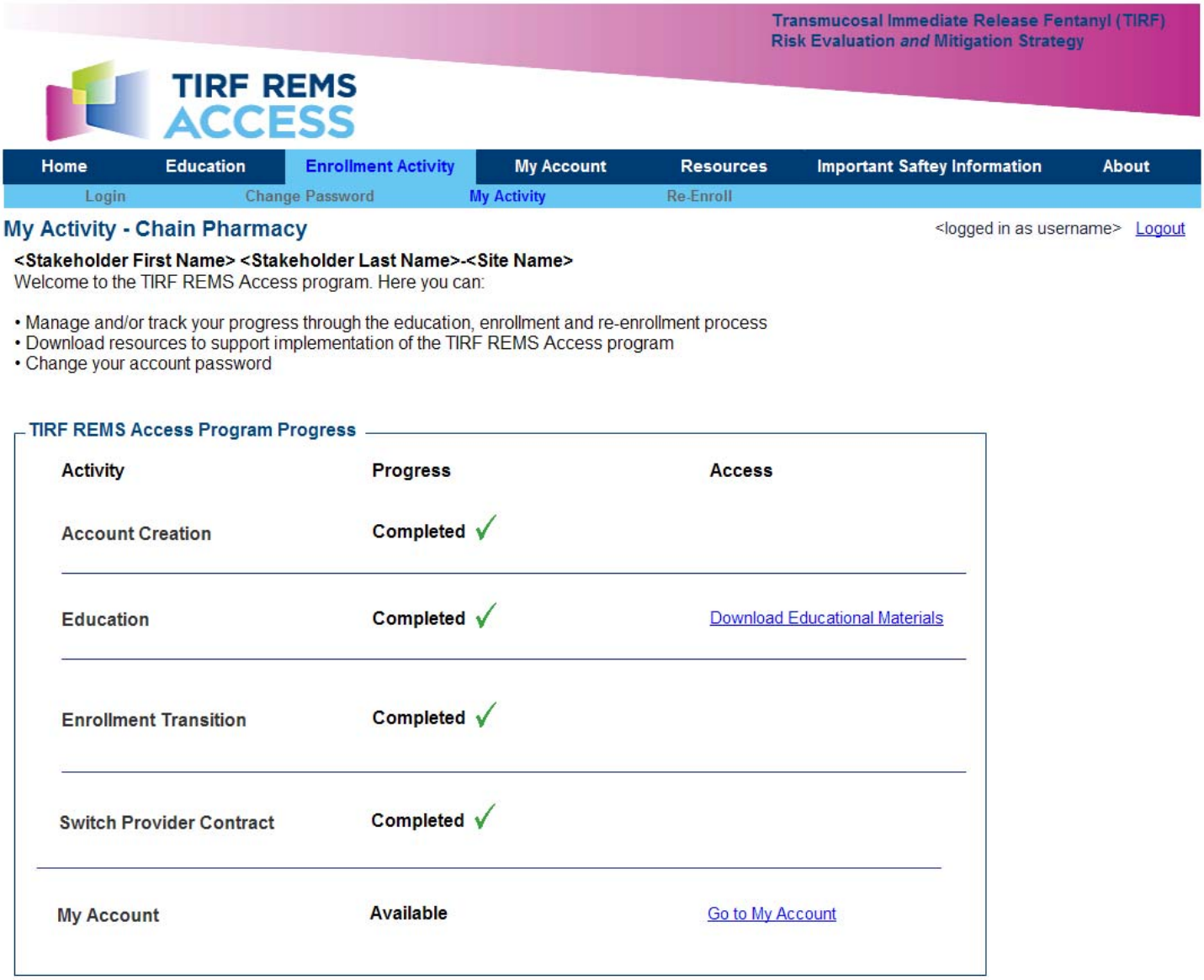
Chain Pharmacy Enrollment Transition



TIRF REMS Access Web Prototype

→See Error Message – Check Box Not Selected 13

Account Status – Enrollment Transition Completed Switch Provider Contract Signed

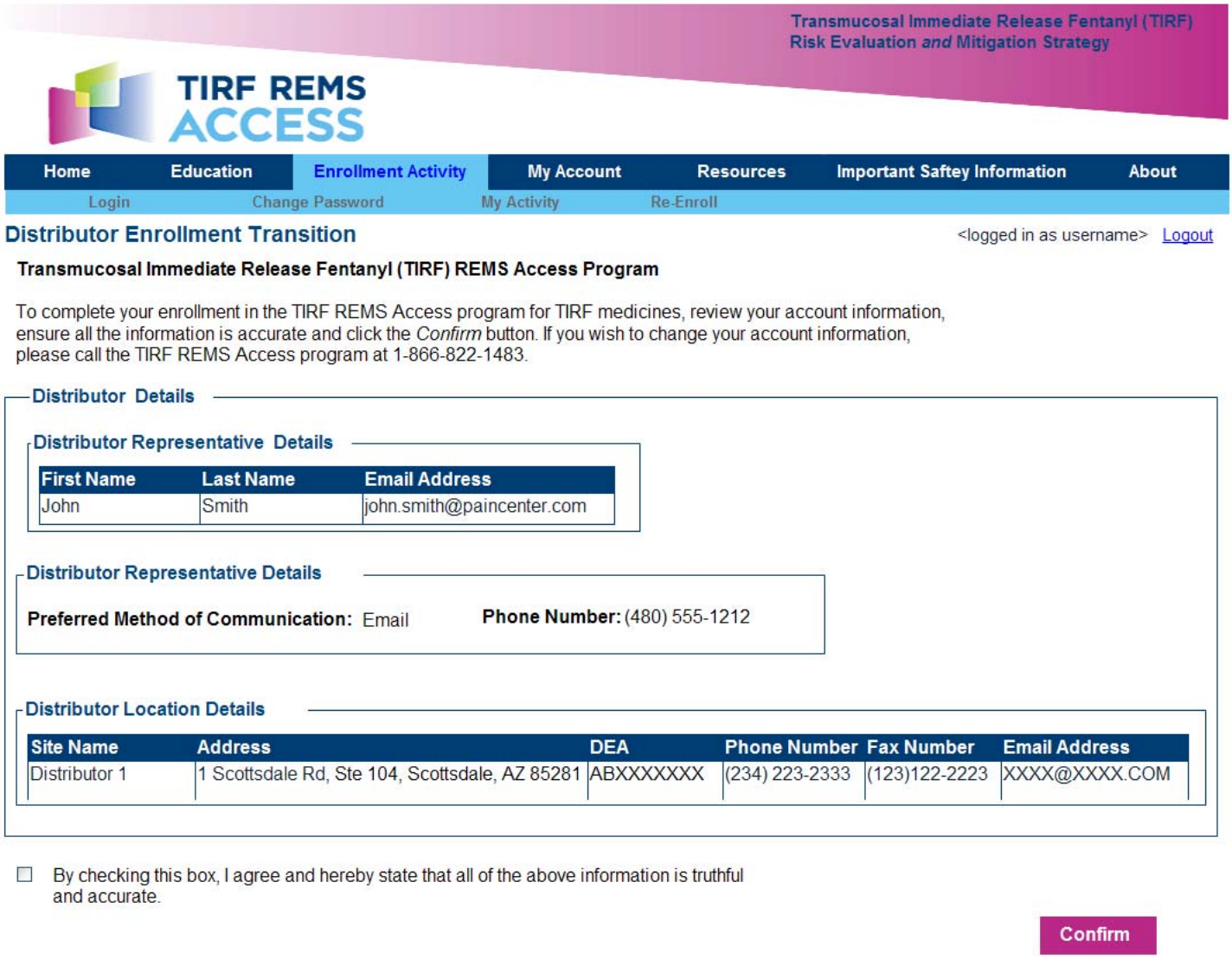


TIRF REMS Access Web Prototype

Transitioned Distributor Enrollment Process

→See Welcome Message page 11

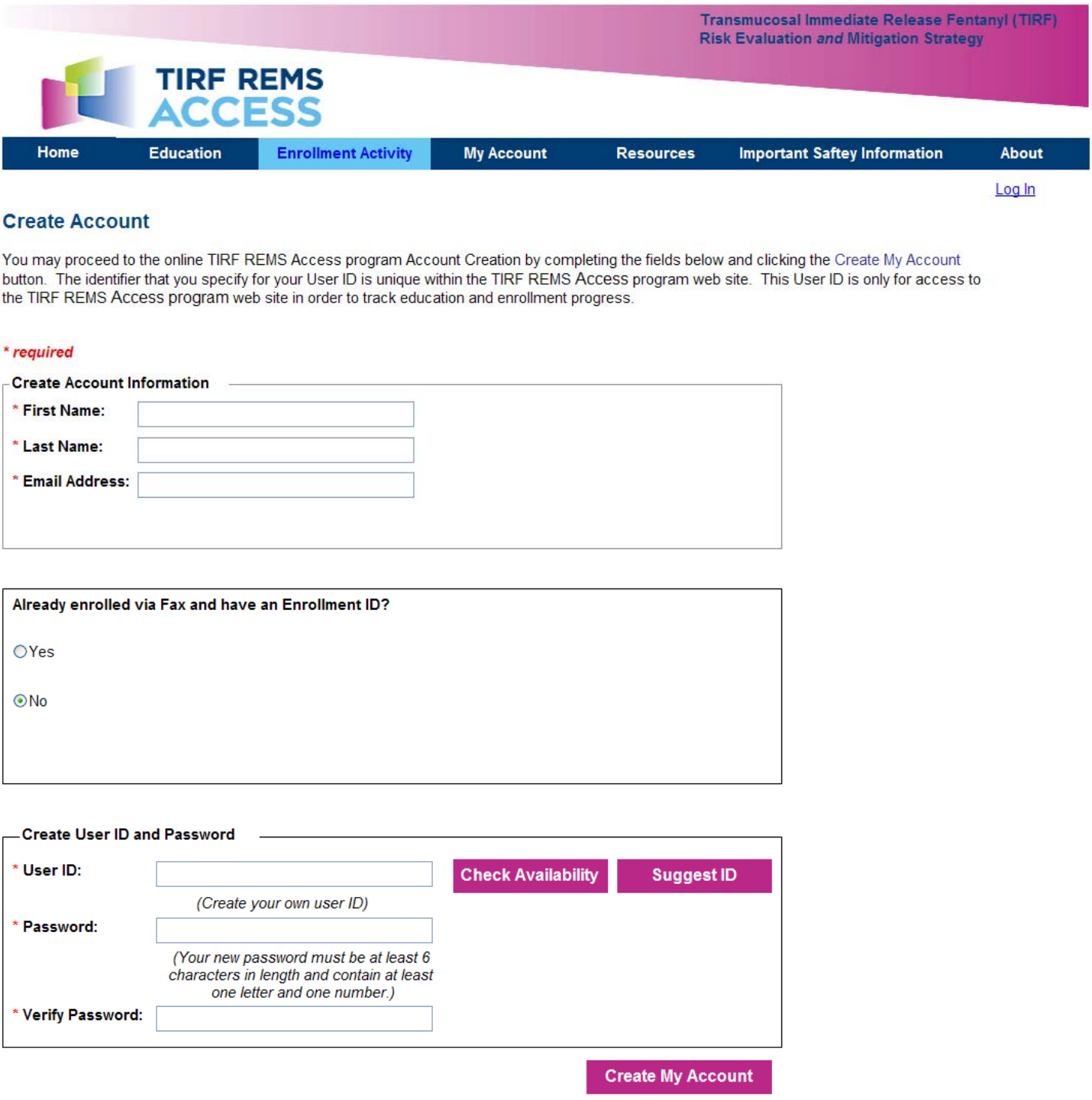
Distributor Enrollment Transition



→See Error Message – Check Box Not Selected page 13
→See Account Status – Enrollment Transition Complete page 14

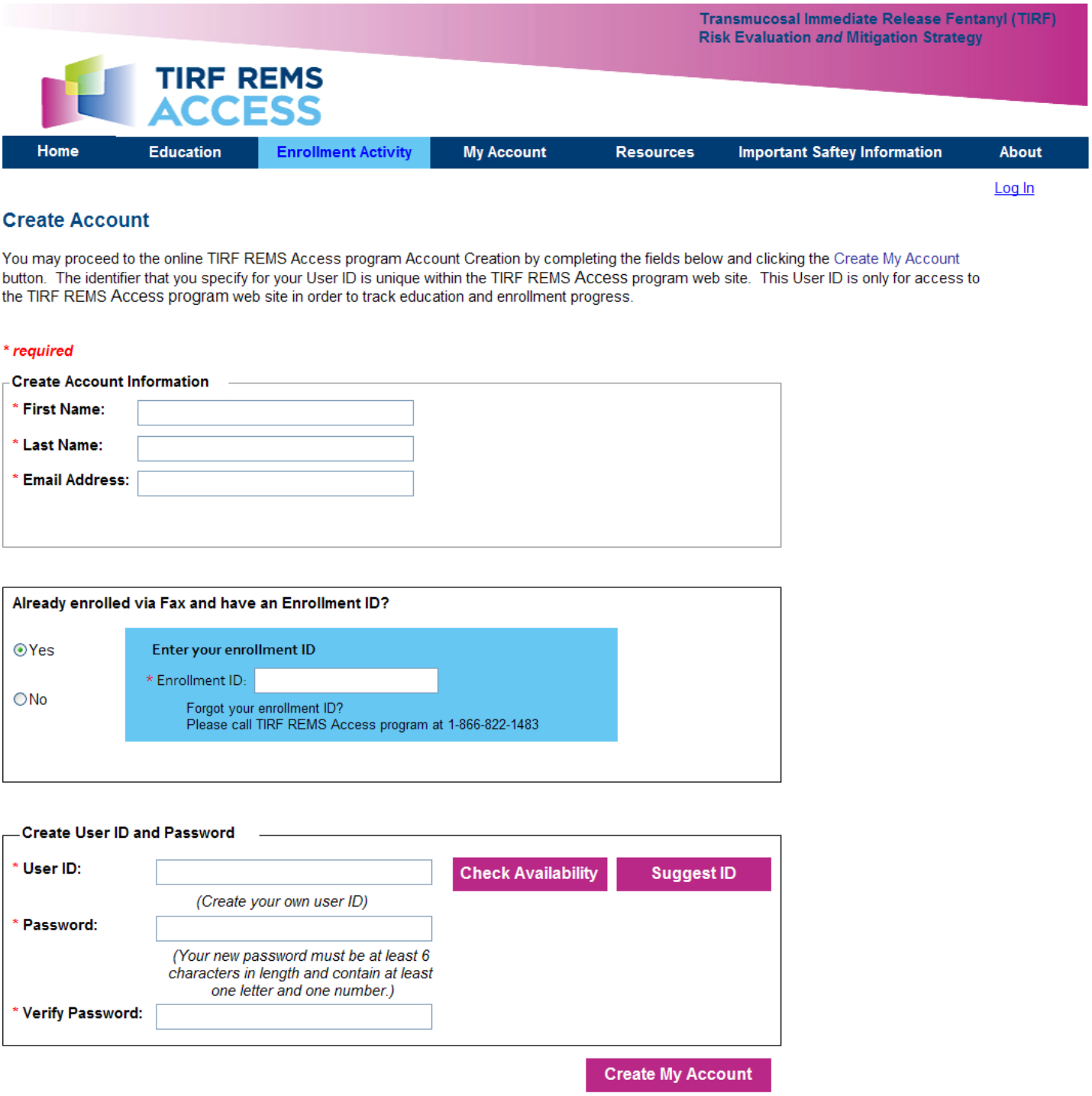
TIRF REMS Access Web Prototype

CREATE ACCOUNT – NEW TO THE PROGRAM



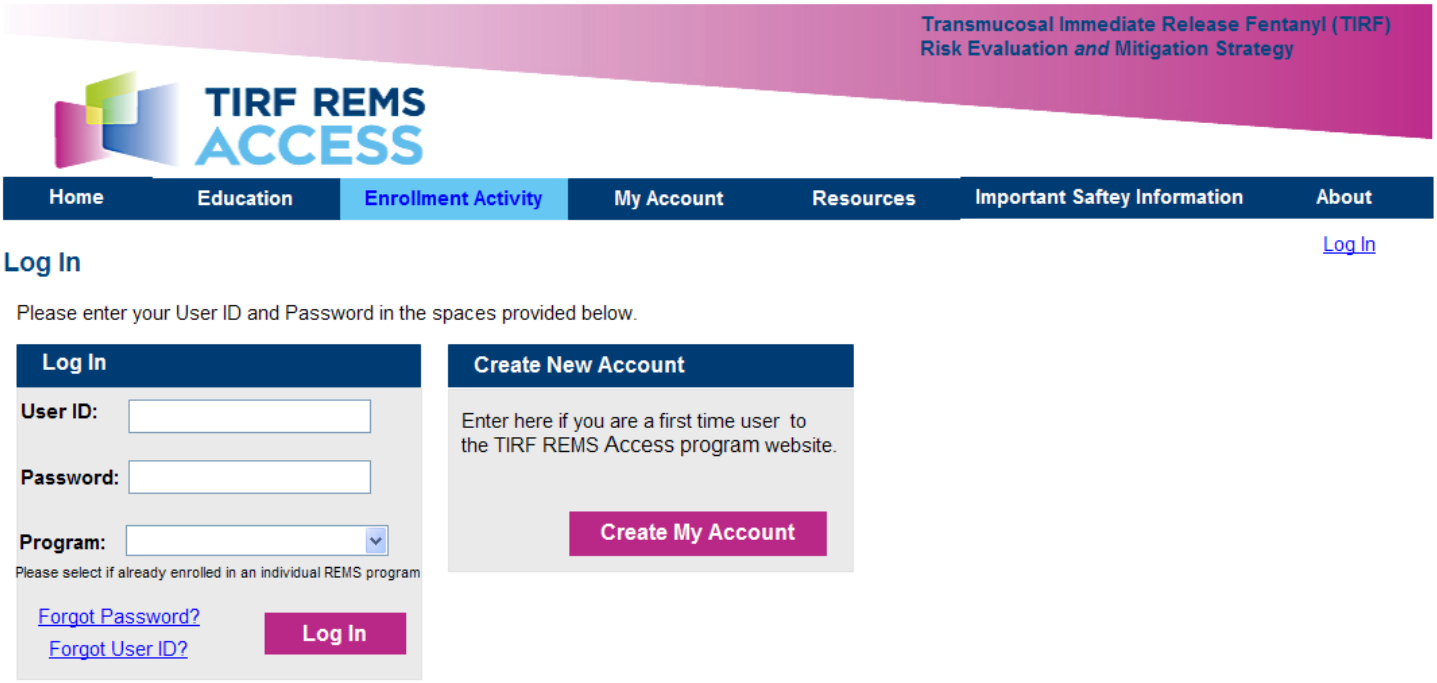
TIRF REMS Access Web Prototype

Create Account – Stakeholder already enrolled manunally



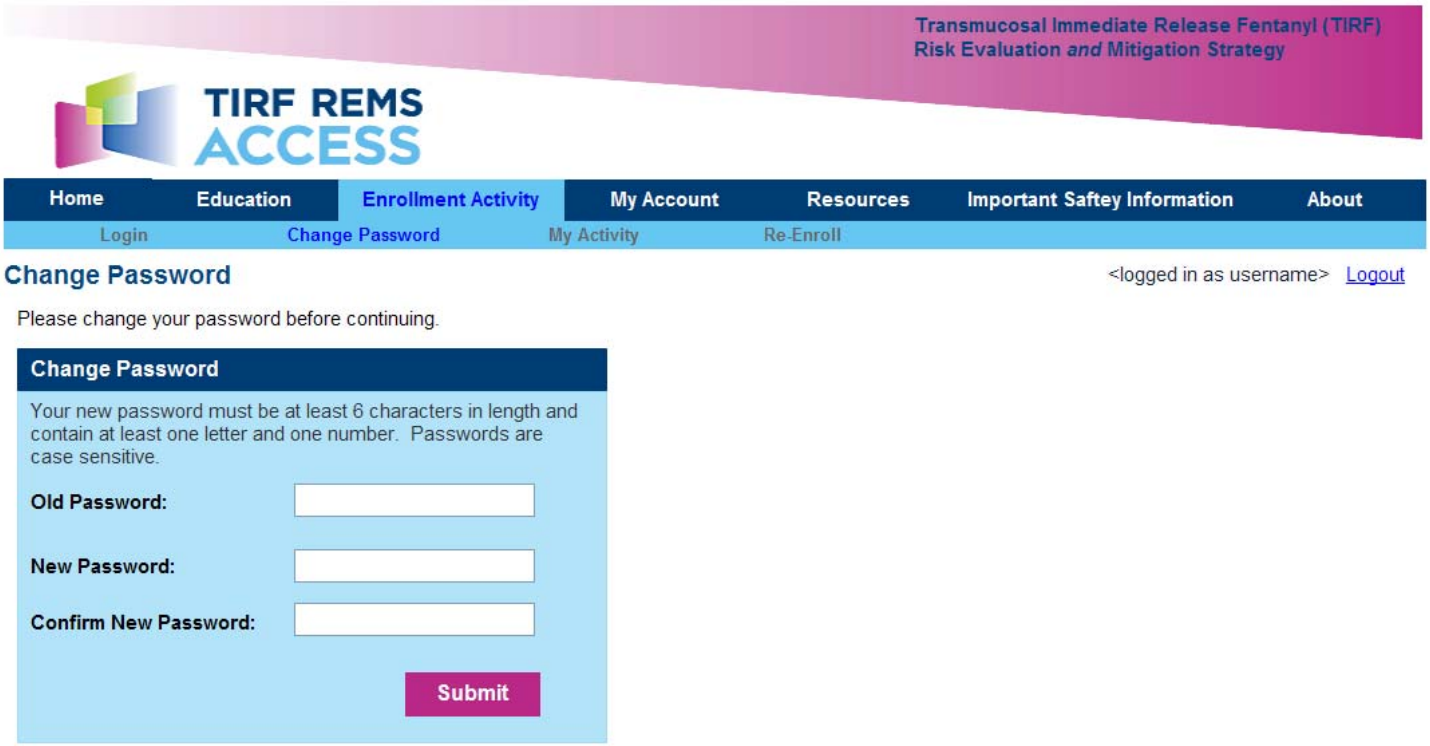
TIRF REMS Access Web Prototype

ACCOUNT LOG IN



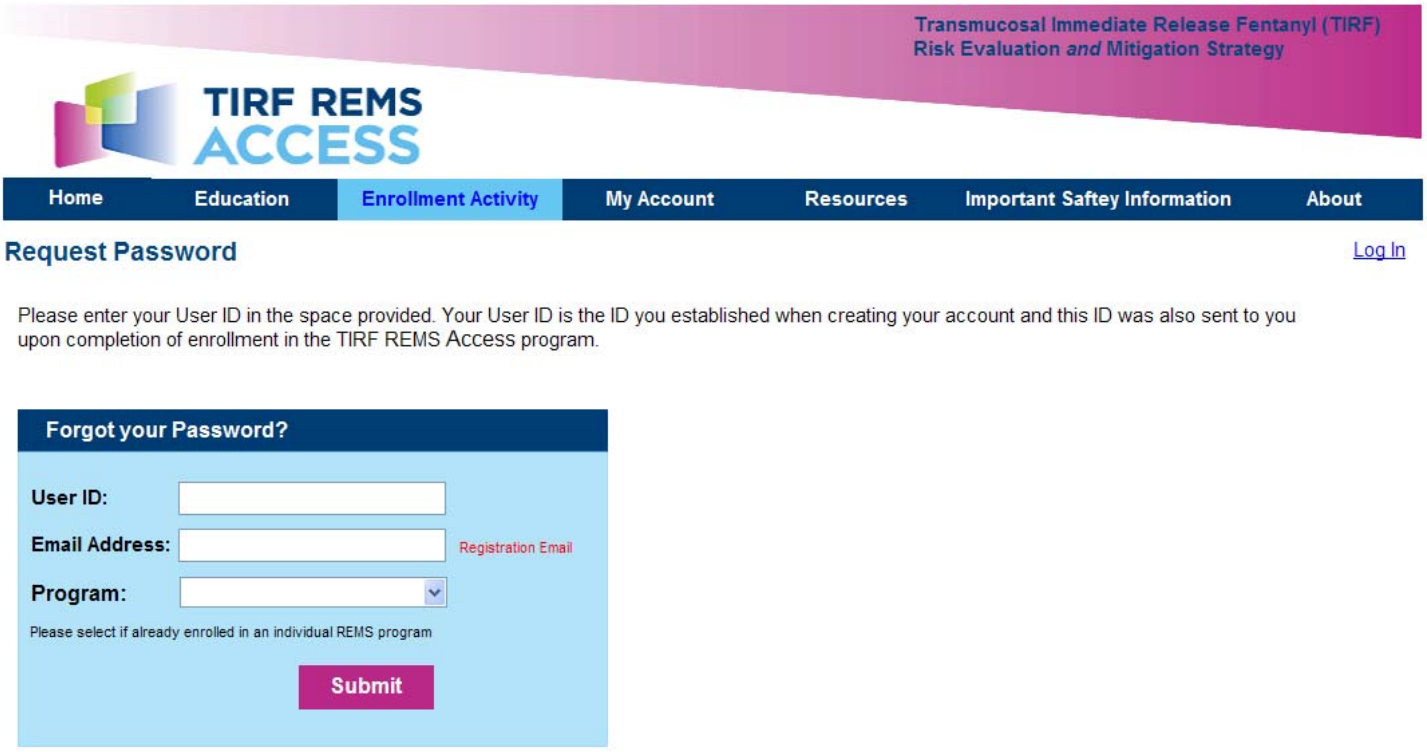
.

CHANGE PASSWORD

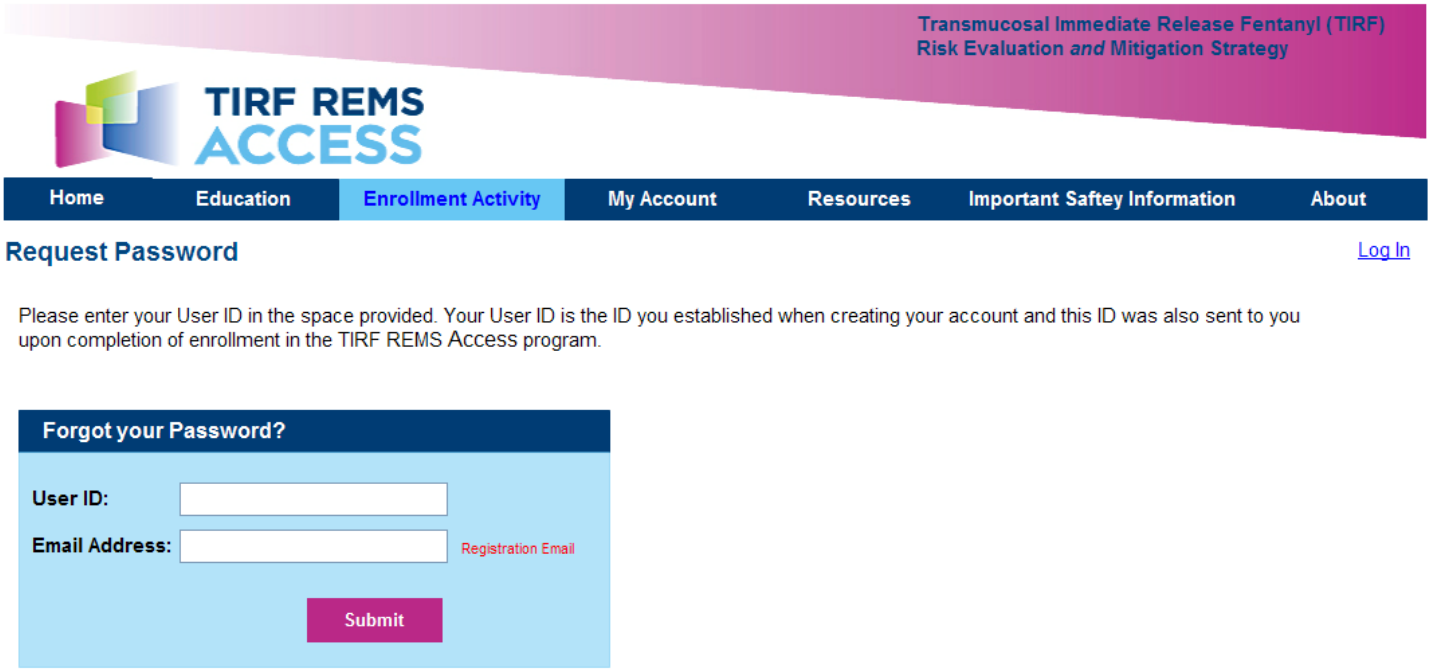


.

FORGOT PASSWORD – TRANSITIONED STAKEHOLDERS

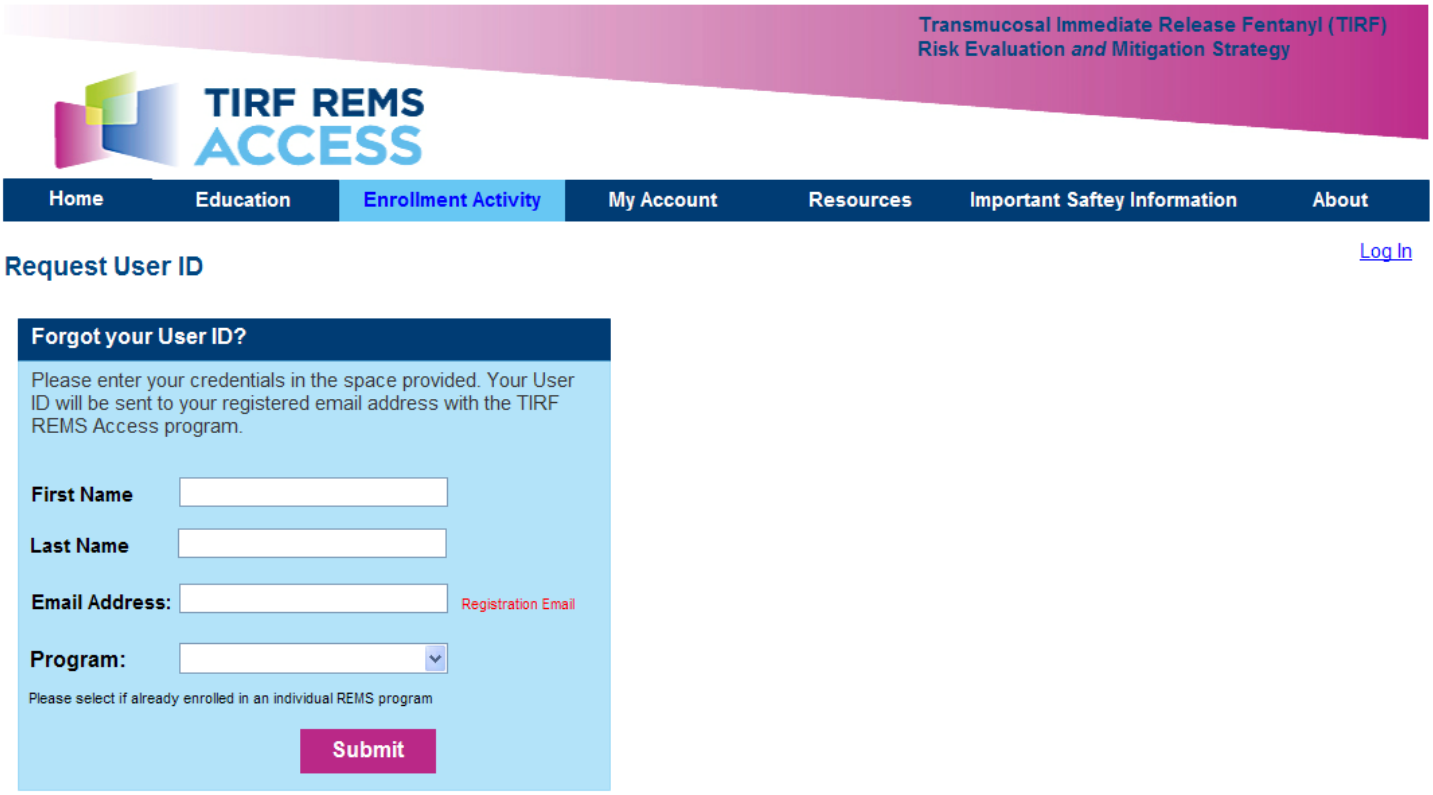


FORGOT PASSWORD – NON-TRANSITIONED STAKEHOLDERS

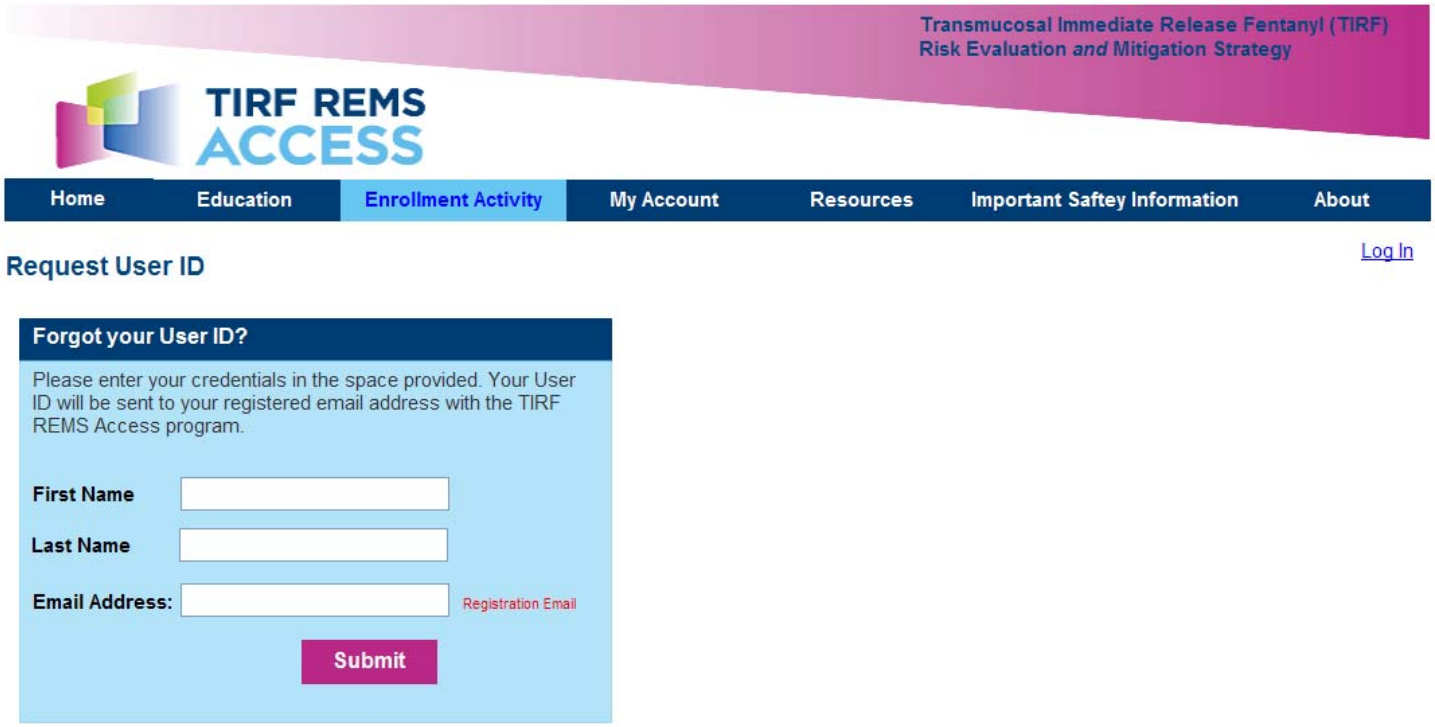


TIRF REMS Access Web Prototype

FORGOT USER ID – TRANSITIONED STAKEHOLDERS

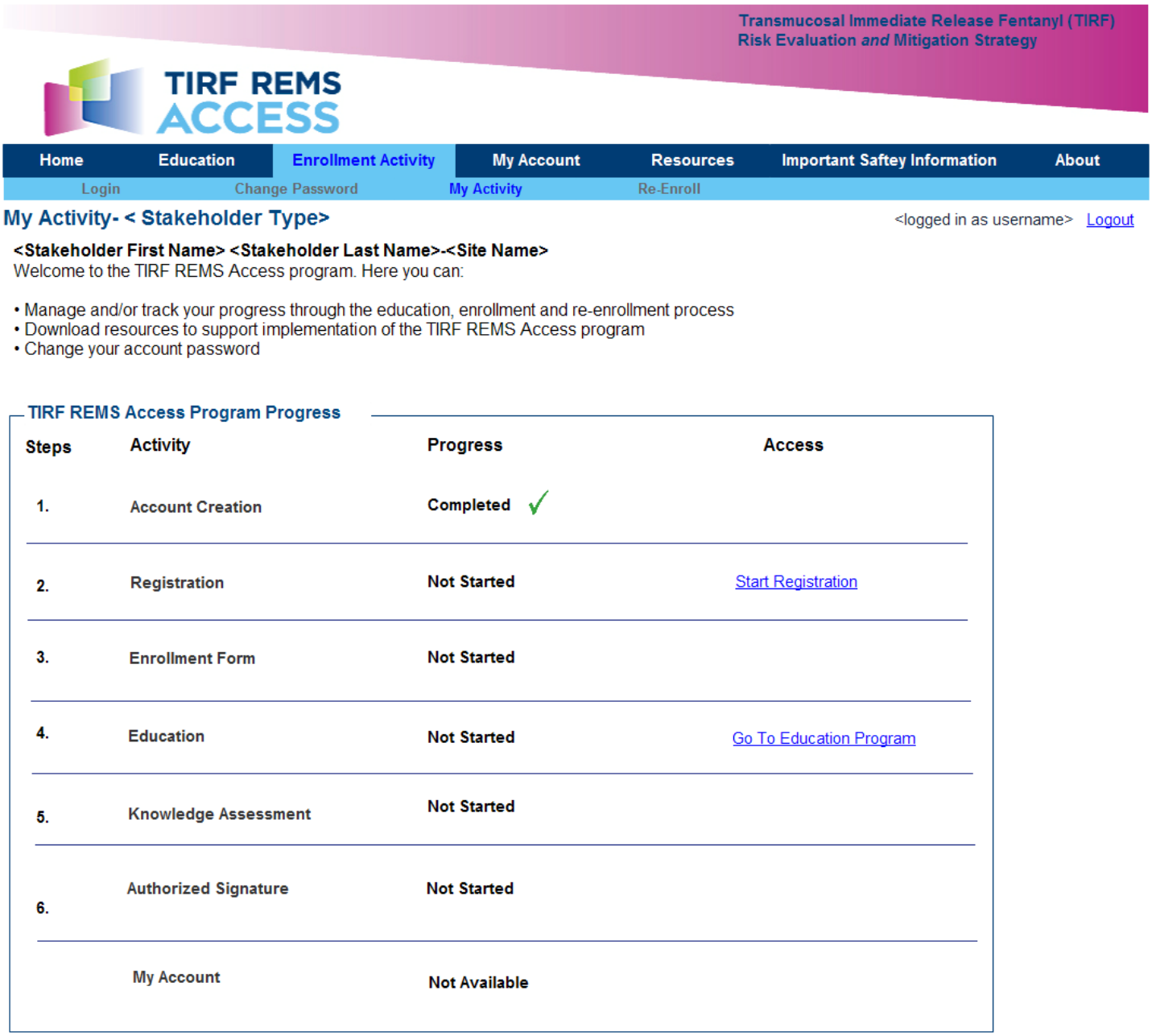


FORGOT USER ID – NON-TRANSITIONED STAKEHOLDERS



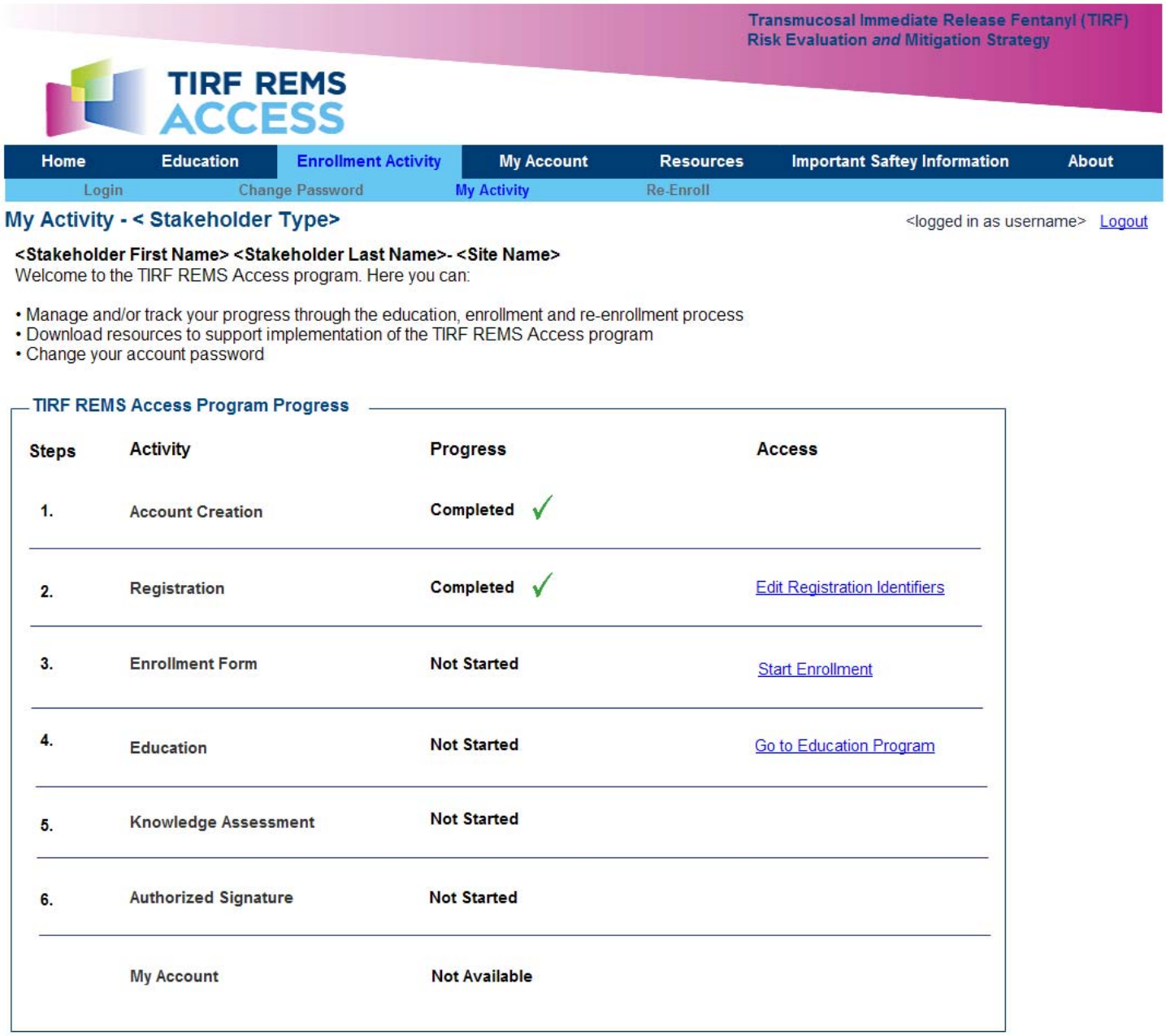
ACCOUNT STATUS

Account Status – Begin Registration

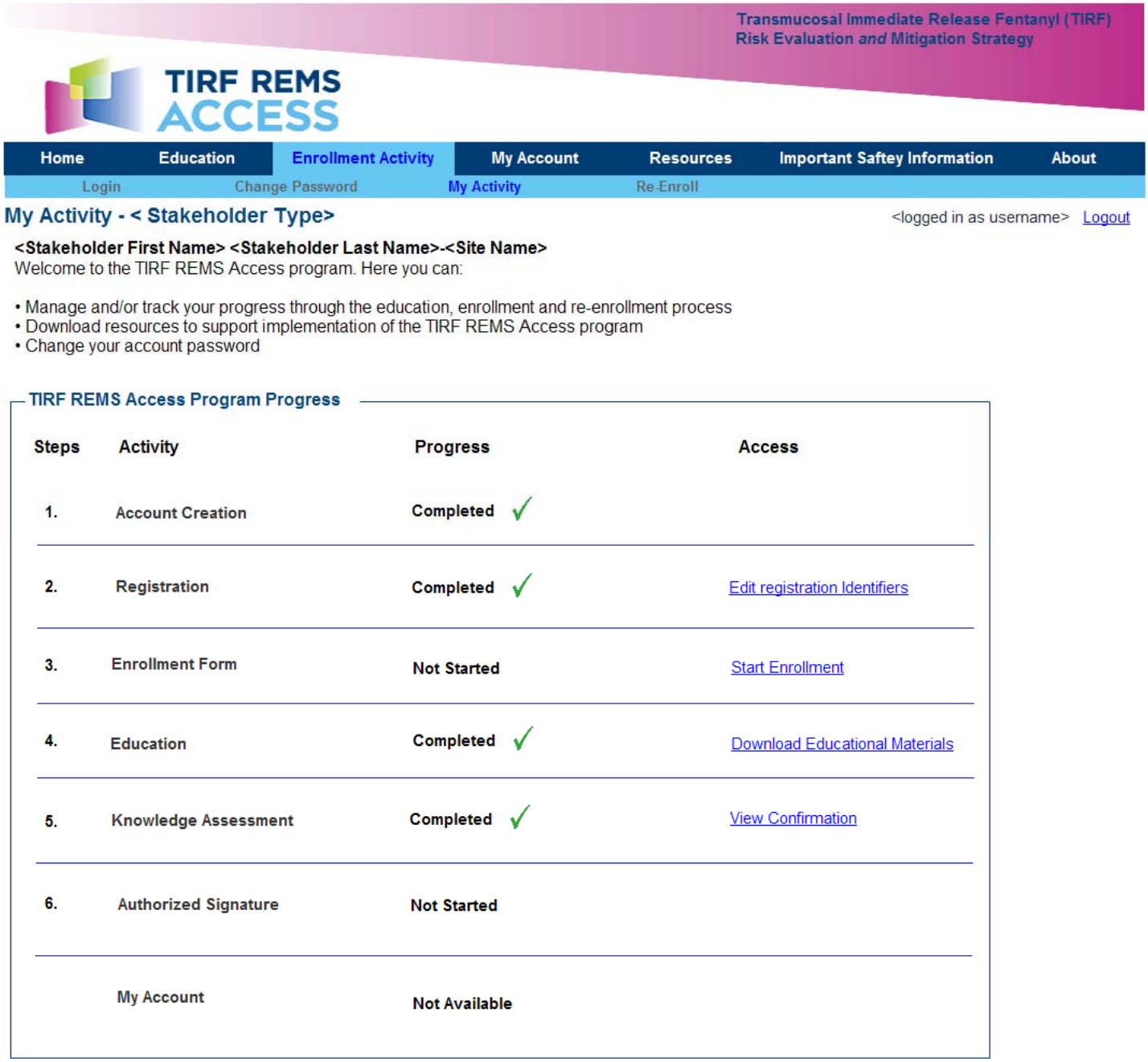


TIRF REMS Access Web Prototype

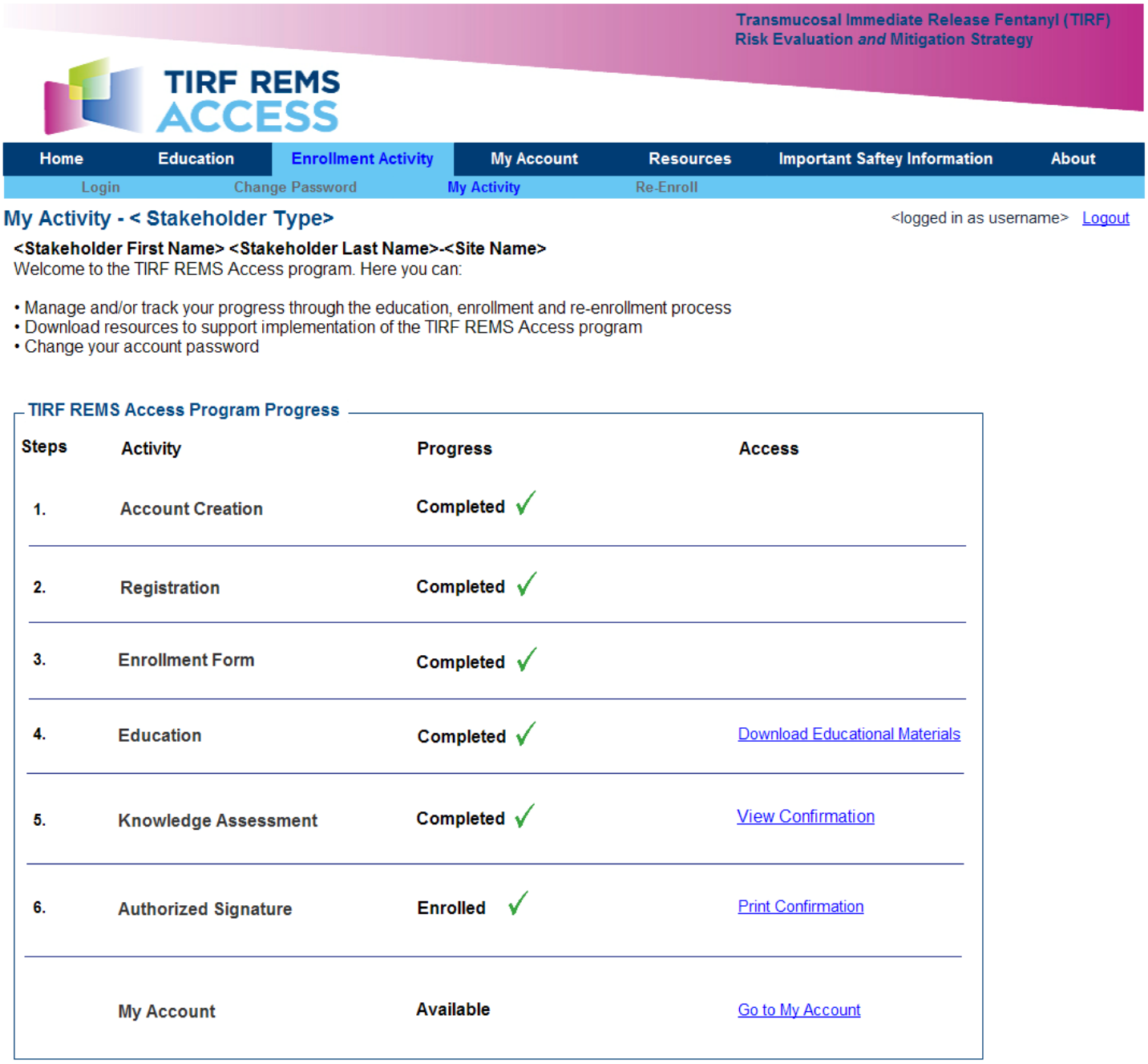
Account Status –Registration Complete



Account Status –Knowledge Assessment Complete

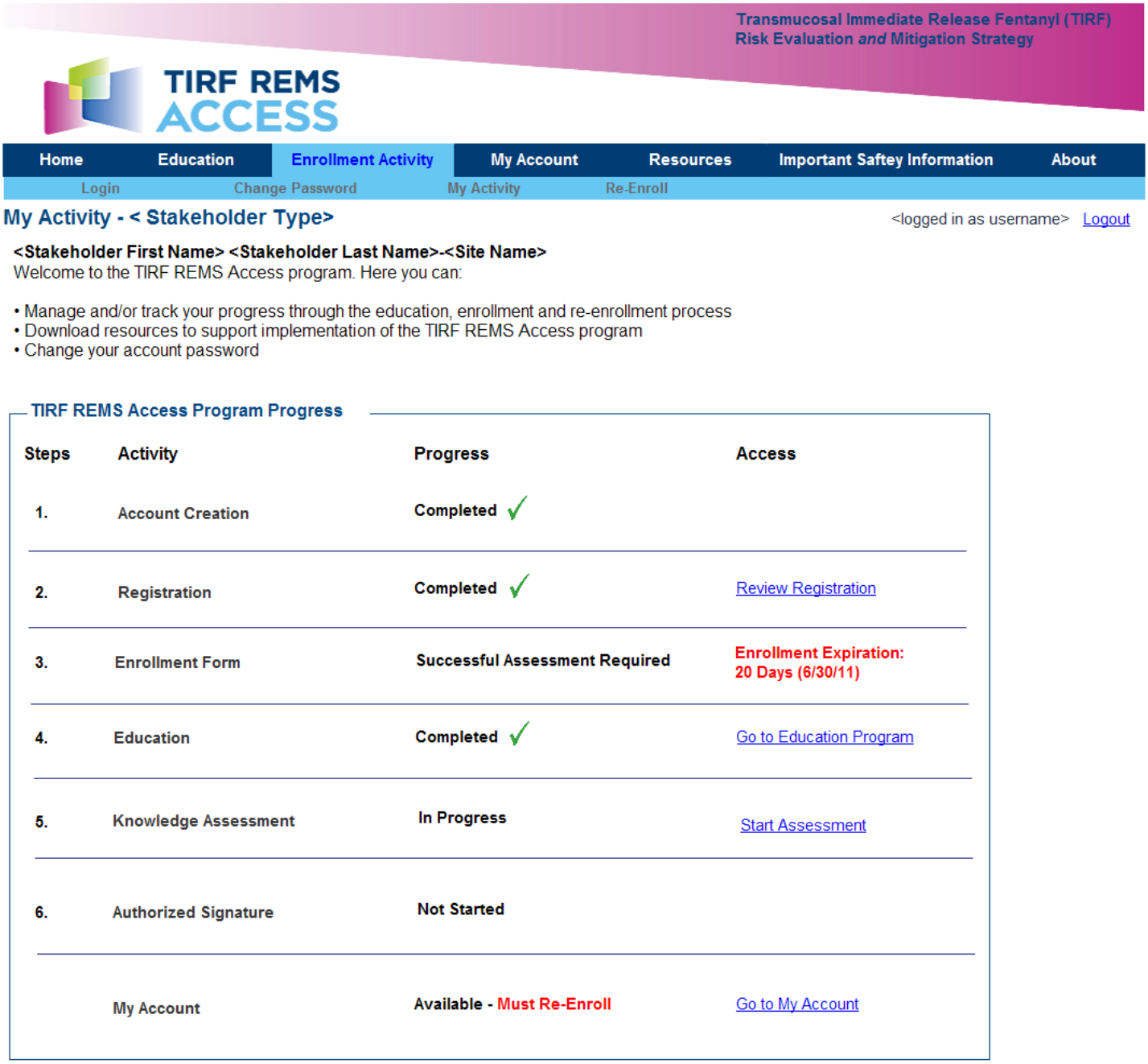


Account Status –Enrollment Complete



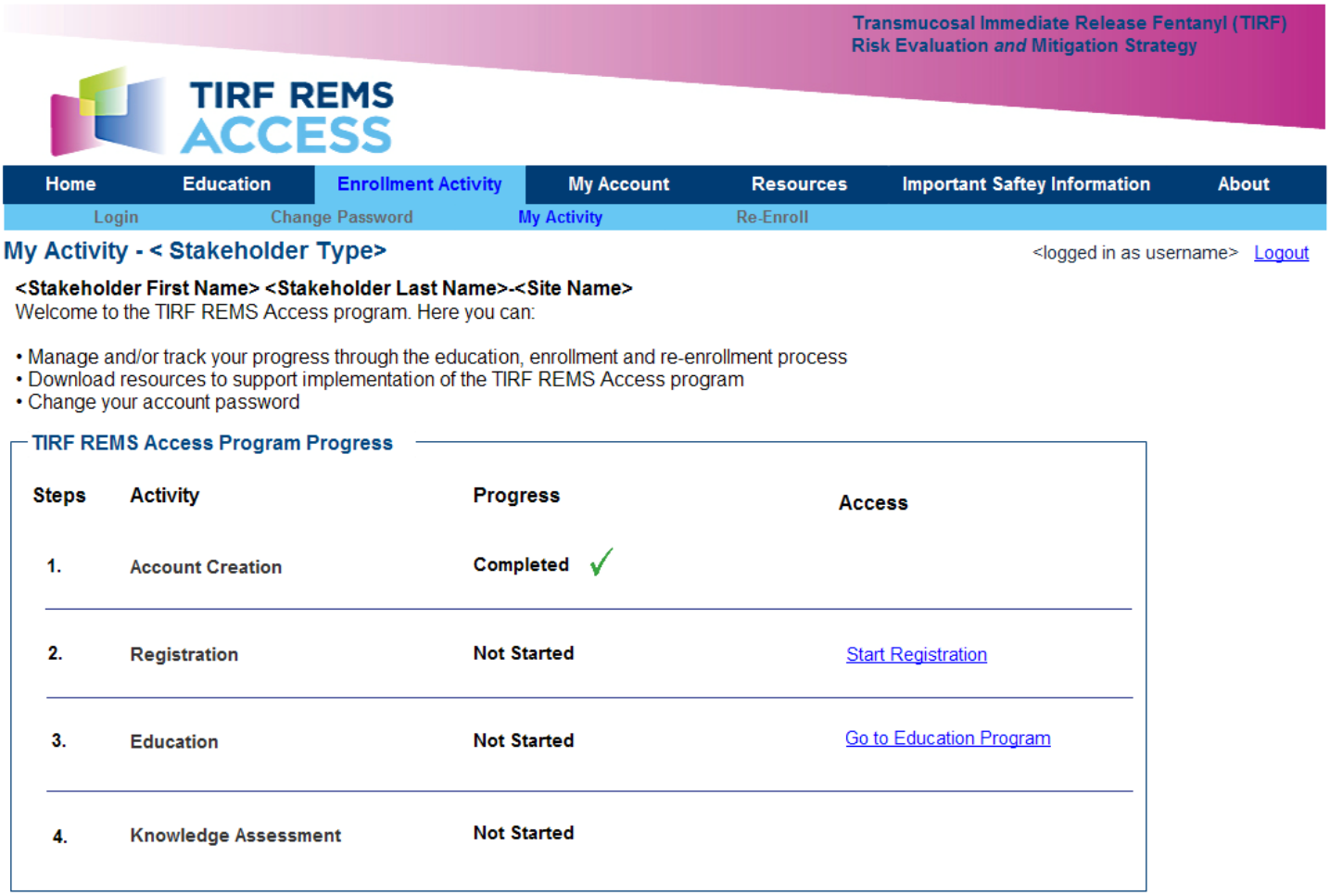
TIRF REMS Access Web Prototype

Account Status –Re-Enrollment

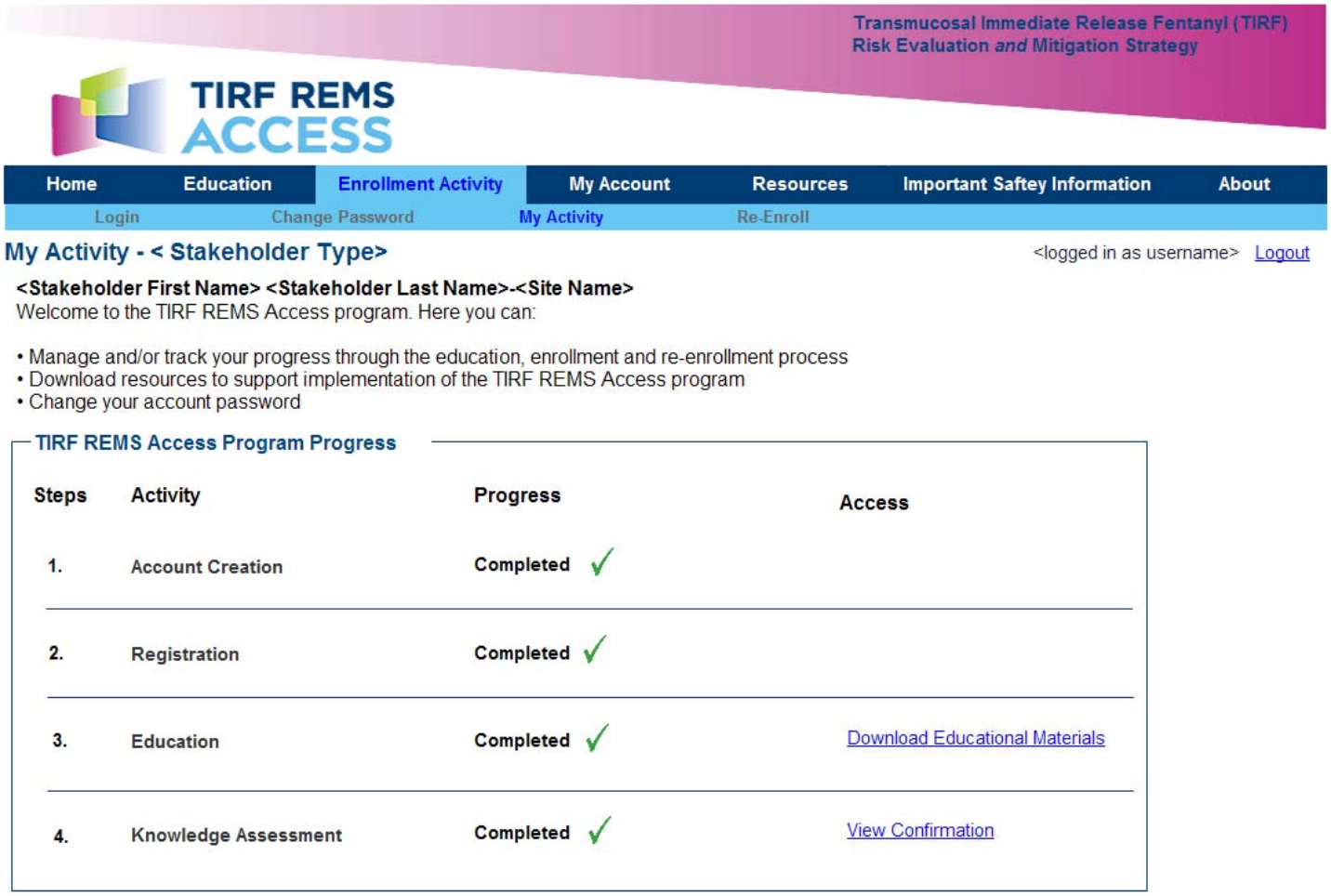


TIRF REMS Access Web Prototype

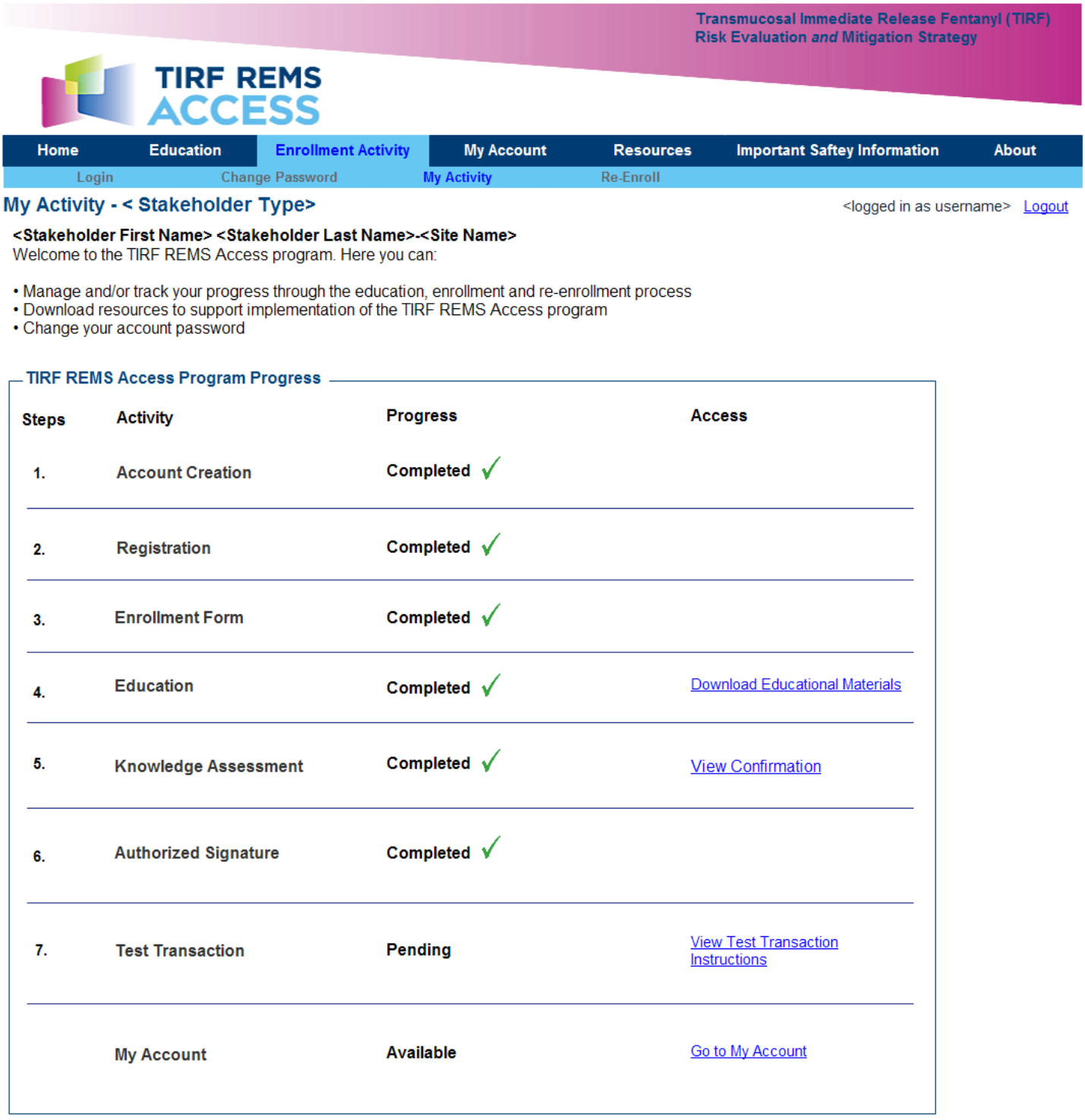
Account Status –Pharmacy Staff Begin Registration



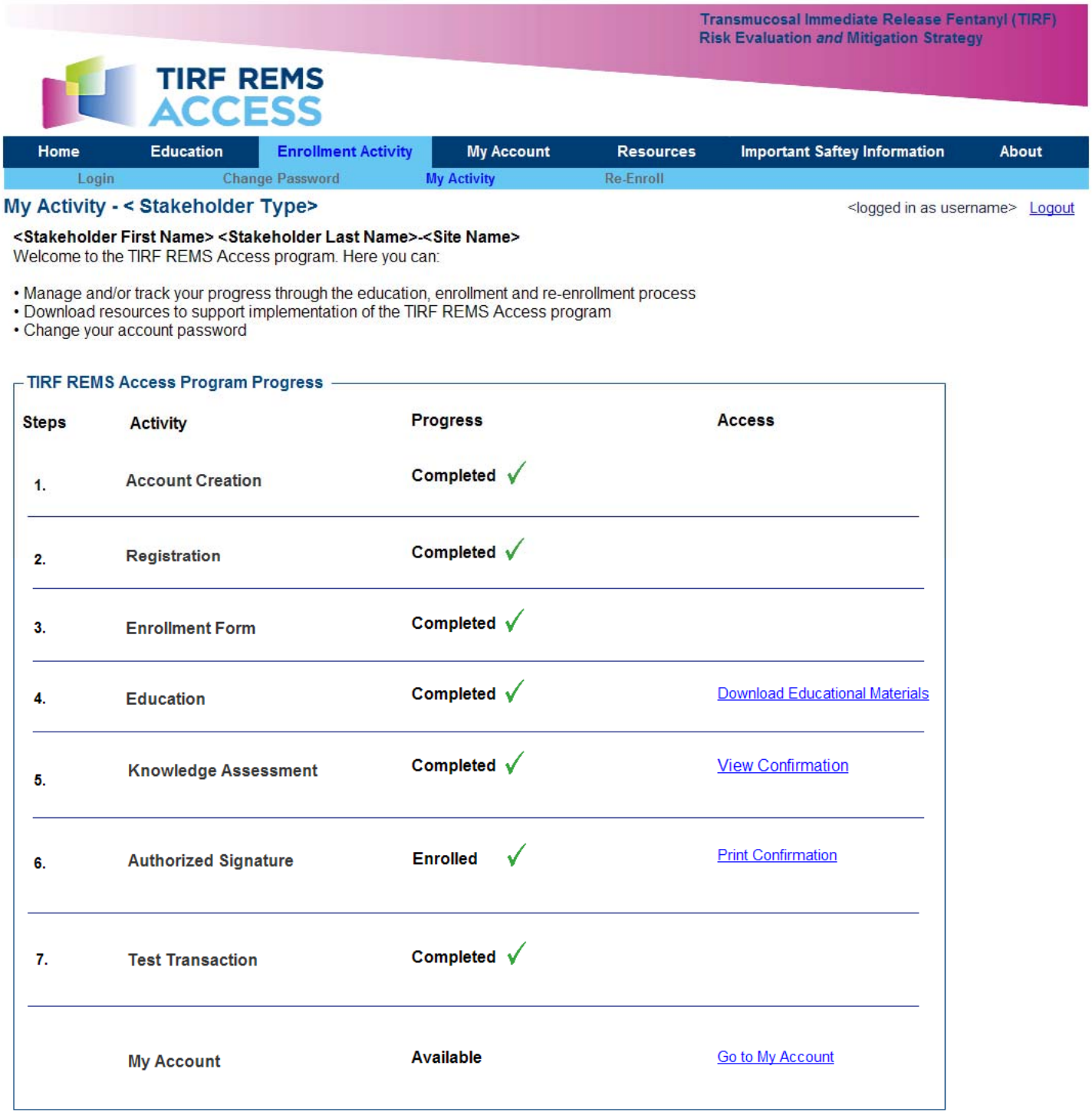
Account Status –Pharmacy Staff Knowledge Assessment Complete



Account Status – Test Transaction Started/Not Started

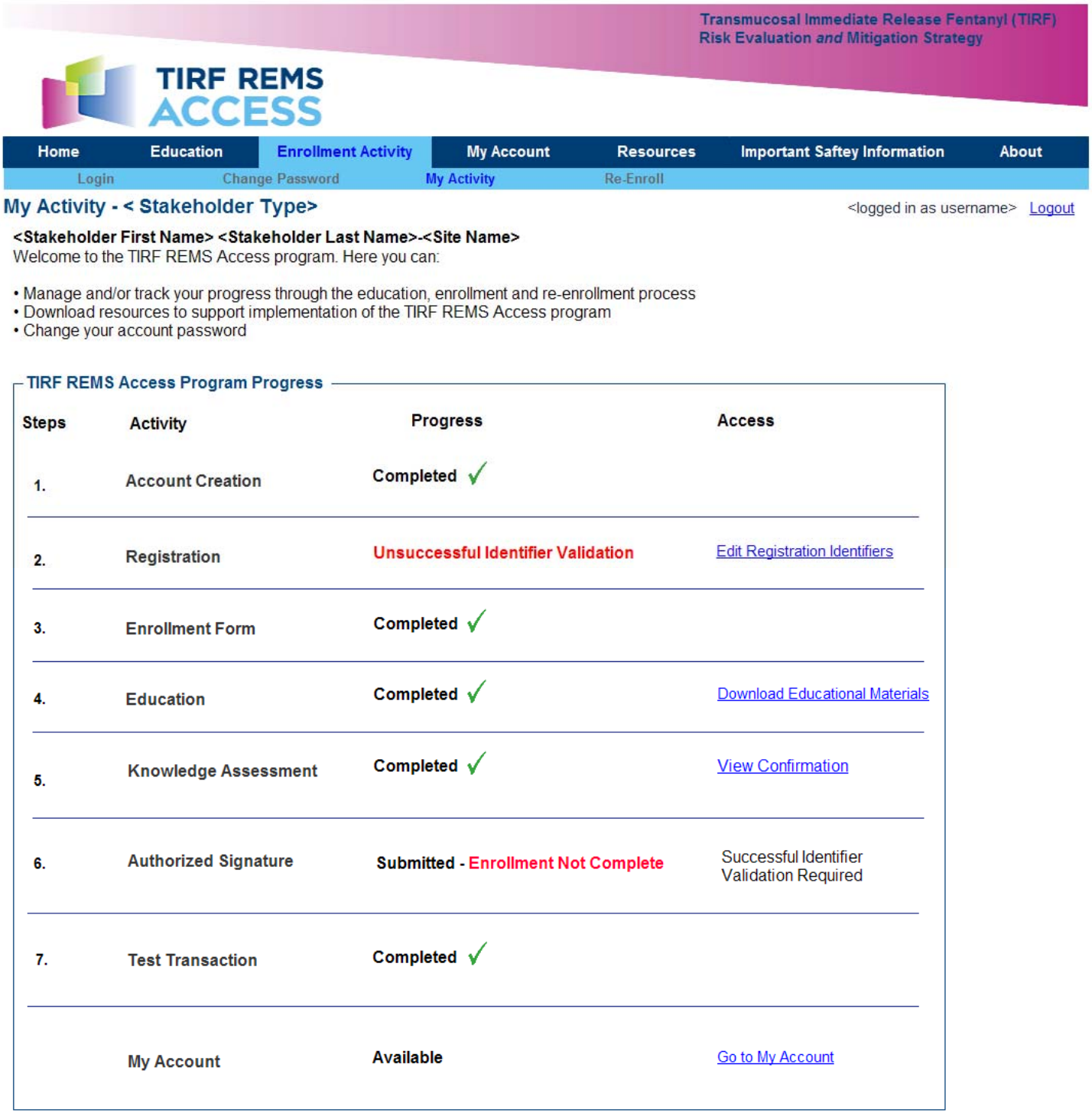


Account Status – Test Transaction Complete

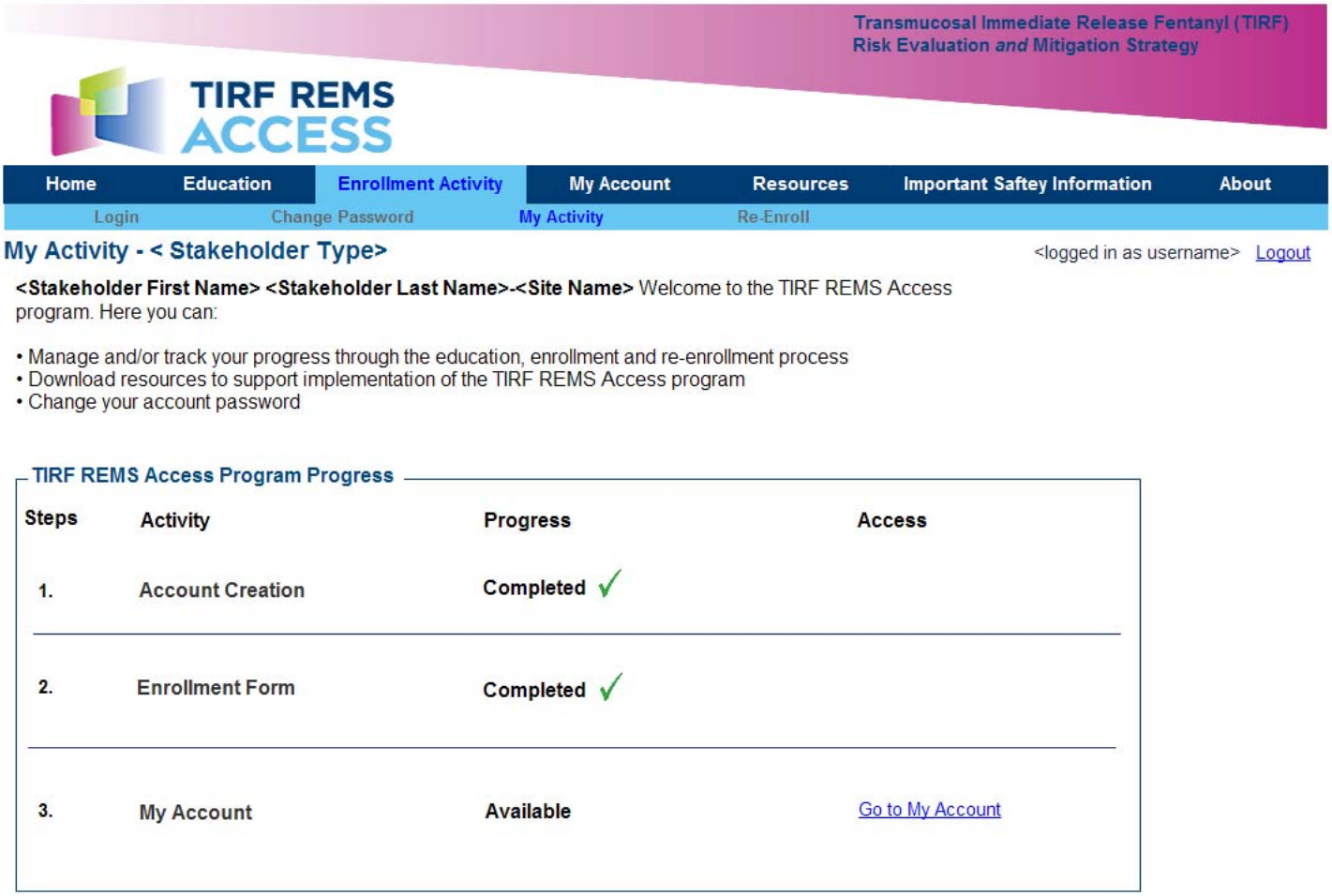


TIRF REMS Access Web Prototype

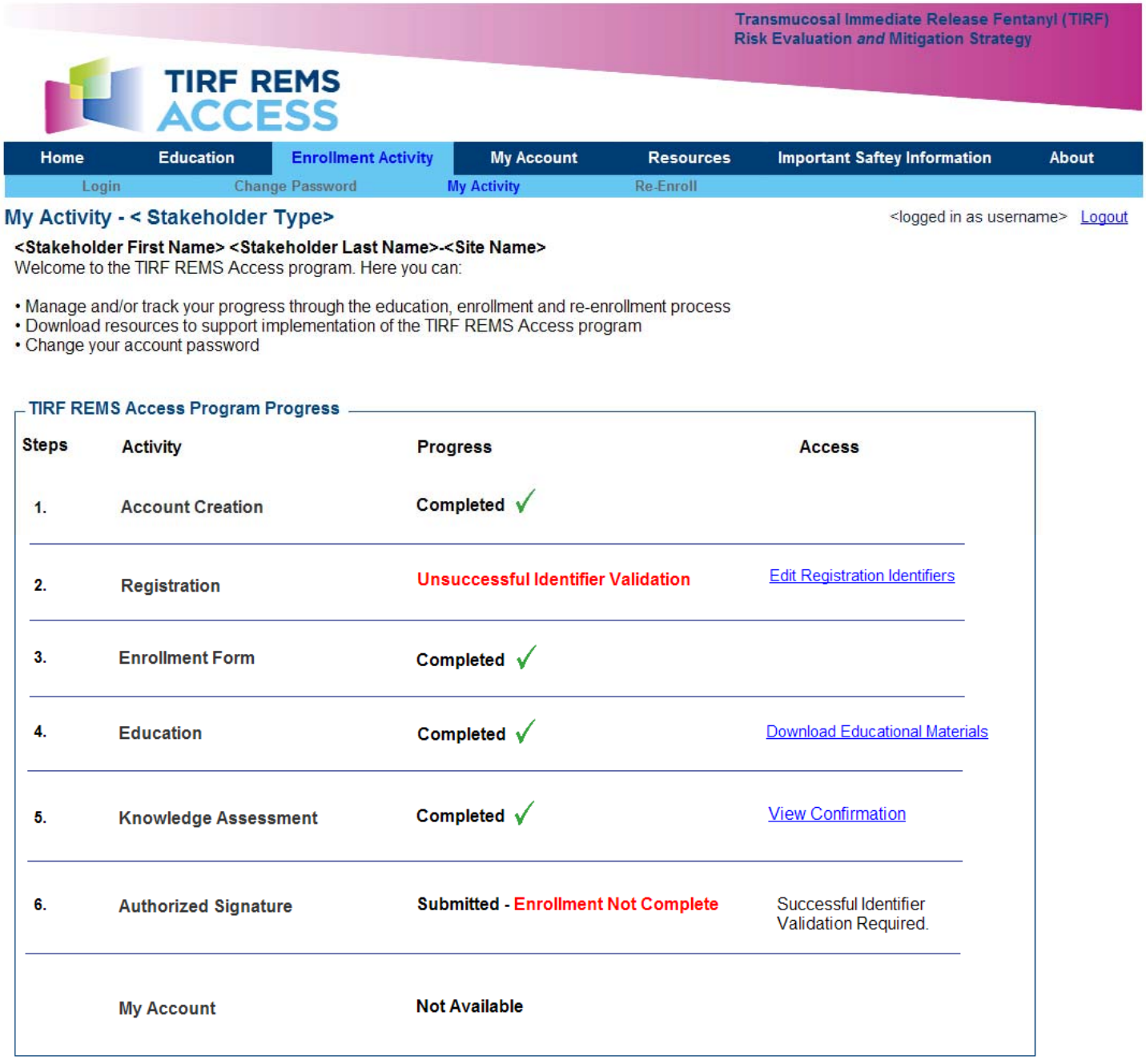
Account Status – Test Transaction Completed With Invalid Identifiers (Outpatient)



Account Status – Distributor My Account Available



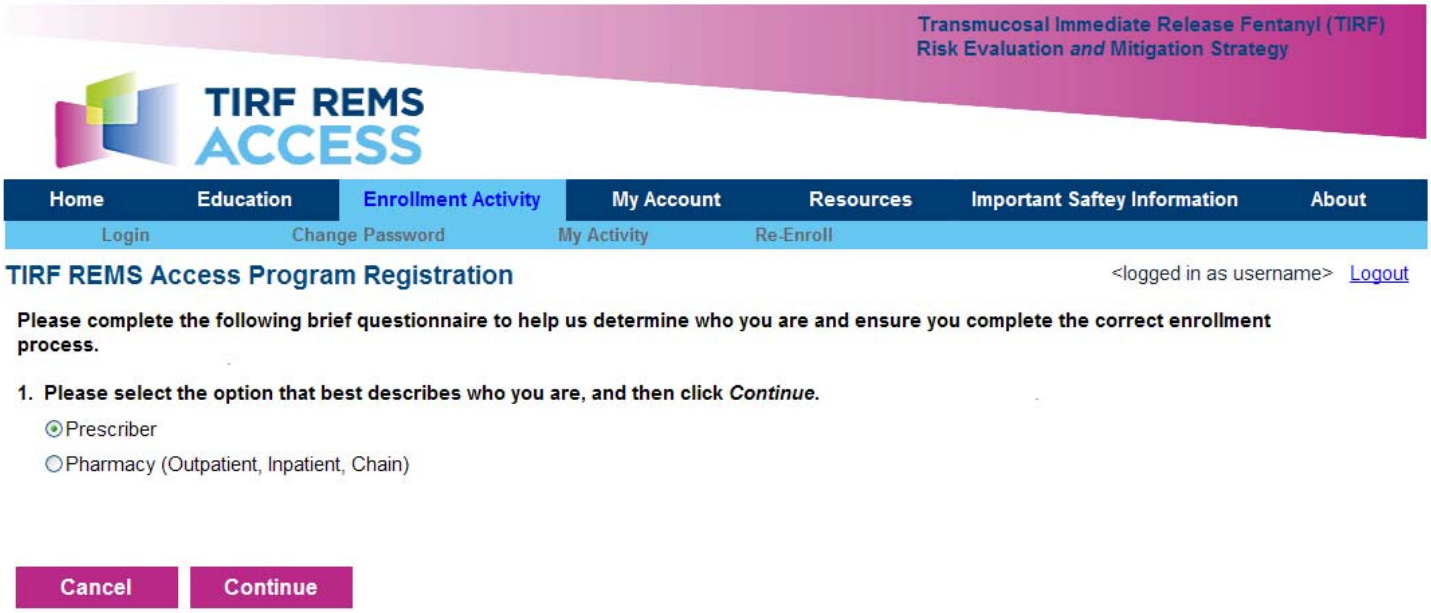
Account Status – Attestation Completed with Invalid Identifiers (Prescriber & Inpatient)



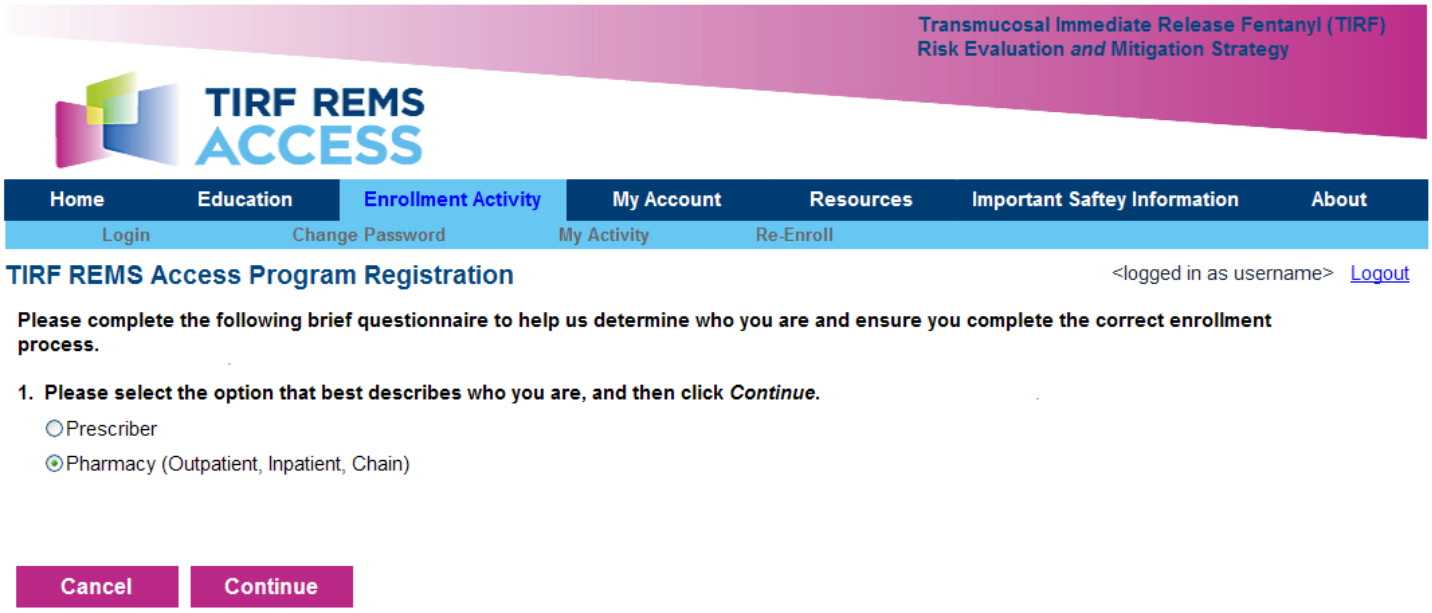
TIRF REMS Access Web Prototype

PROGRAM REGISTRATION

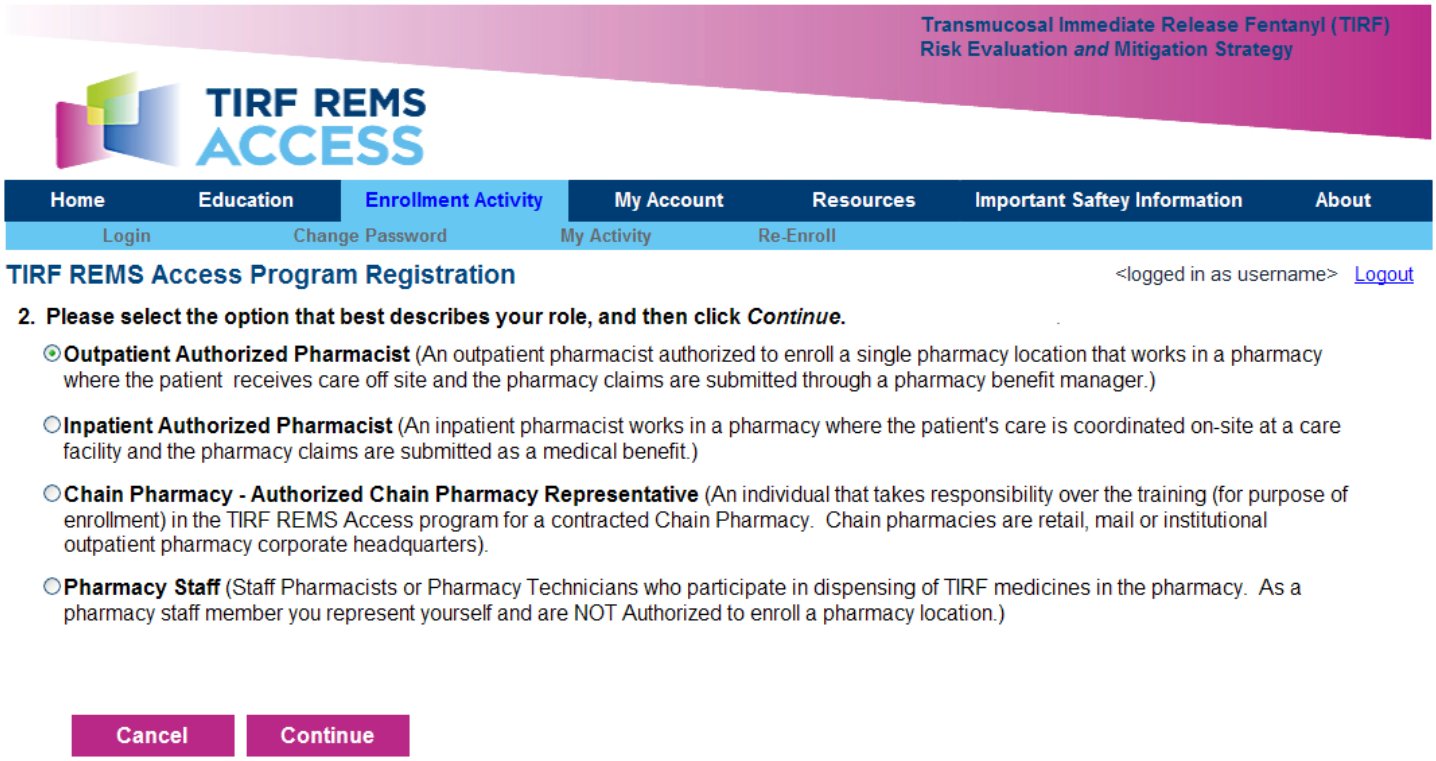
Registration Identifier Question 1 – Prescriber



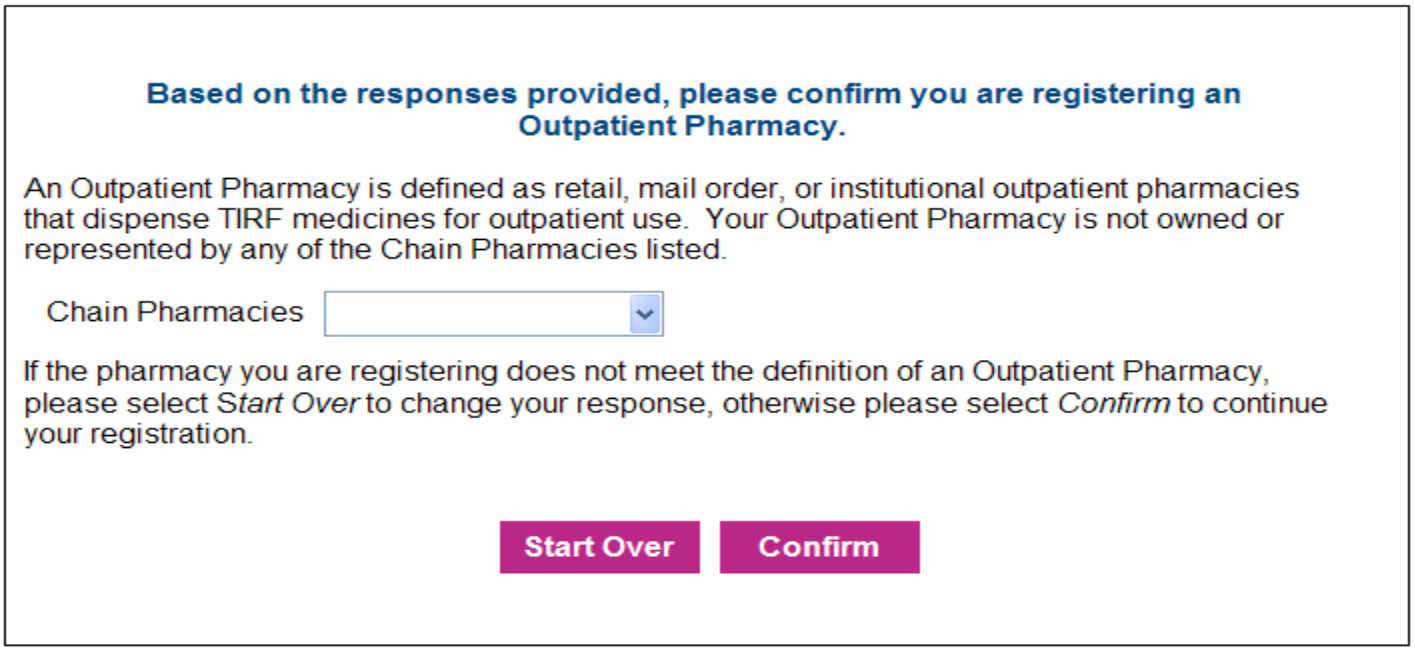
Registration Identifier Question 1 –Pharmacy



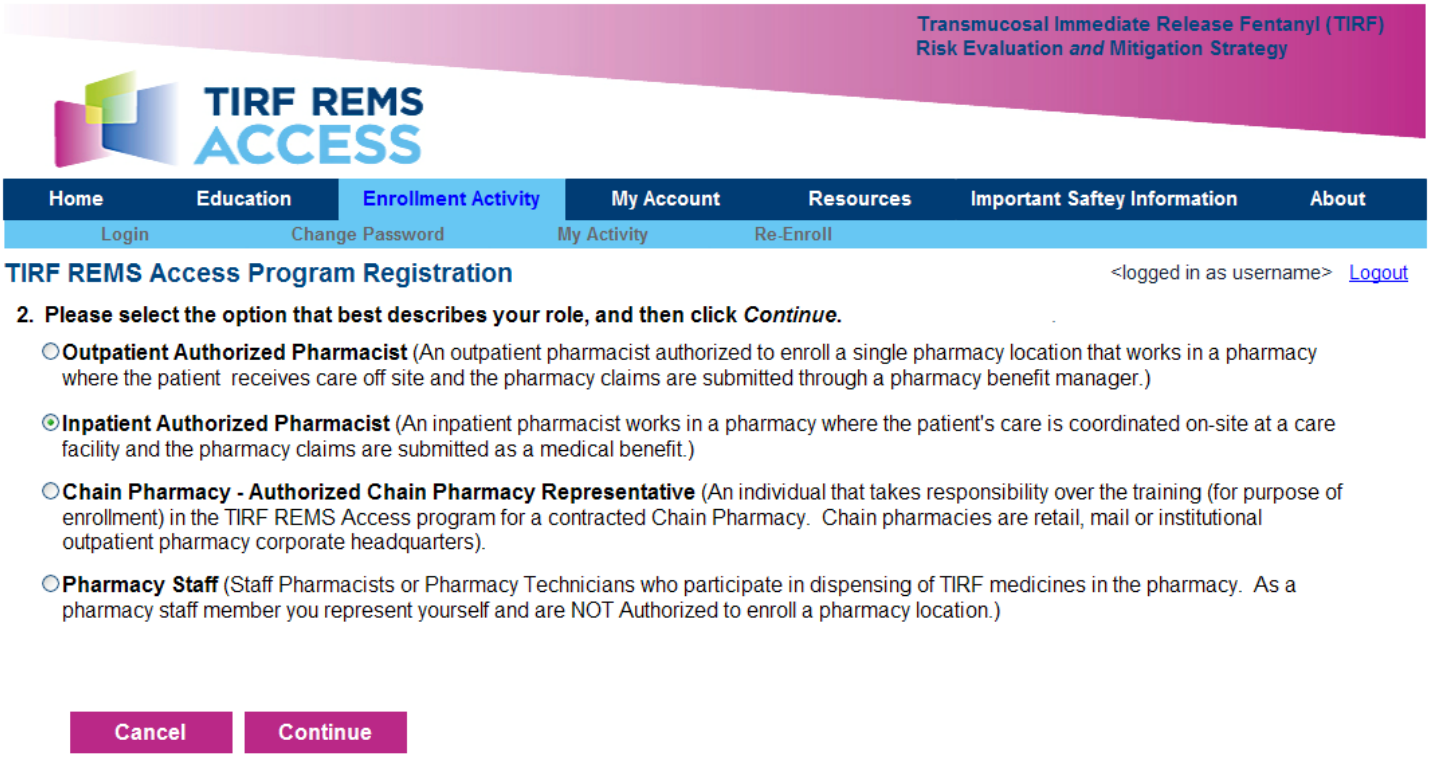
Registration Identifier Question 2 –Outpatient Pharmacy



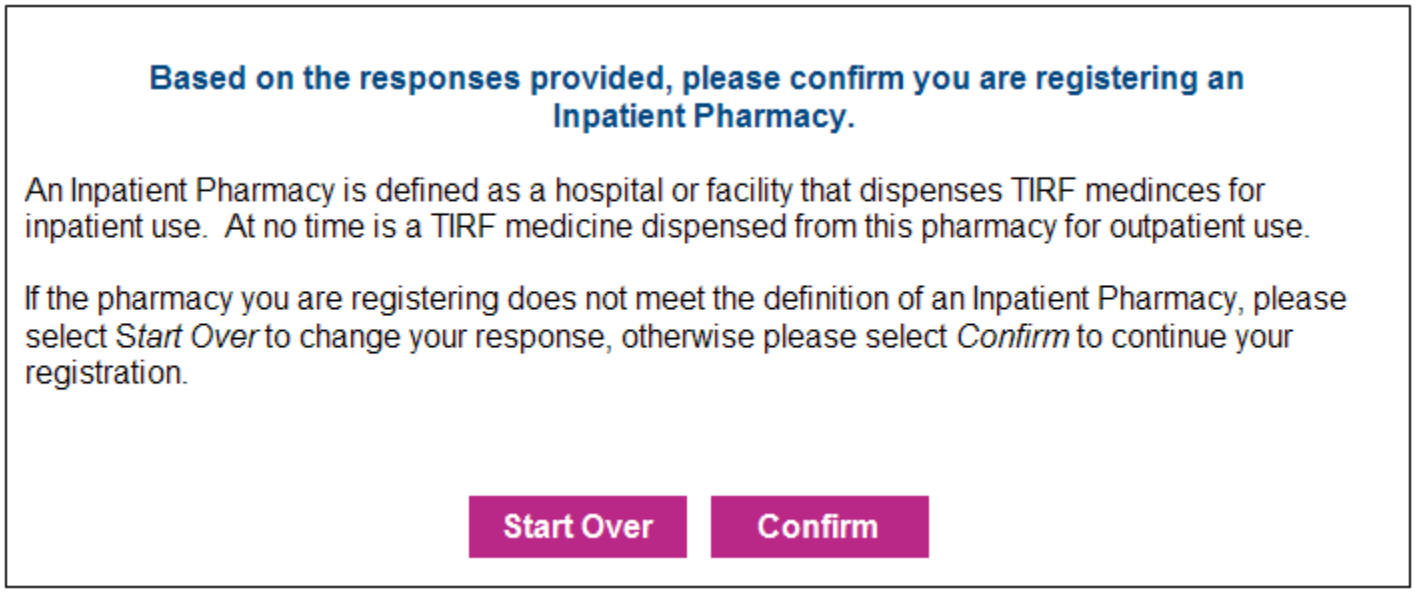
Registration Identification Confirm Outpatient Pharmacy



Registration Identifier Question 2 –Inpatient Pharmacy



Registration Identification Confirm Inpatient Pharmacy



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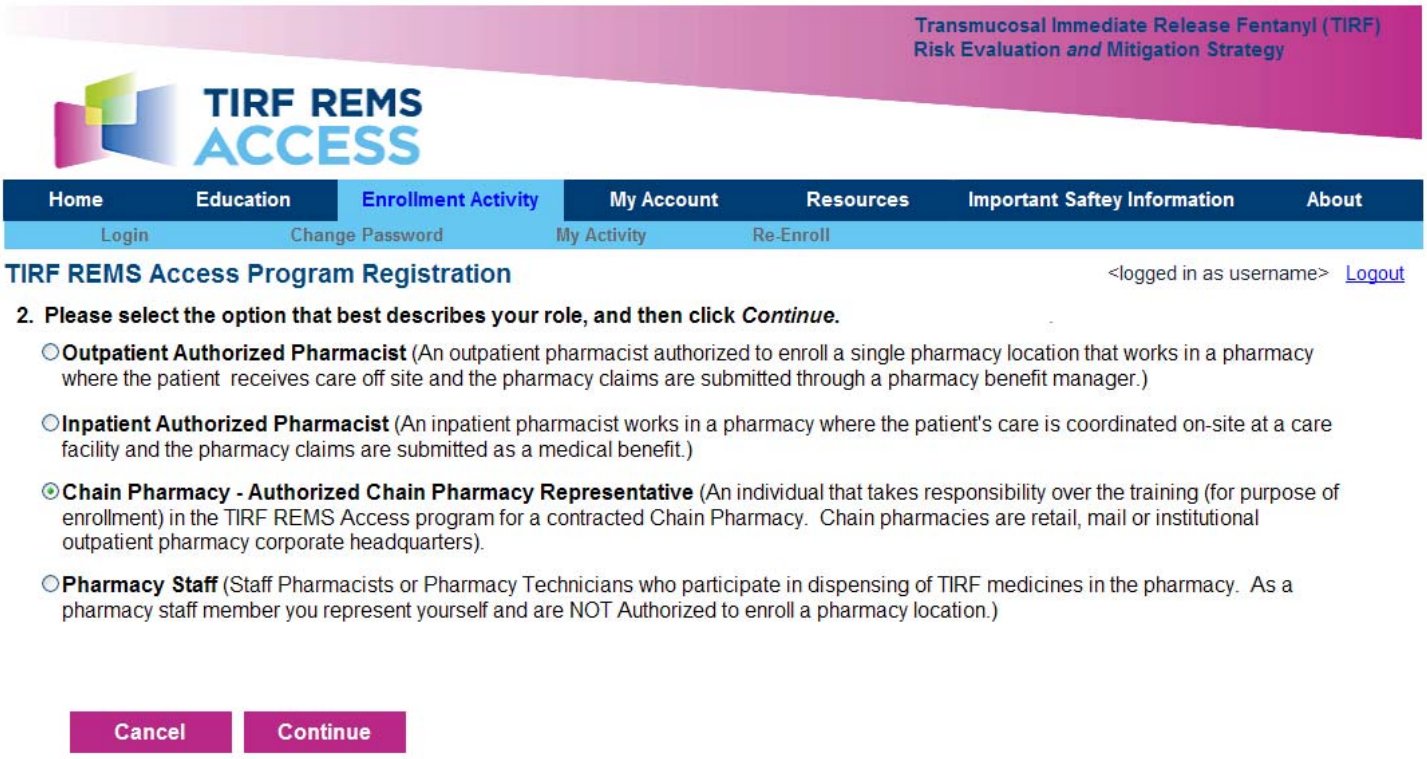

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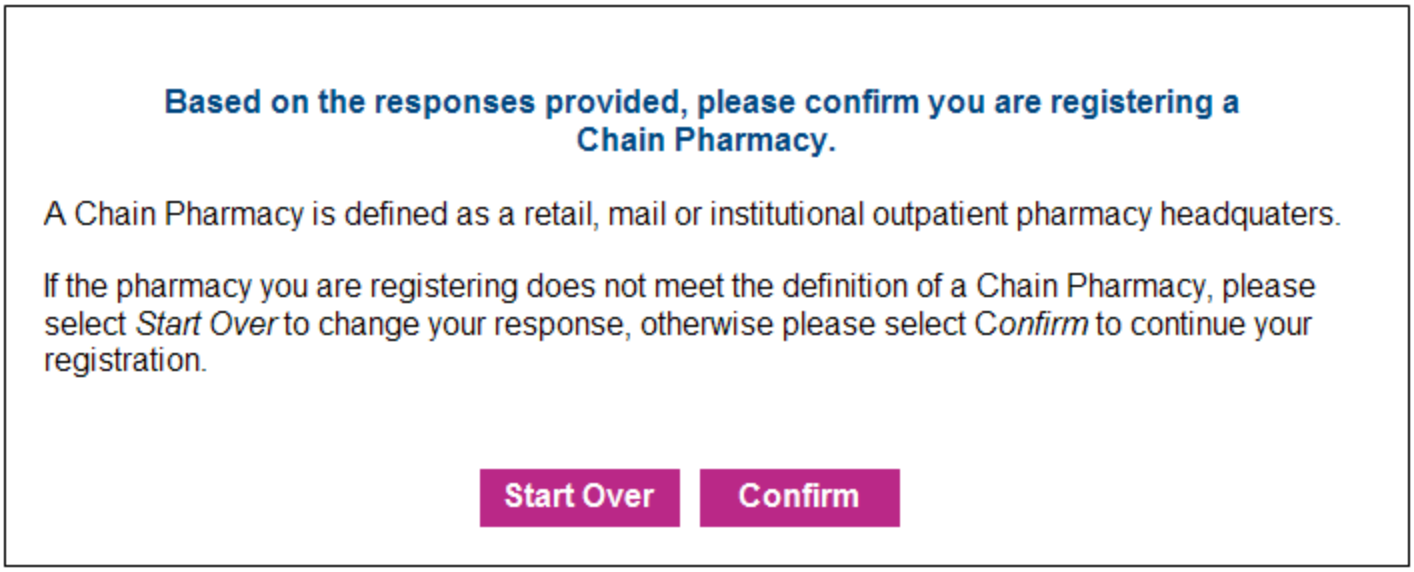
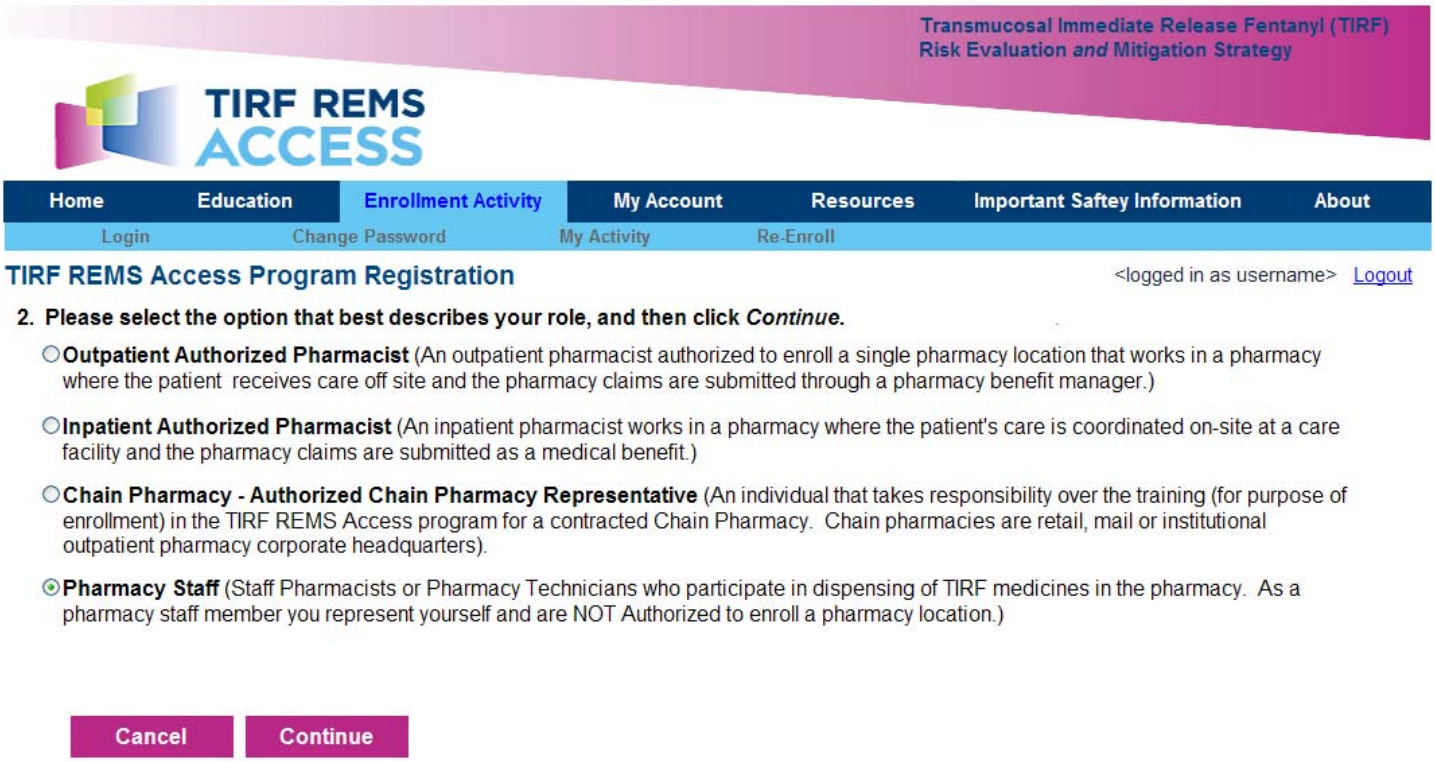
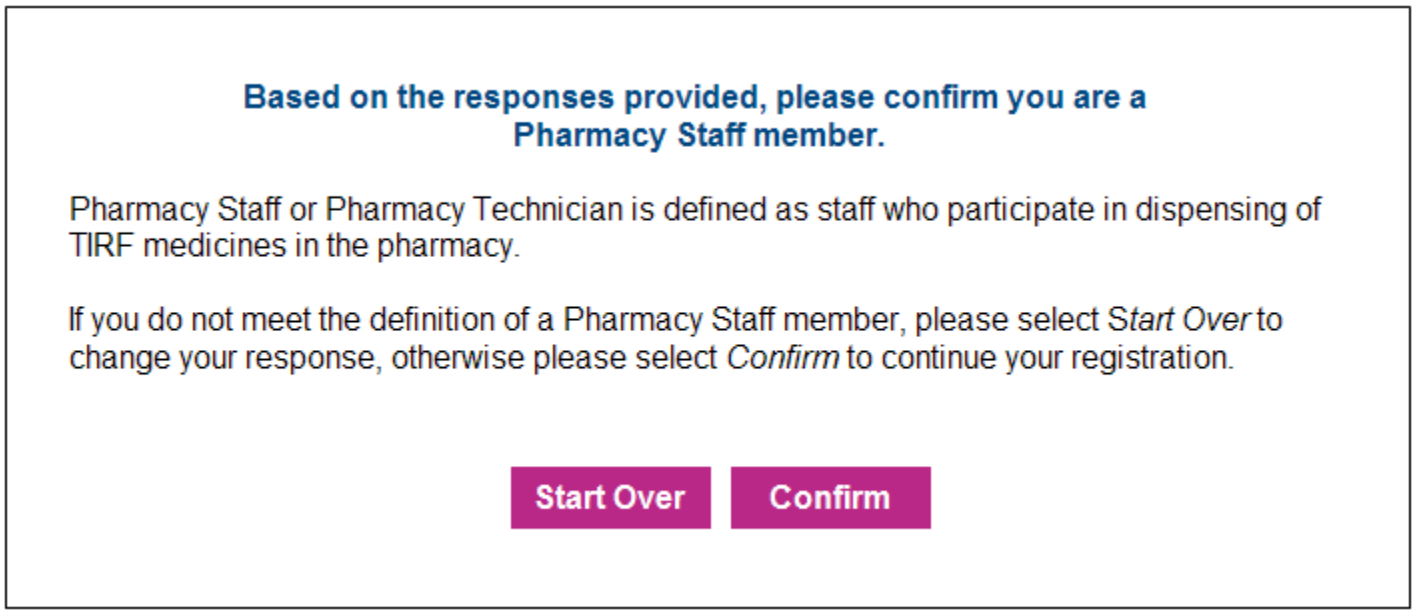


Registration Identifier Question 2 –Pharmacy Staff



Registration Identification Confirm Pharmacy Staff



TIRF REMS Access Web Prototype

EDUCATION PROGRAM

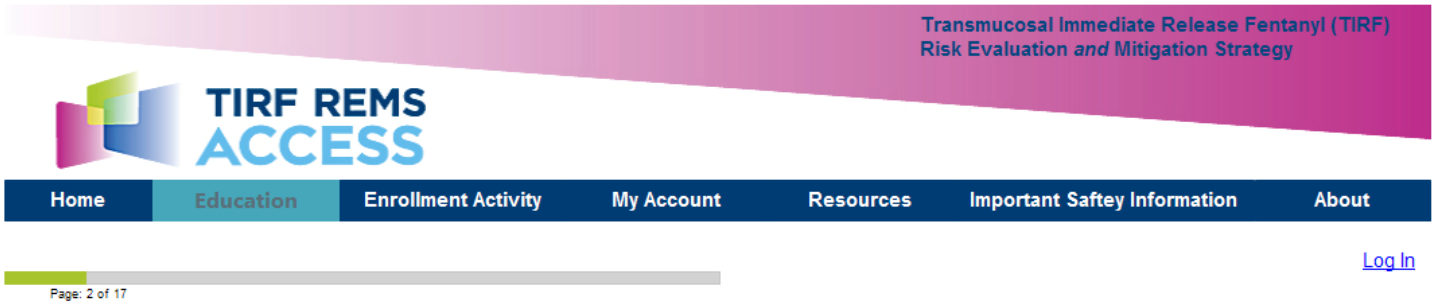
Start Education Program

TIRF REMS Access Web Prototype

Education Program – Page 1

TIRF REMS Access Web Prototype

Education Program – Page 2



TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

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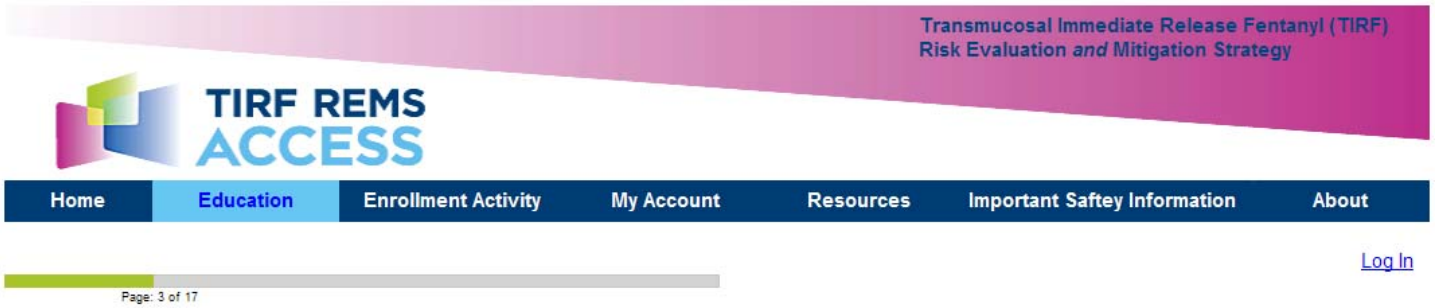
Education Program – Page 3



TIRF REMS Access Education Program Overview

- This education program contains key safety information critical for minimizing the risks of abuse, misuse, overdose and addiction associated with TIRF medicines.

- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up
  - Appropriate patient selection

- Information on the TIRF REMS Access program requirements and operations is provided in overview documents for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com .

- The TIRF REMS Access Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.

- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

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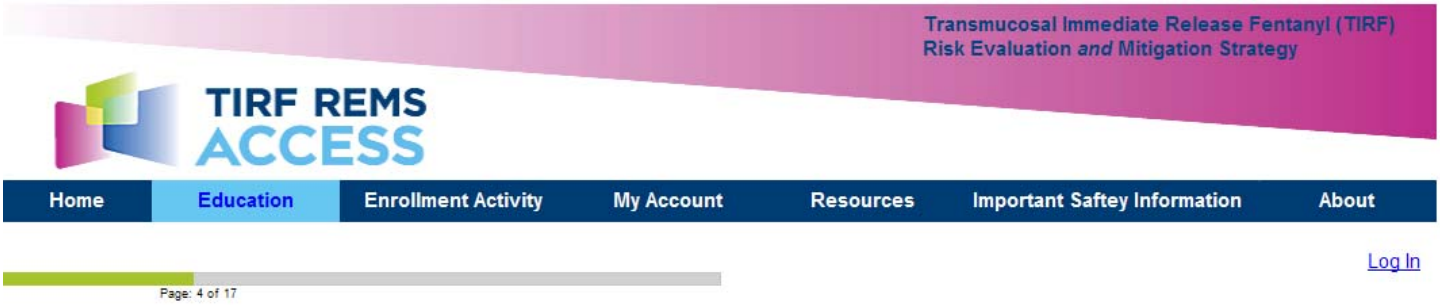

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain**.
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

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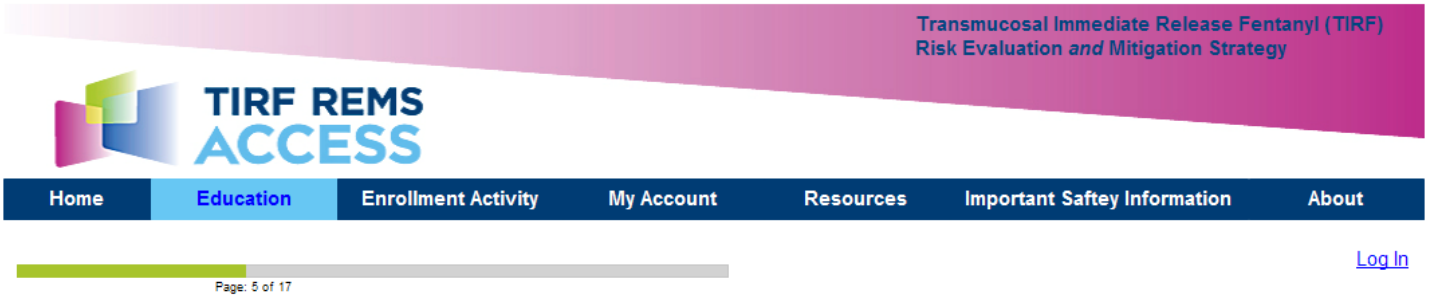

Appropriate Patient Selection

Definition of Opioid Tolerance:

• Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hour
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day
- OR an equianalgesic dose of another oral opioid

• TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

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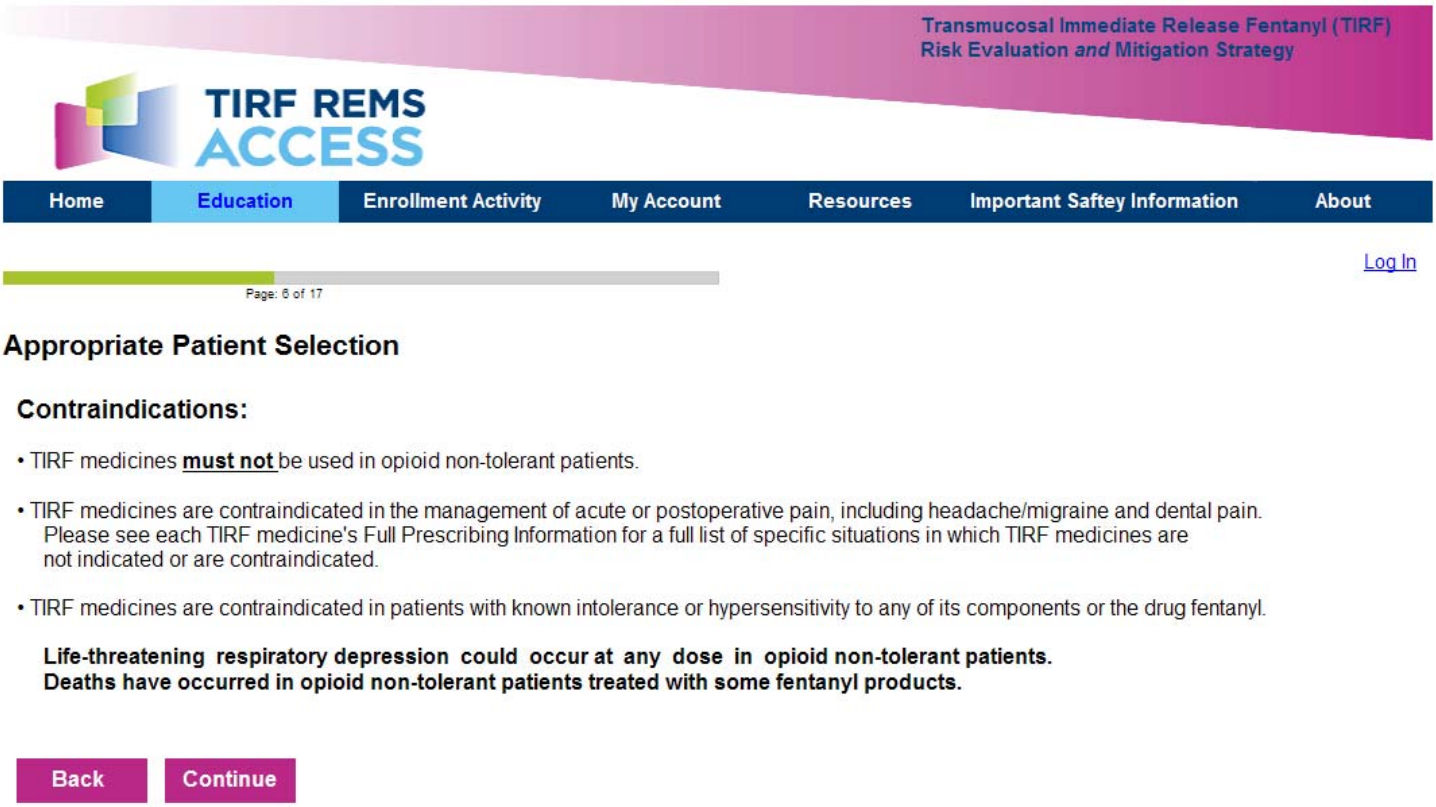
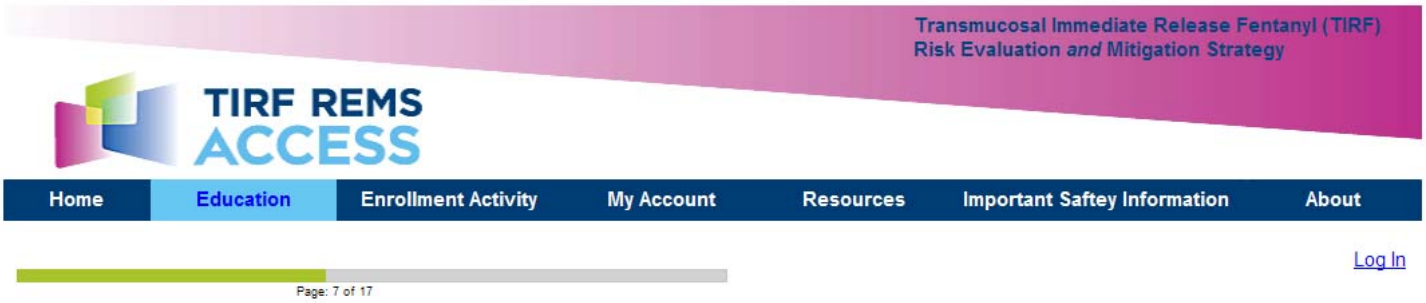


TIRF REMS Access Web Prototype

Education Program- Page 7



Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid against and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.
- All patients treated with opioid require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

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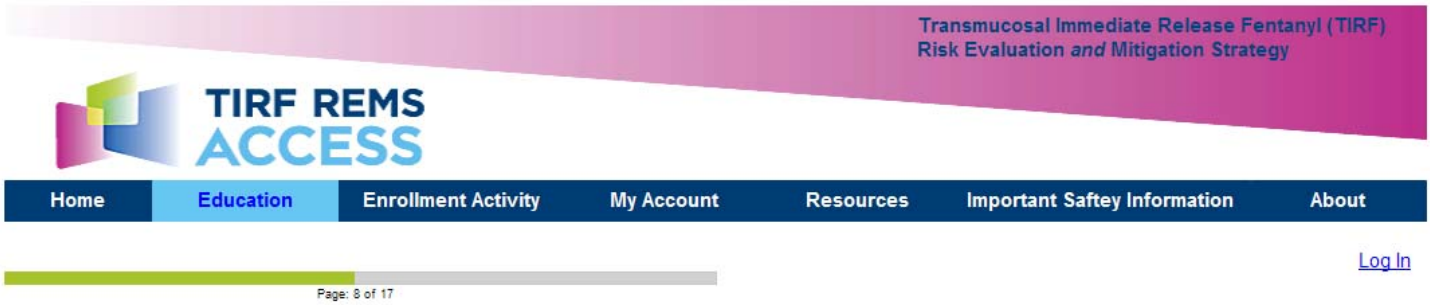

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these formulations have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage of TIRF medicines.

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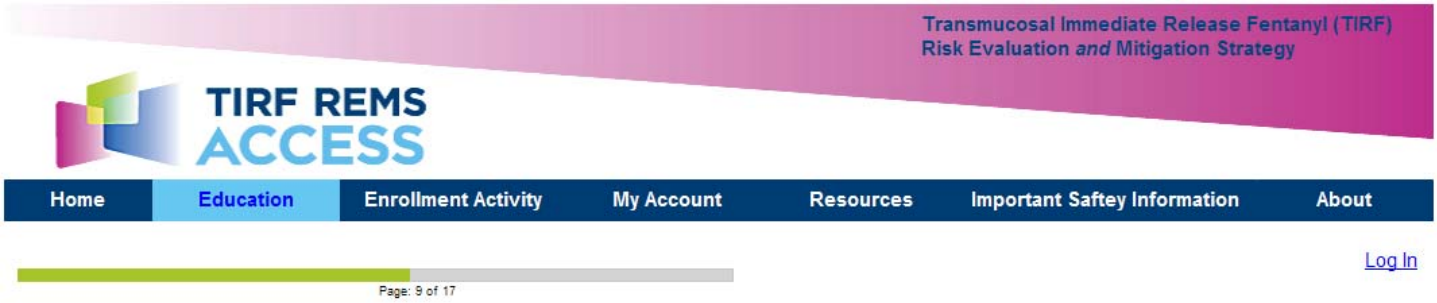

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in a potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

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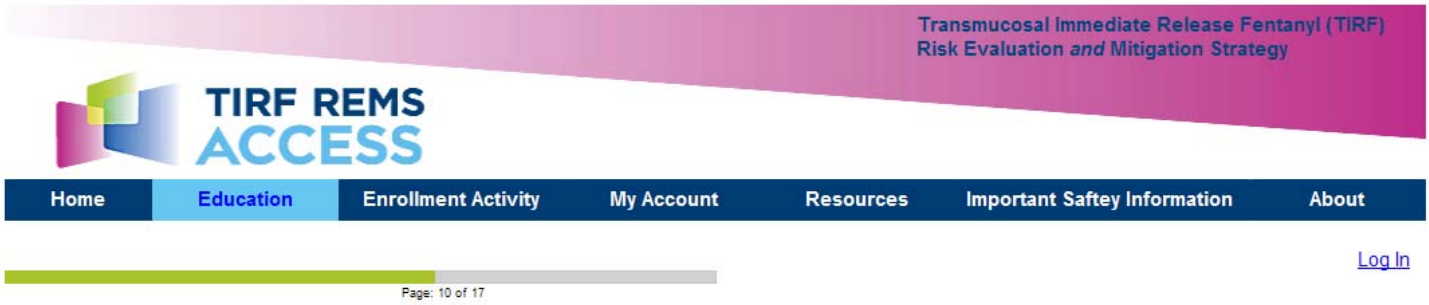

Dosage and Administration General

Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product,even if they have taken another TIRF medicine. Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are not equivalent to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for branded TIRF medicine.
- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in a fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, you must refer to the Full Prescribing Information for detailed instructions.

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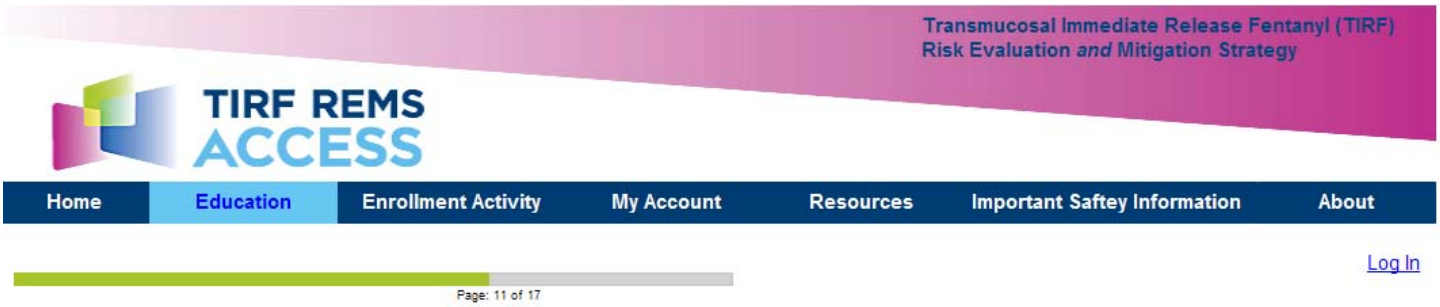

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the cancer breakthrough pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

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Products Covered Under the TIRF REMS Acess Program:

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide

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Products Covered Under the TIRF REMS Access Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl citrate) buccal tablet	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per breakthrough pain cancer episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide

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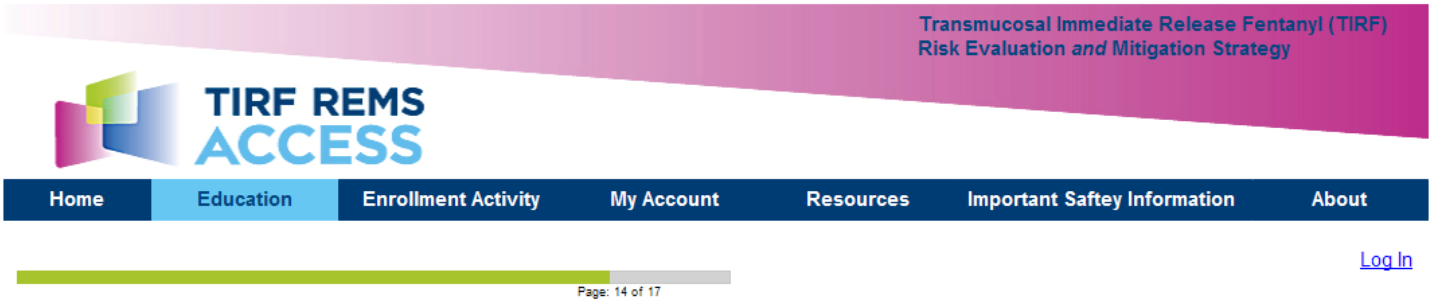

Products Covered Under the TIRF REMS Access Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl) buccal soluble film	Always 200 mcg.	**ONSOLIS should be used only once per cancer breakthrough pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.

Note: This table is also available to print for use as a quick reference guide

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Patient Counseling

Before initiating treatment with TIRF medicines, review the product specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.

- Tell patients exactly how to take the TIRF medicines. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking the TIRF medicine.
- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You must take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicne remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away TIRF medicine. Doing so is against the law.

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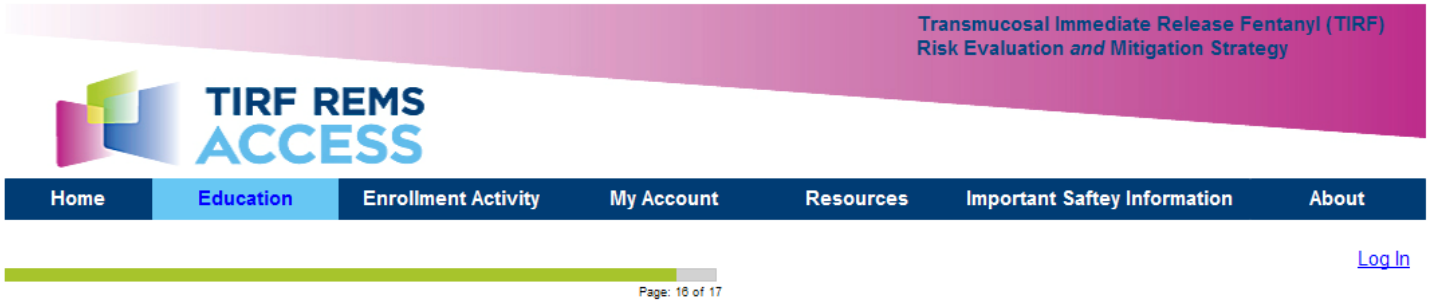

Effective Patient Management & Follow-up

All patients treated taking opioids require careful monitoring. At follow-up visits:

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of the around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

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Conclusion

You have now reached the end of TIRF REMS Access Education Program.

You will need to complete the Knowledge Assessment in the following pages to enroll in the TIRF REMS Access program. Alternatively, you may proceed to the Enrollment Activity to view your activity progress.

Thank you for taking the time to participate in this TIRF REMS Access Education Program.

Go to Knowledge Assessment | Go to My Activity

Education Program Conclusion - User not Loged

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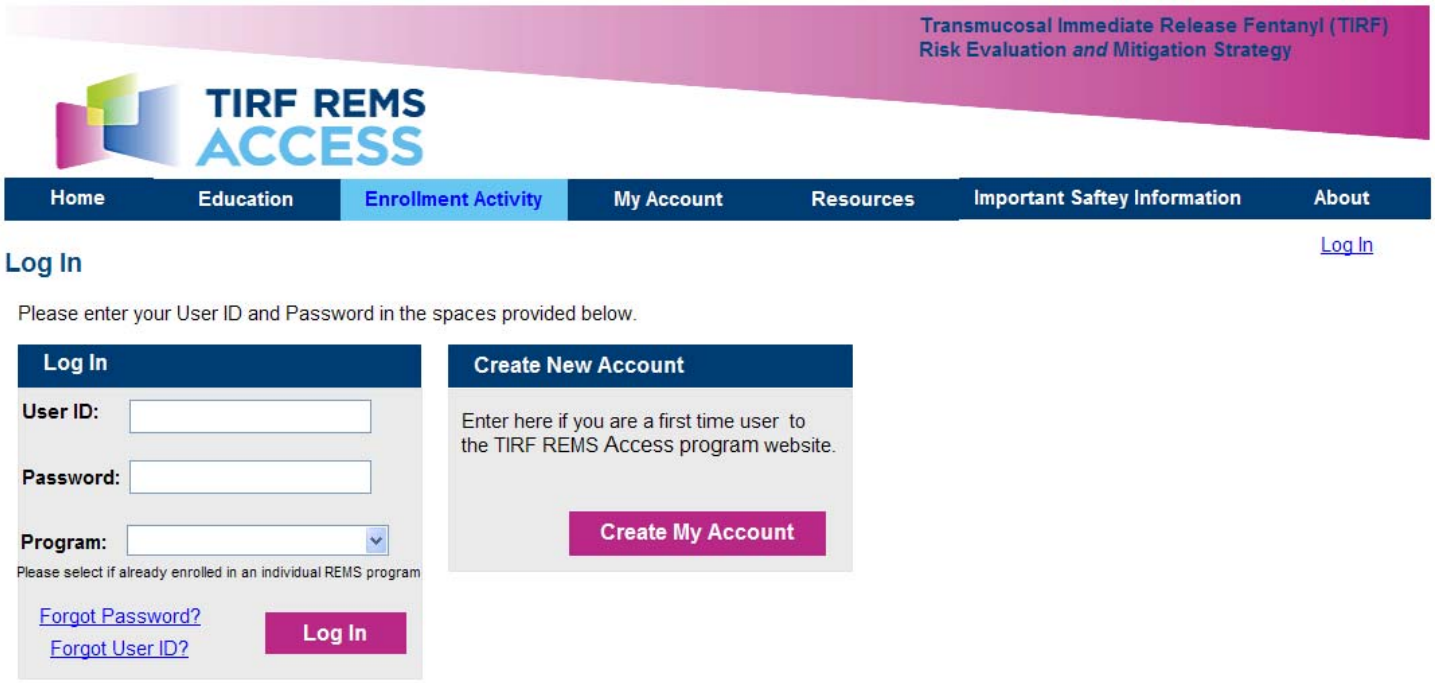

KNOWLEDGE ASSESSMENT

Knowledge Assessment - Question 1

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Knowledge Assessment

You are now going to review eleven questions that will test your knowledge of appropriate use and prescribing of TIRF medicines .

Question 1

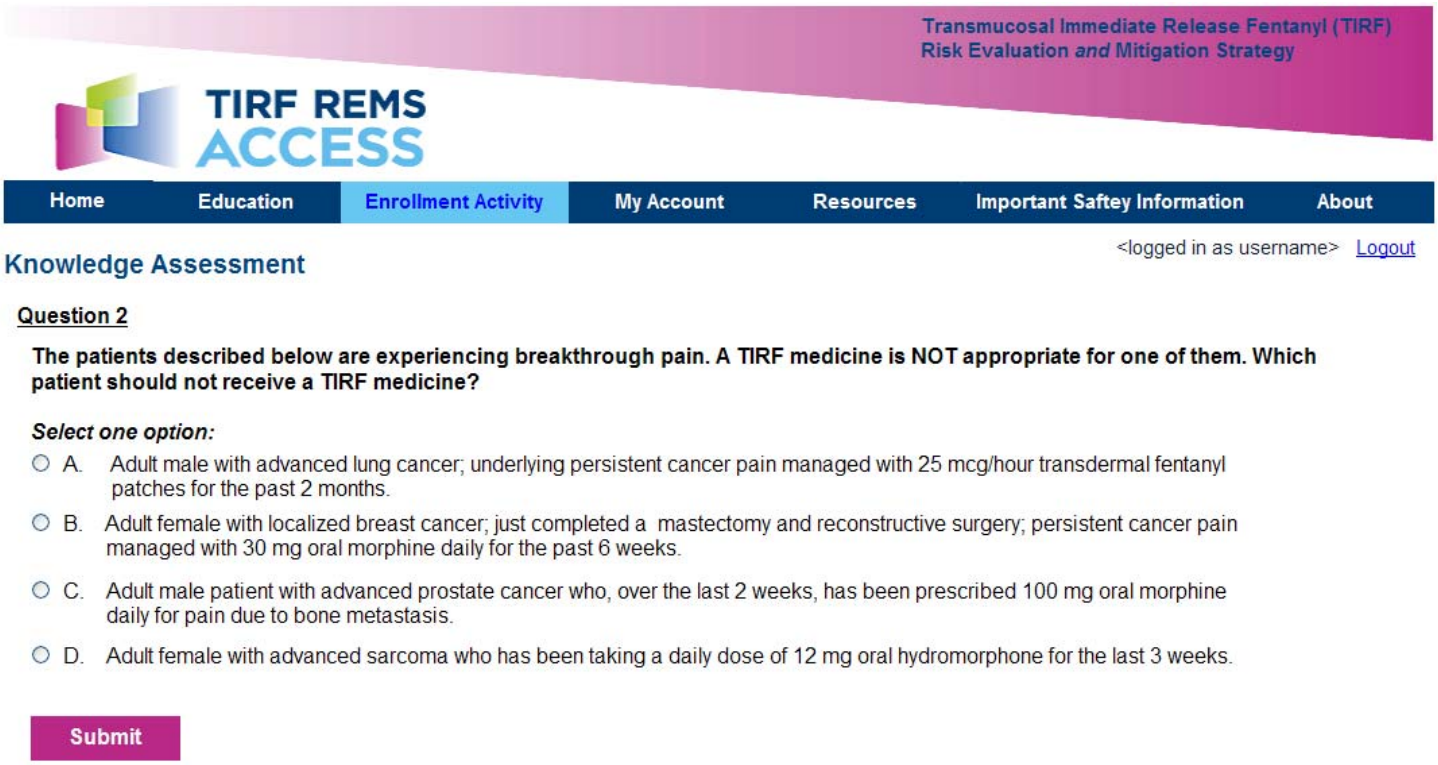
The patients described below are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine . Which patient should NOT receive a TIRF medicine ?

Select one option:

- ○ A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
- ○ B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
- ○ C. Adult male with advanced lung cancer, his underlying persistent cancer pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
- ○ D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Submit

Knowledge Assessment - Question 2



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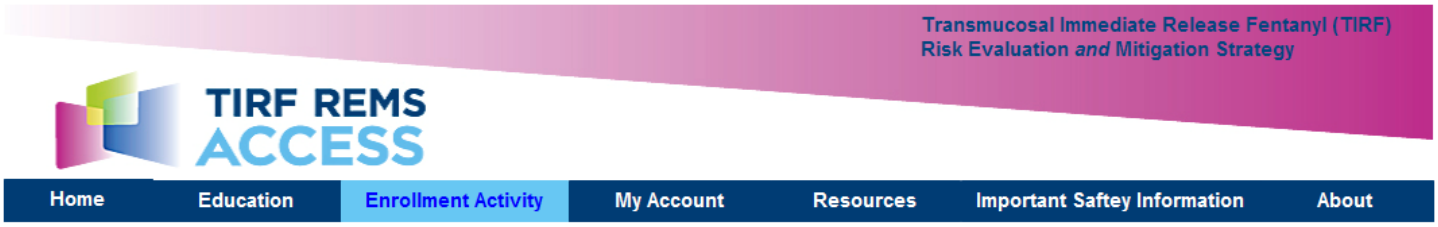
Knowledge Assessment - Question 3



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Knowledge Assessment

Question 3

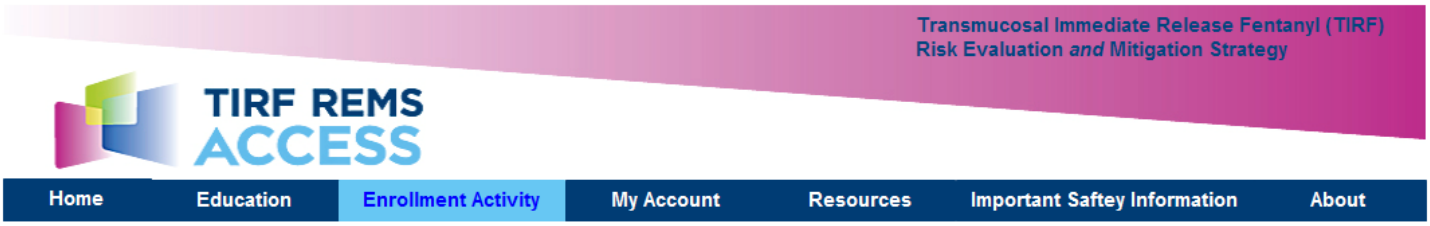
Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?

Select one option:

- ○ A. A history of alcohol abuse with the patient or close family members.
- ○ B. The patient has a household member with a street drug abuse problem.
- ○ C. The patient has a history of prescription drug misuse.
- ○ D. All of the above.

Submit

Knowledge Assessment - Question 4



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Knowledge Assessment

Question 4

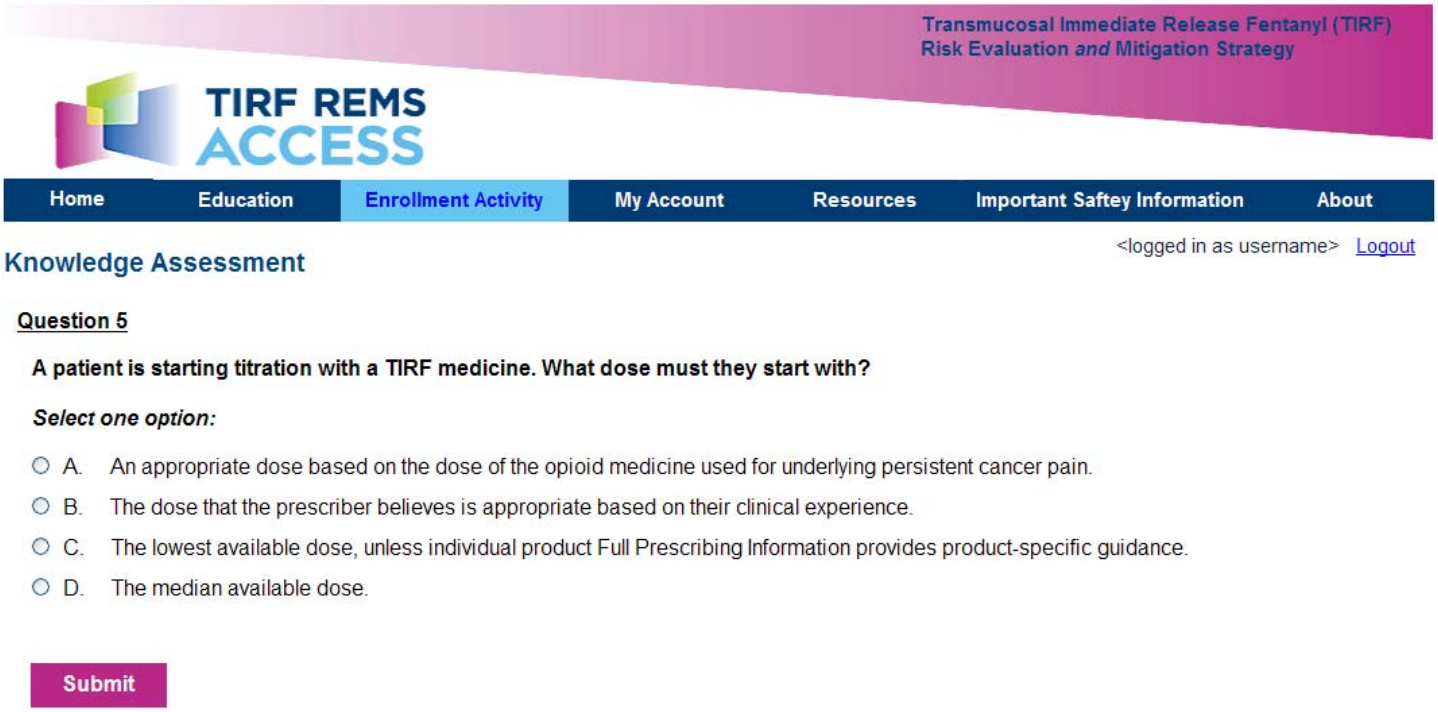
A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?

Select one option:

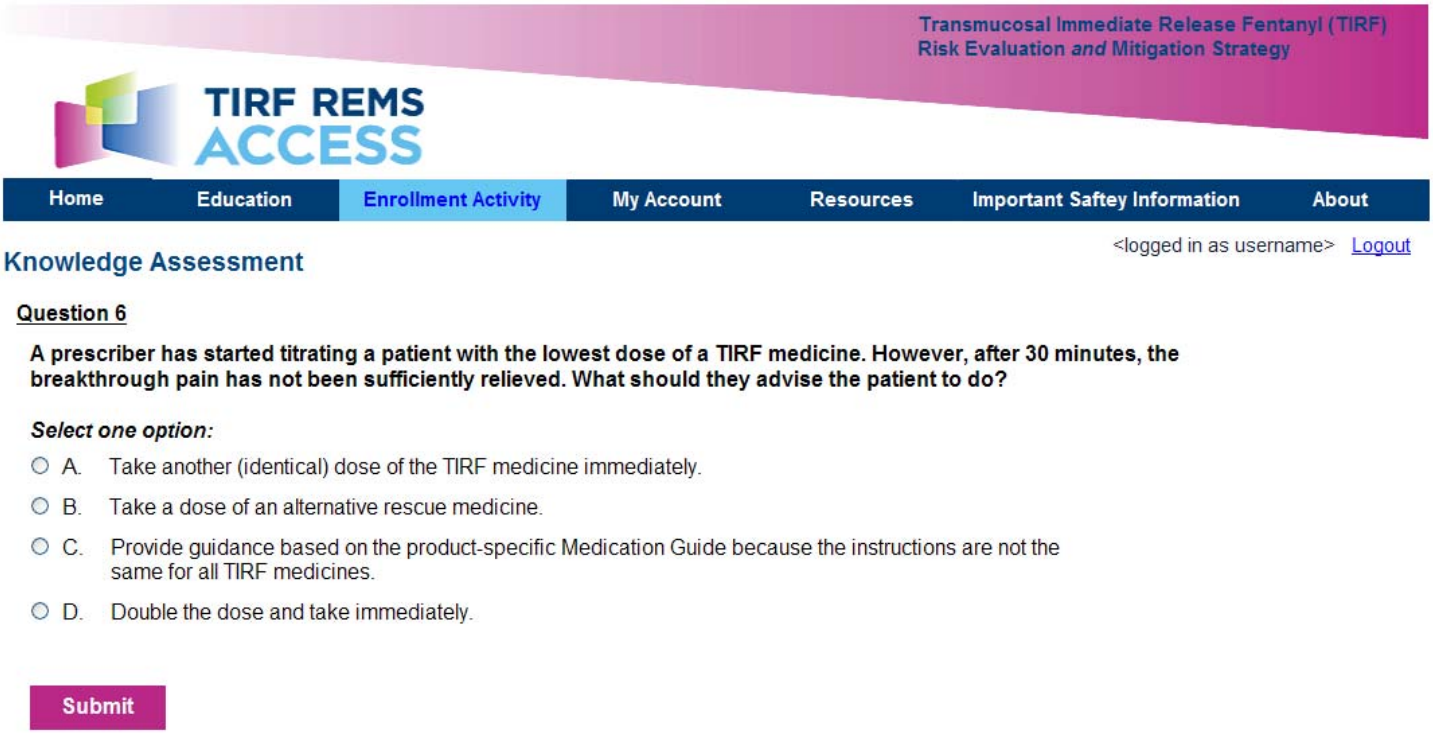
- ○ A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines. .
- ○ B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
- ○ C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
- ○ D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medication used for their underlying persistent cancer pain.

Submit

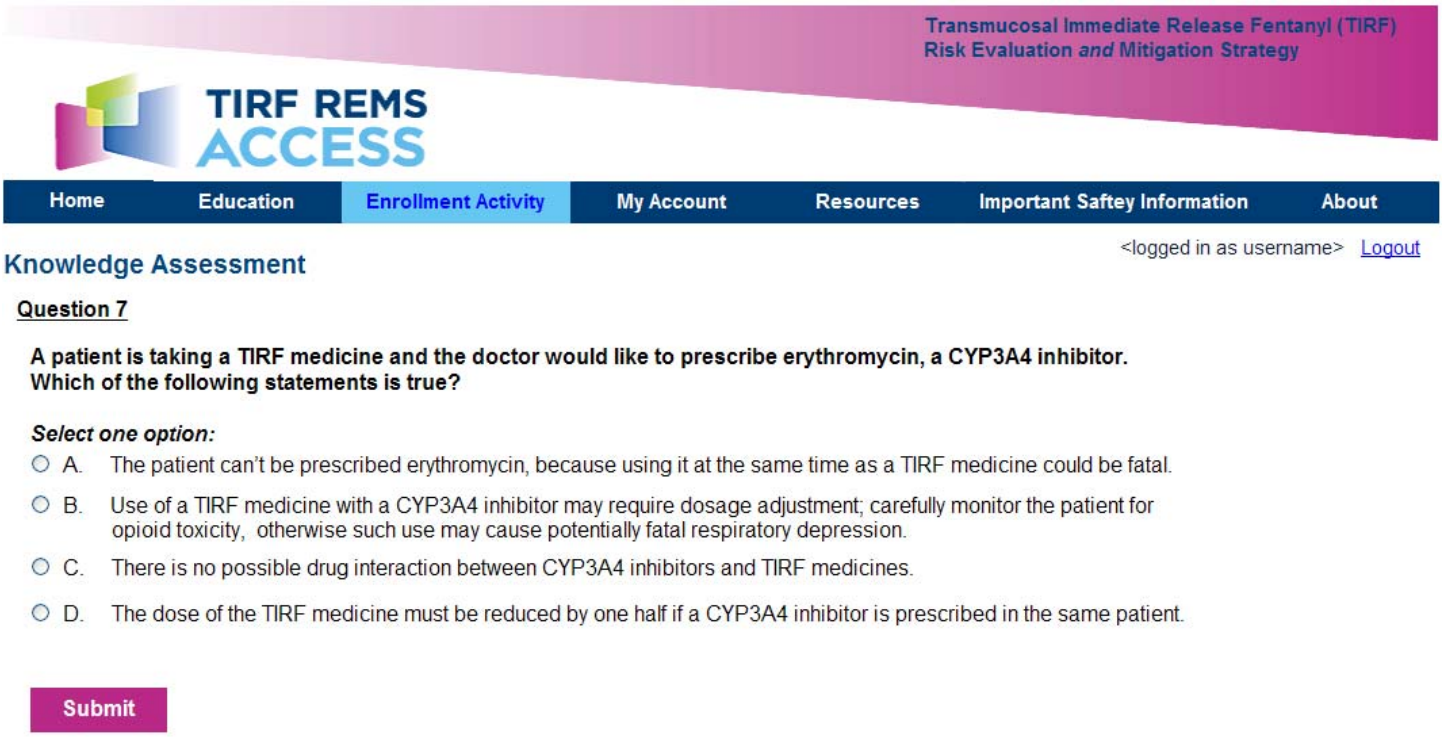
Knowledge Assessment - Question 5



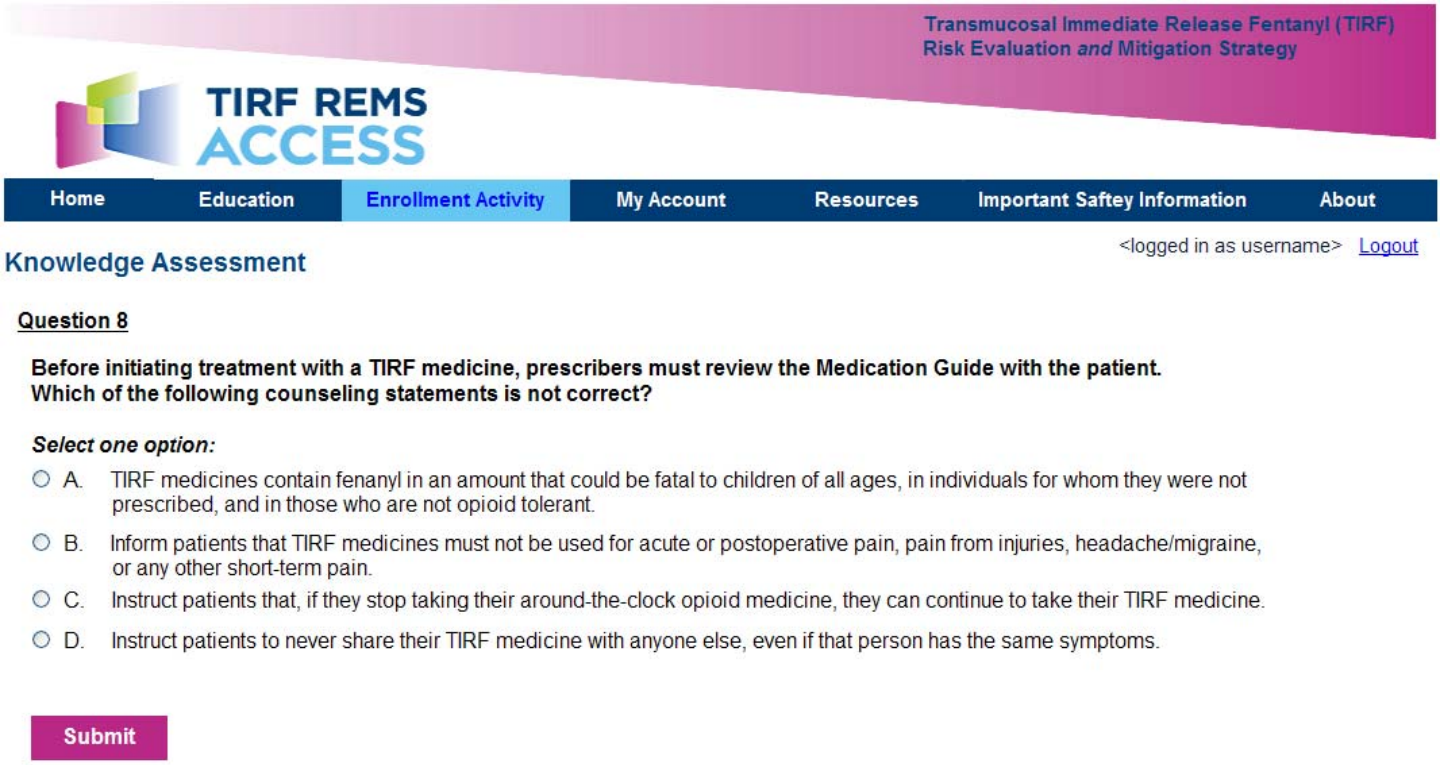
Knowledge Assessment - Question 6



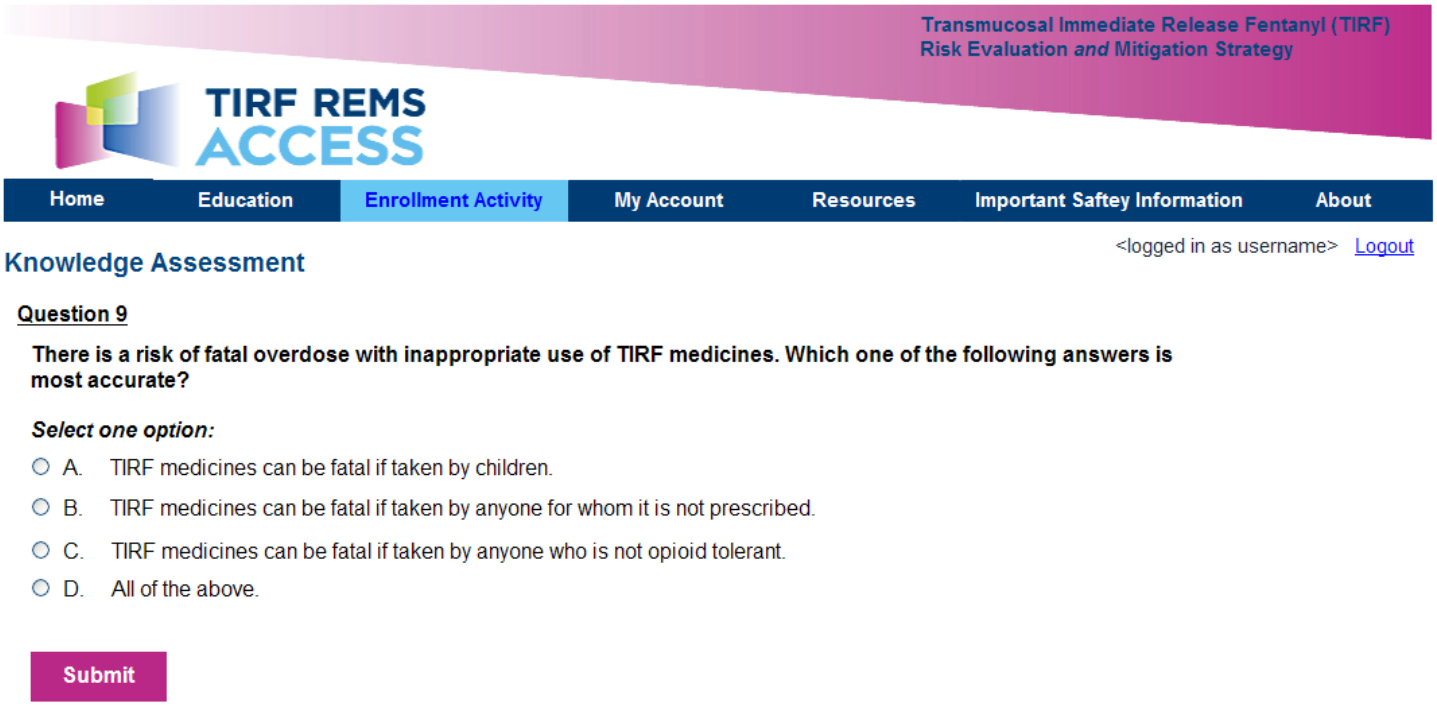
Knowledge Assessment - Question 7



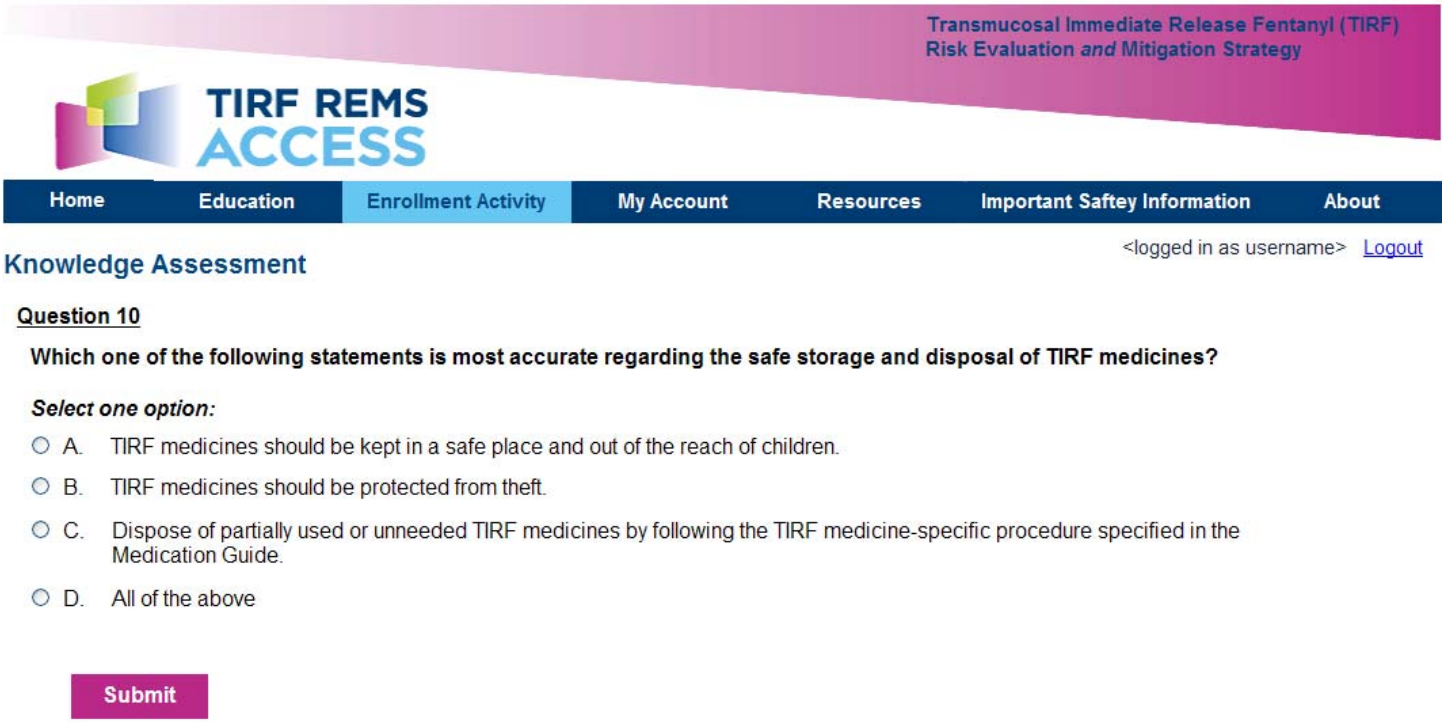
Knowledge Assessment - Question 8



Knowledge Assessment - Question 9

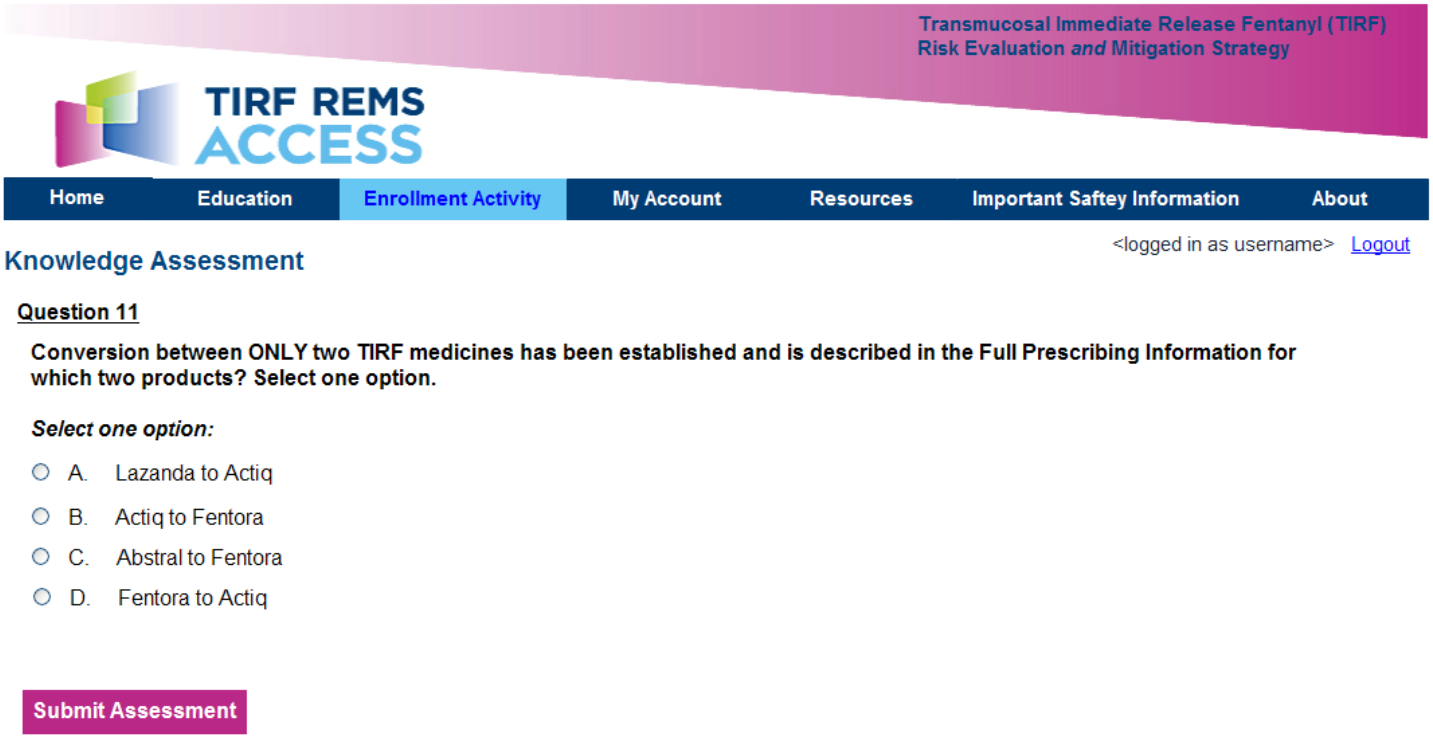


Knowledge Assessment - Question 10



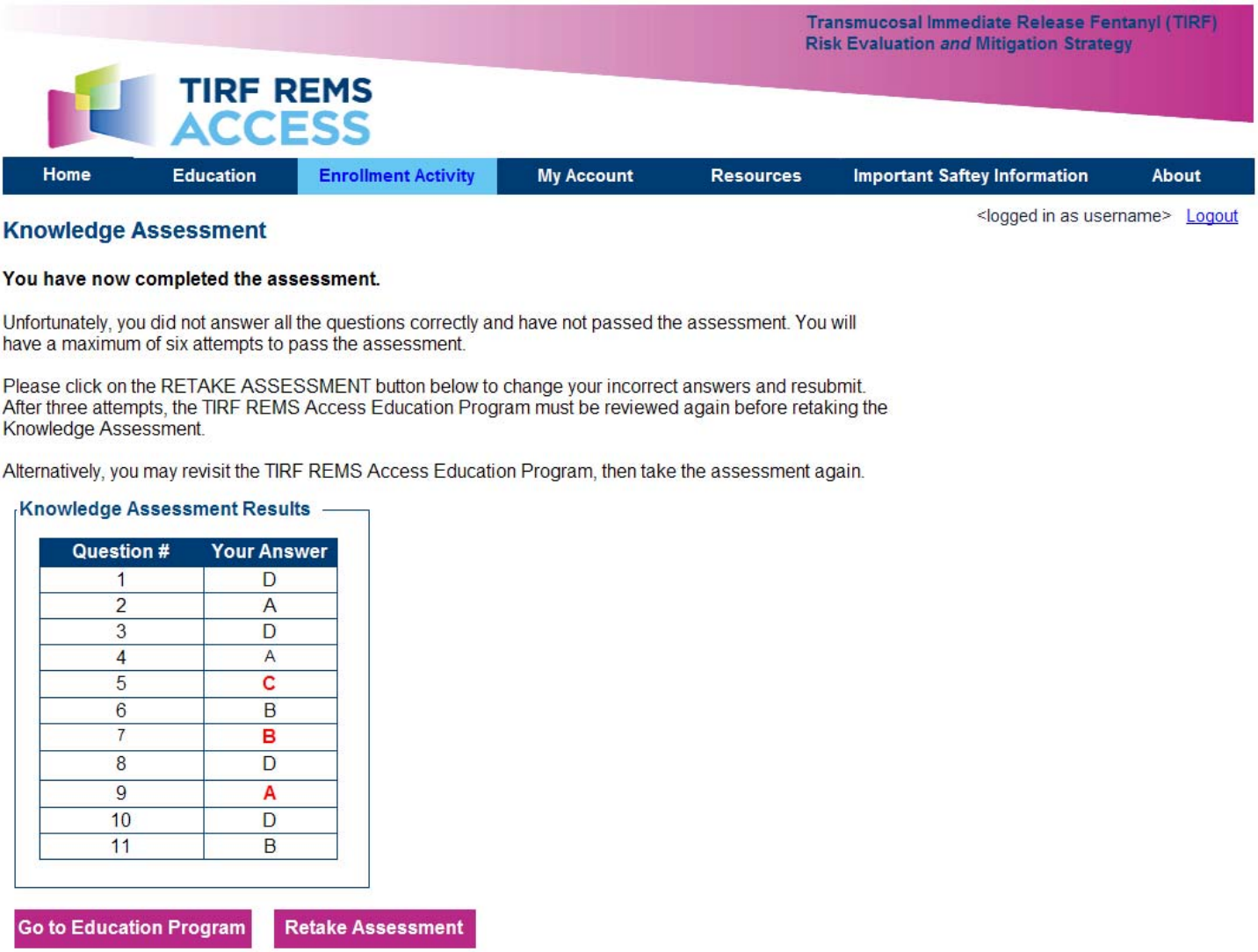
TIRF REMS Access Web Prototype

Knowledge Assessment - Question 11



TIRF REMS Access Web Prototype

Assessment Results - Incorrect



Results - Correct

<logged in as username> Logout

Knowledge Assessment

You have now completed the assessment.

Congratulations!

You answered all the questions correctly and have passed the assessment.

Click on the *Complete Enrollment* button to complete the last enrollment step

Knowledge Assessment Results

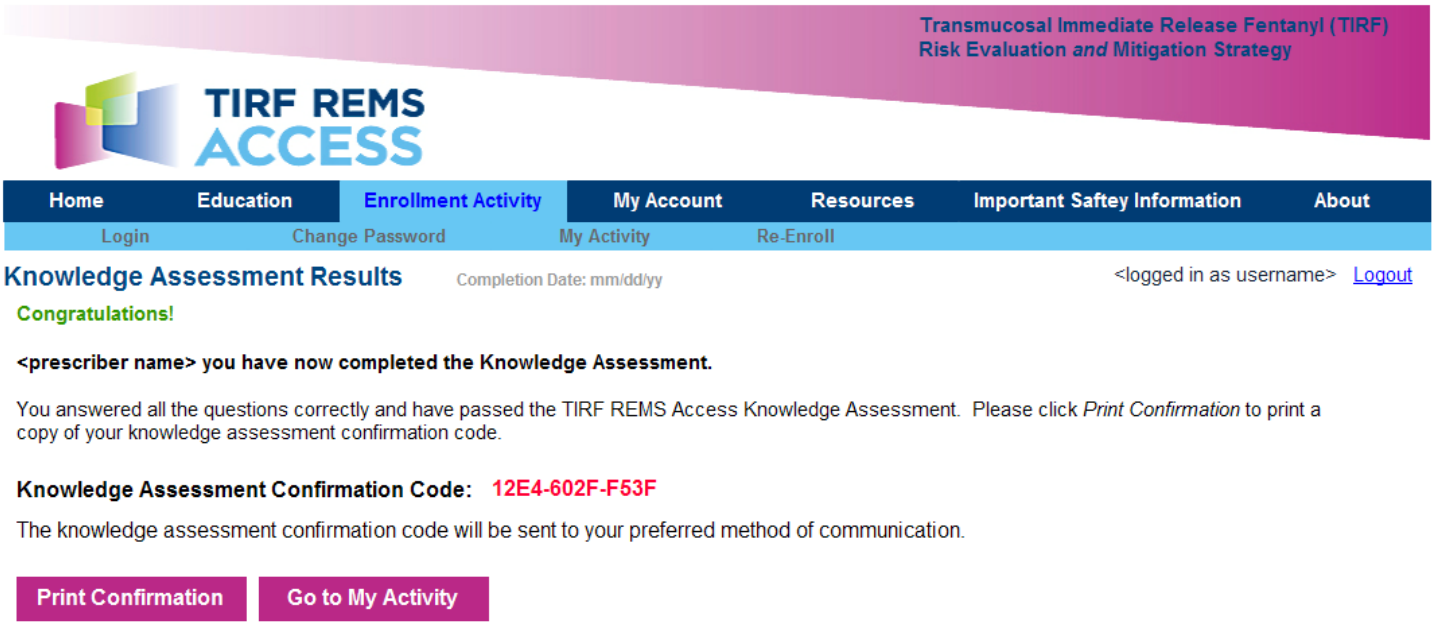
Question #	Your Answer
1	D
2	A
3	D
4	A
5	D
6	B
7	C
8	D
9	D
10	D
11	B

Knowledge Assessment Confirmation Code: 12E3-64B5-570A

Your knowledge assessment confirmation code has been sent to your preferred method of communication.

Complete Enrollment

Stakeholder Assessment Confirmation

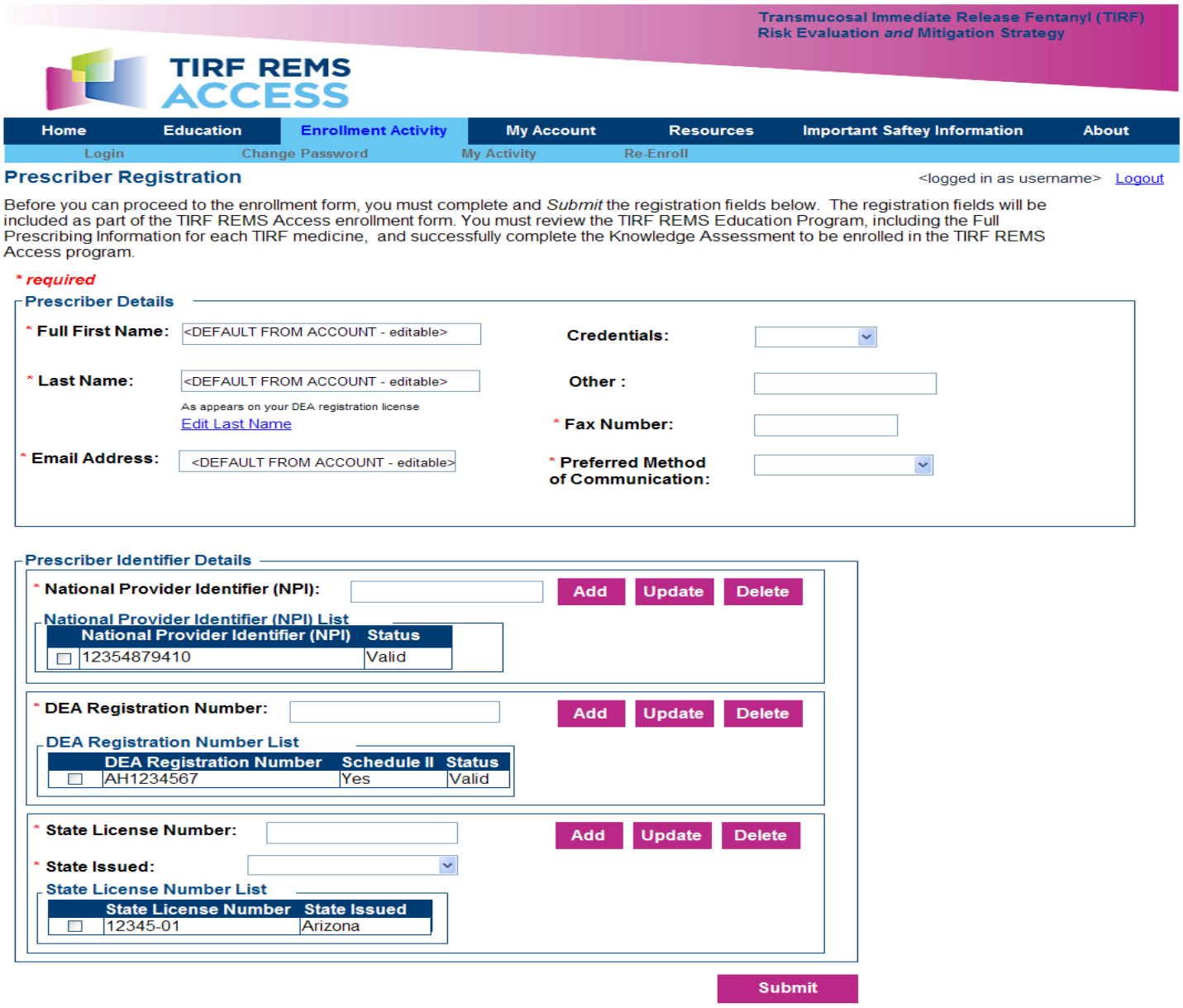


TIRF REMS Access Web Prototype

PRESCRIBER ENROLLMENT PROCESS

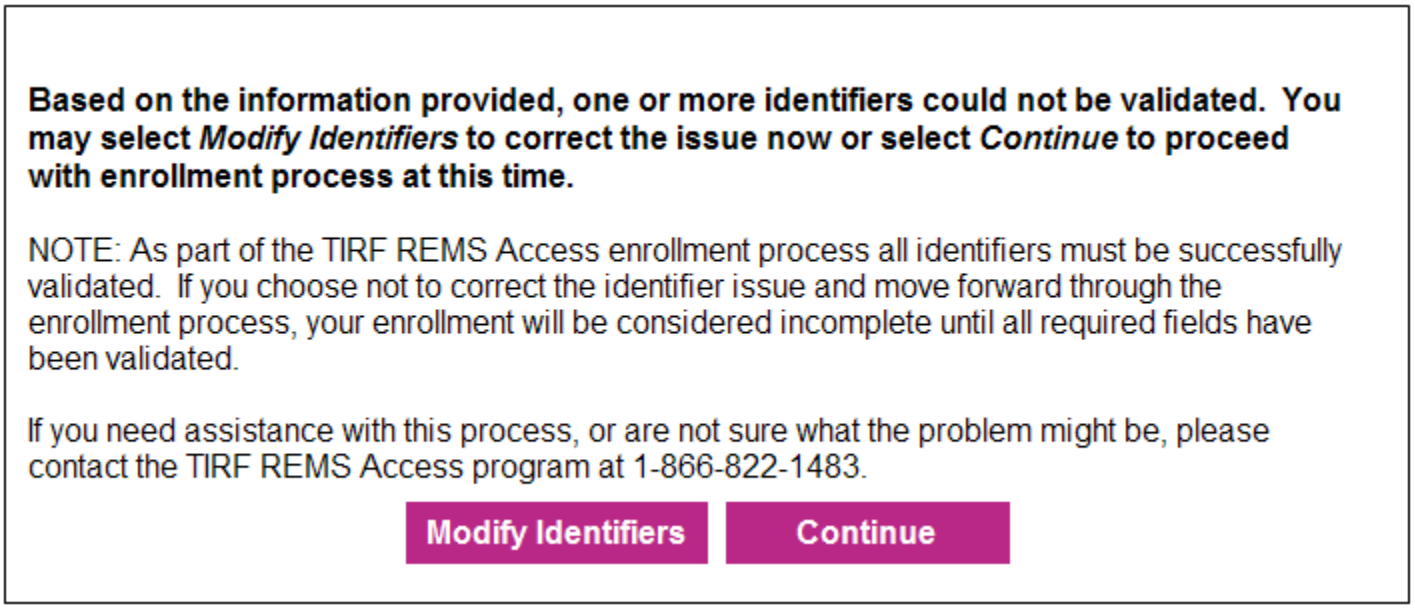
➔ See Enrollment Activity section on page 49 and follow for Prescriber

Prescriber Registration – Identifiers

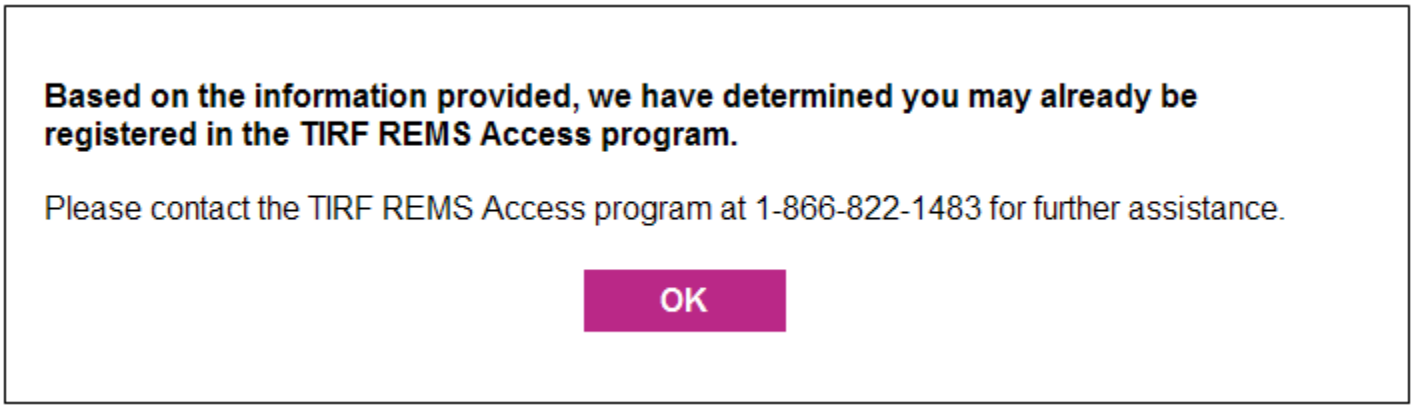


Prescriber Registration Warnings

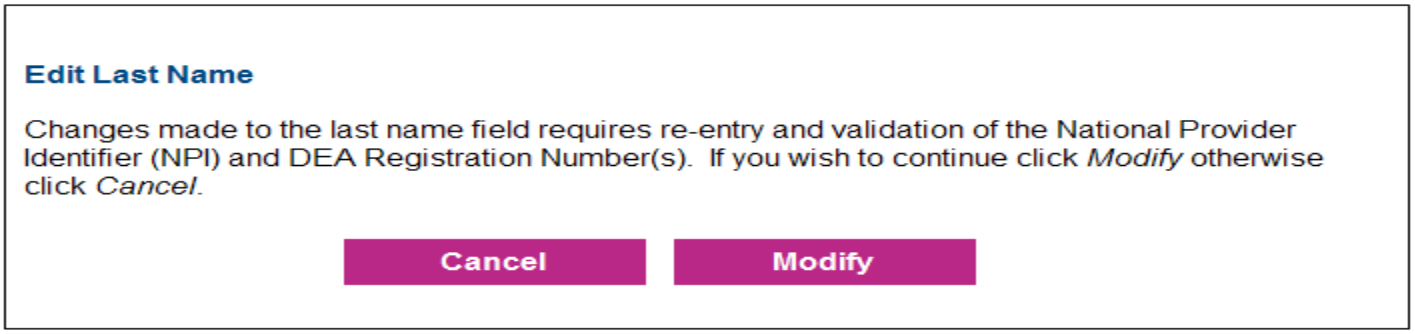
Prescriber Registration – Invalid Identifier Warning



Prescriber Registration – Duplicate Error

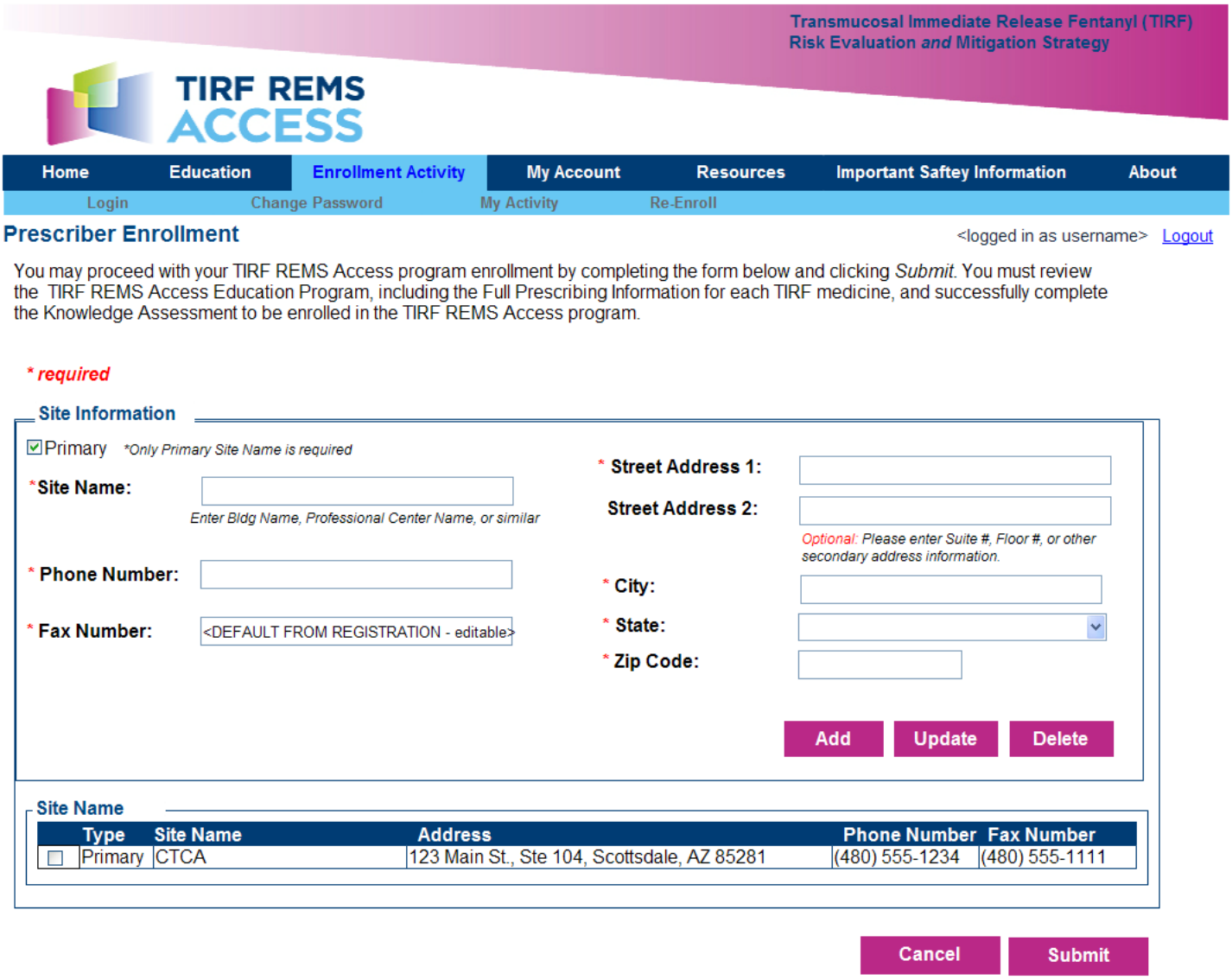


Prescriber Registration Edit Last Name



TIRF REMS Access Web Prototype

Prescriber Registration - Demographics



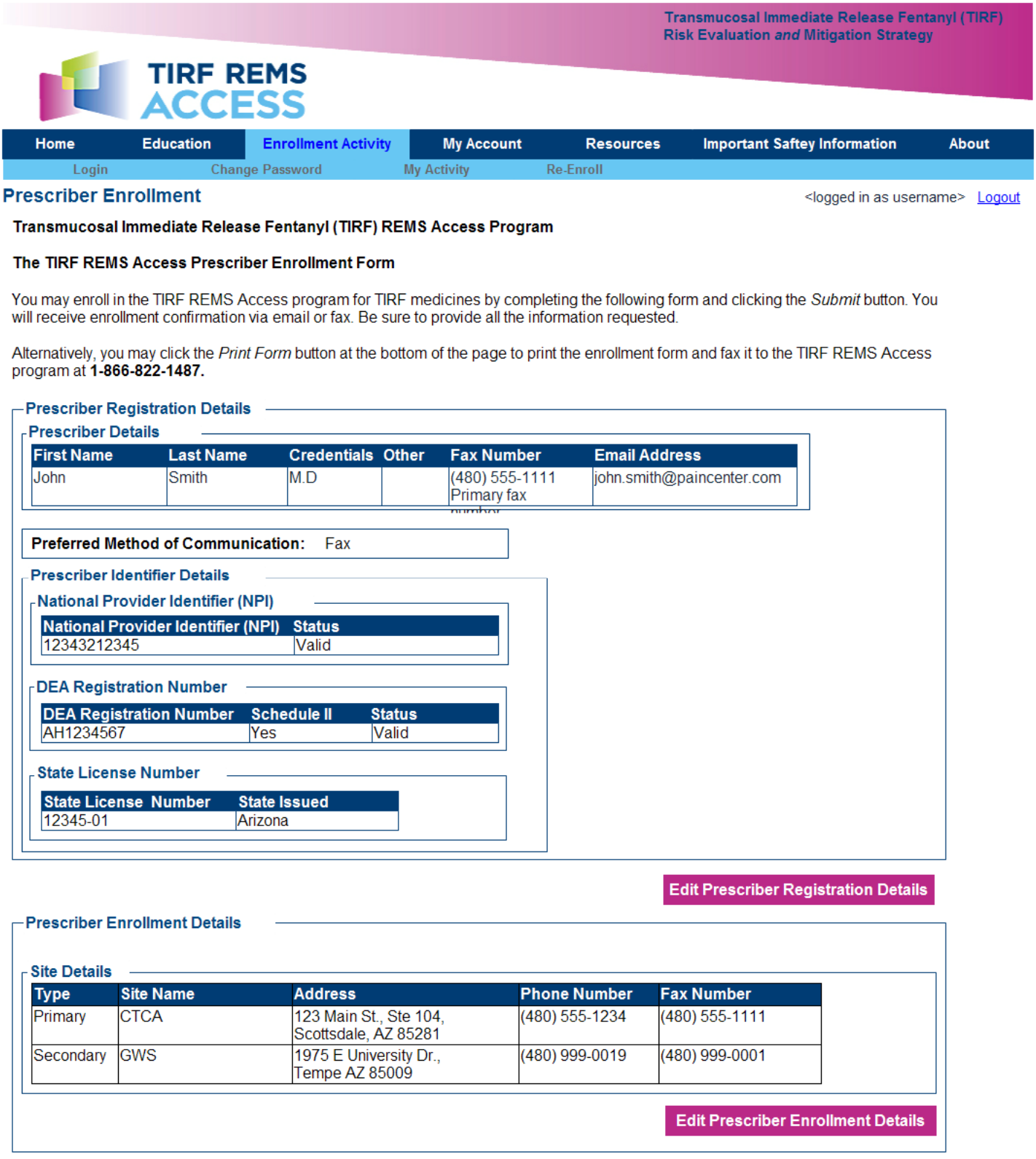
Registration Complete

Education and Assessment

See Education and Assessments sections starting on page 55

TIRF REMS Access Web Prototype

Prescriber Enrollment and Attestation



Web Page Continued on Next Page

TIRF REMS Access Web Prototype

Prescriber Attestation

By signing below, I affirm that I understand that TIRF medicinces are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicines prescribed, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specfic conversion recommnedations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I have prescribed to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new product will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every (2) years.

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

Signature (Full First & Last Name typed): _____ **Date:** _____

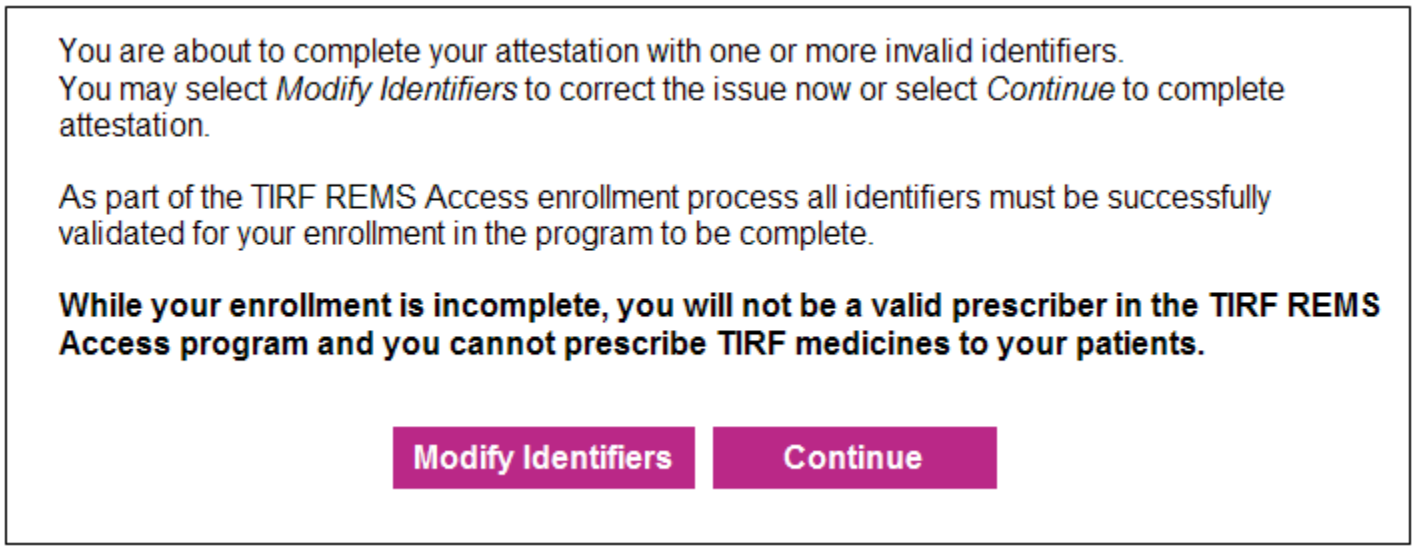
☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Print Form Submit

TIRF REMS Access Web Prototype

Error Message from Enrollment Page

Prescriber Attestation Submission - Invalid Identifiers



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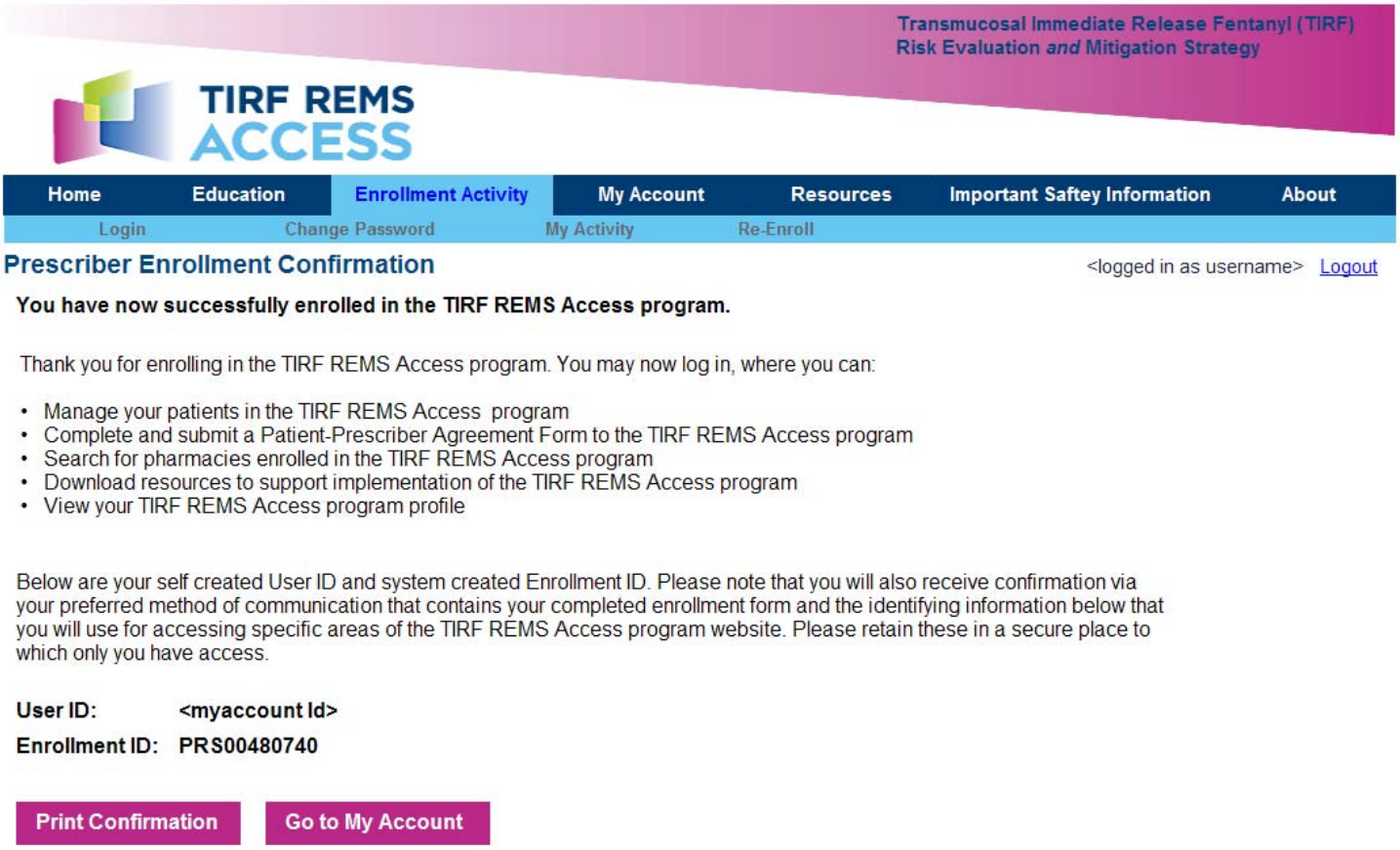
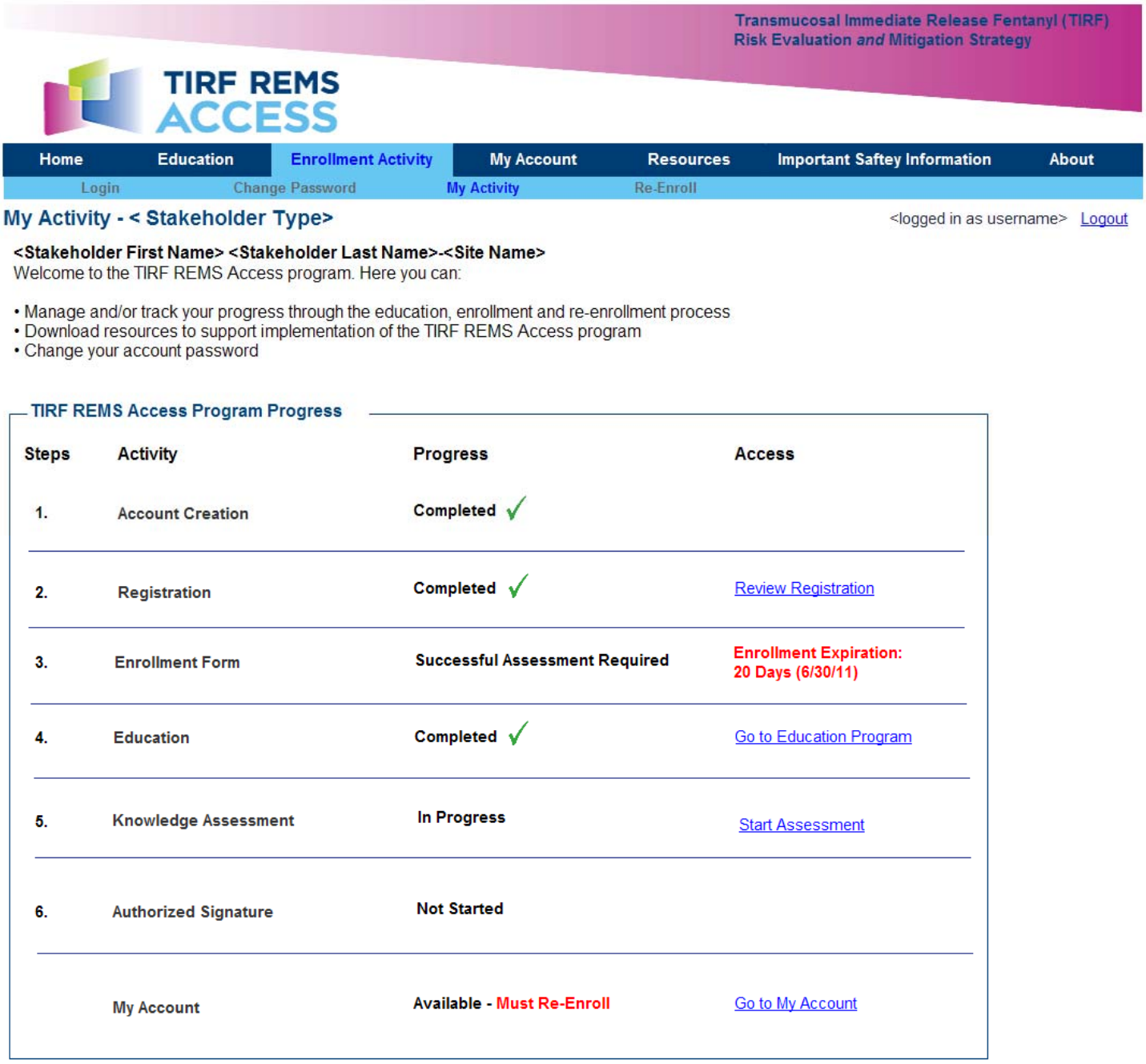
Prescriber Enrollment Confirmation



Prescriber Re-Enrollment

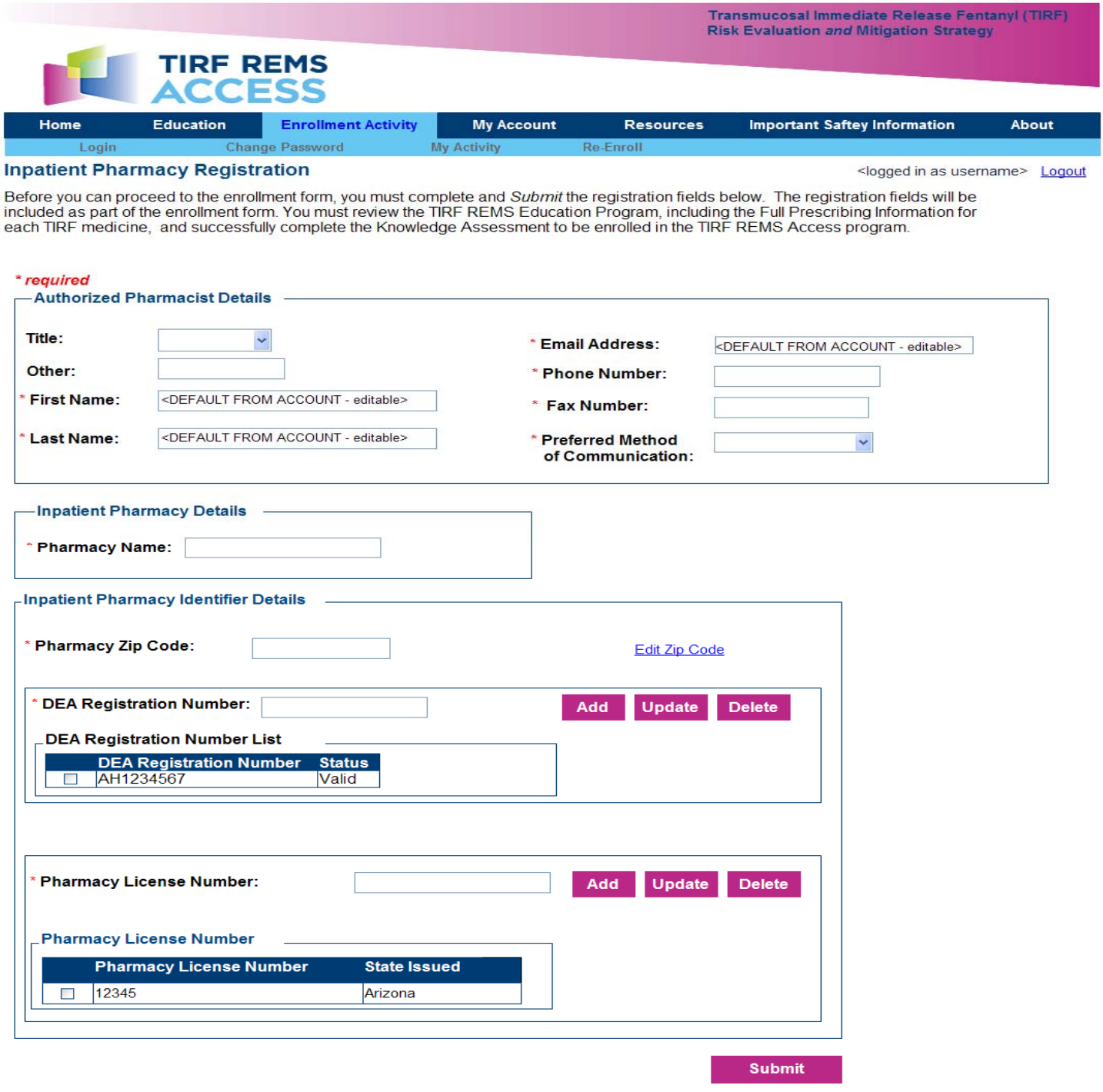


TIRF REMS Access Web Prototype

INPATIENT PHARMACY ENROLLMENT PROCESS

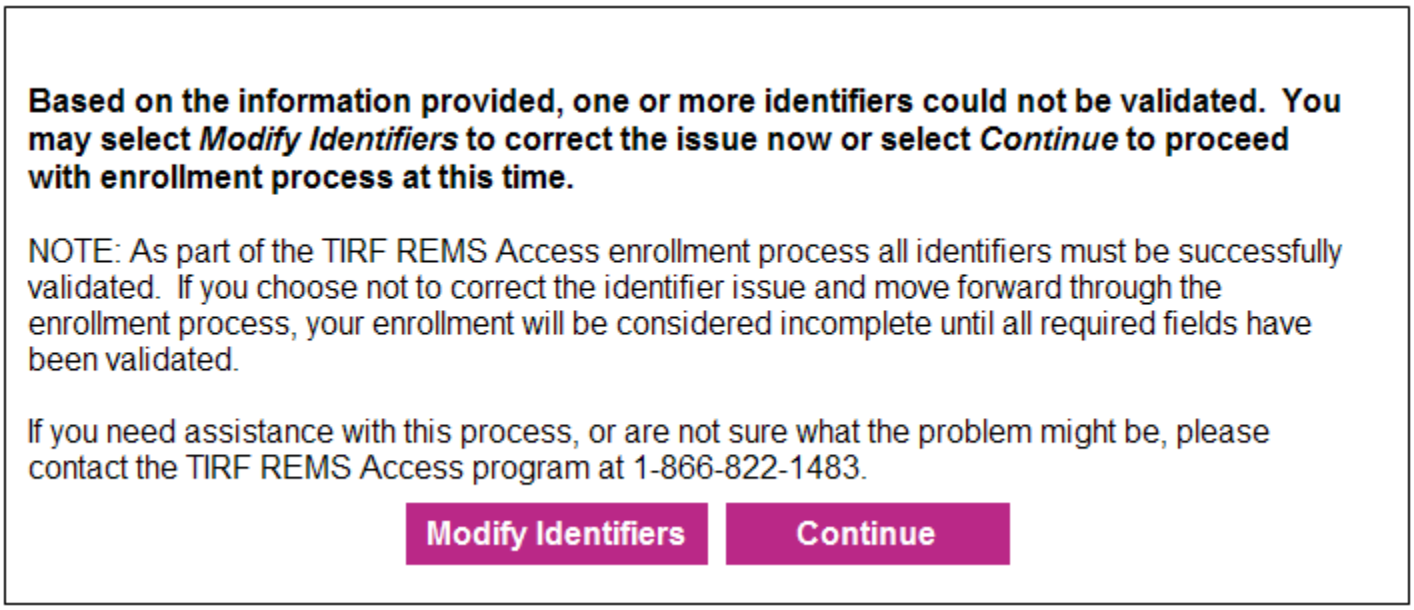
➔ See Enrollment Activity section on page 50 and follow for Inpatient

Inpatient Pharmacy Registration - Identifiers

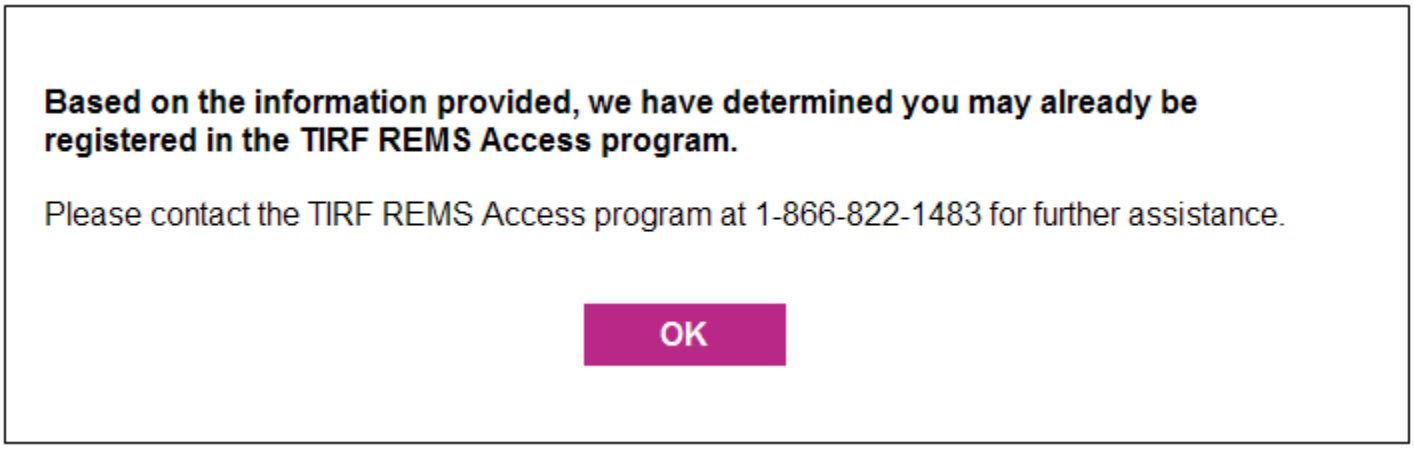


Inpatient Pharmacy Registration Warnings

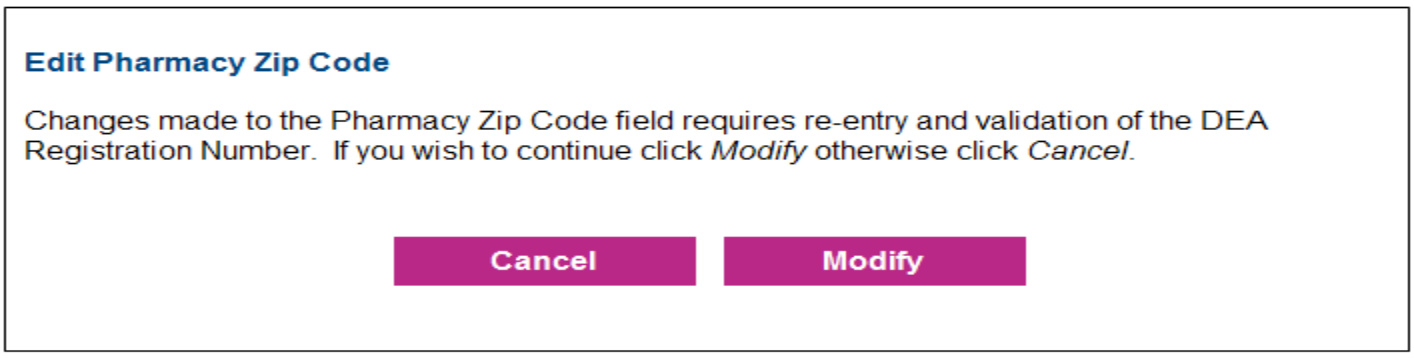
Inpatient Pharmacy Registration – Invalid Identifer Warning



Inpatient Pharmacy Registration – Duplicate Error

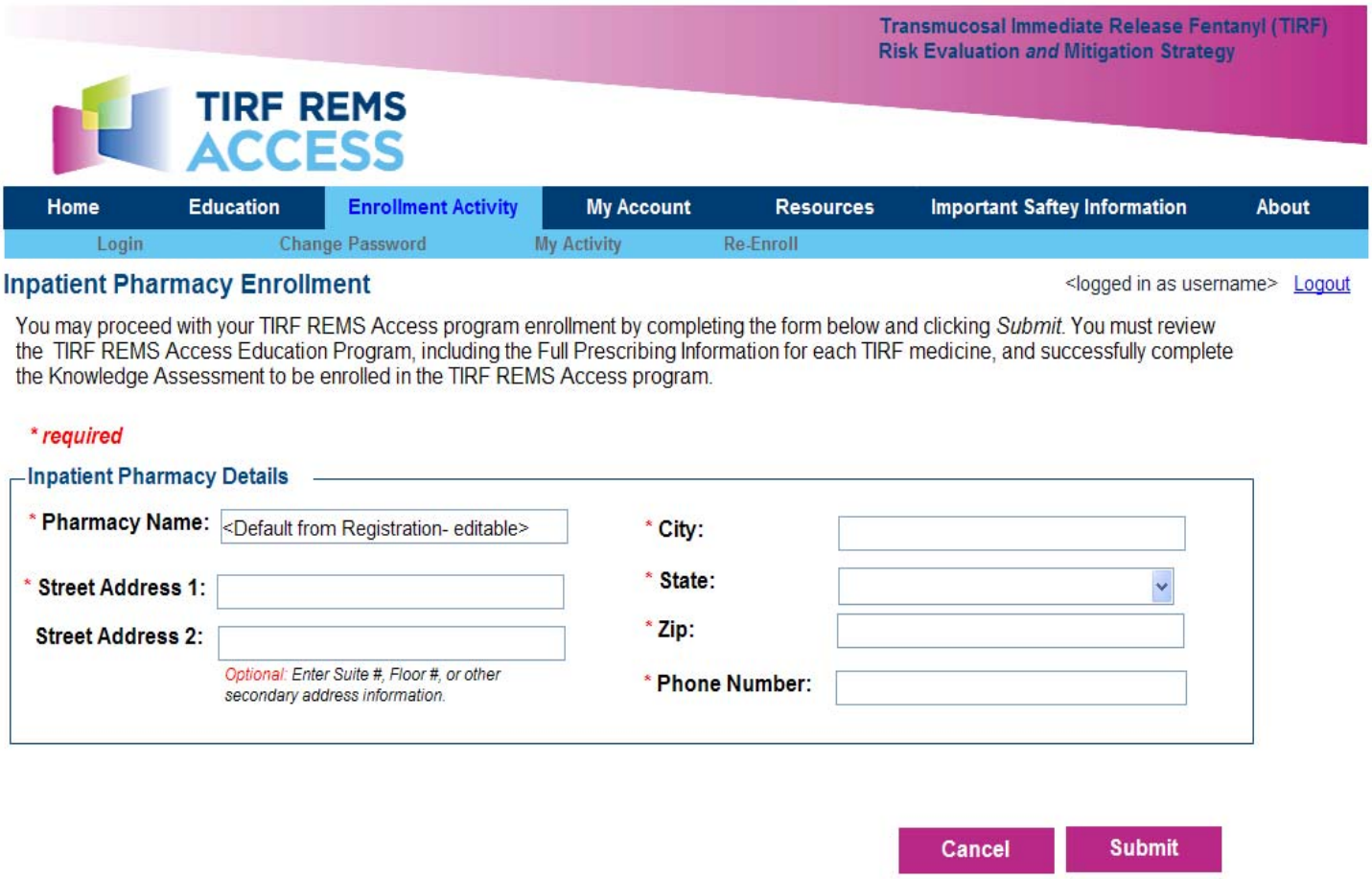


Inpatient Pharmacy Registration – Edit Zip Code



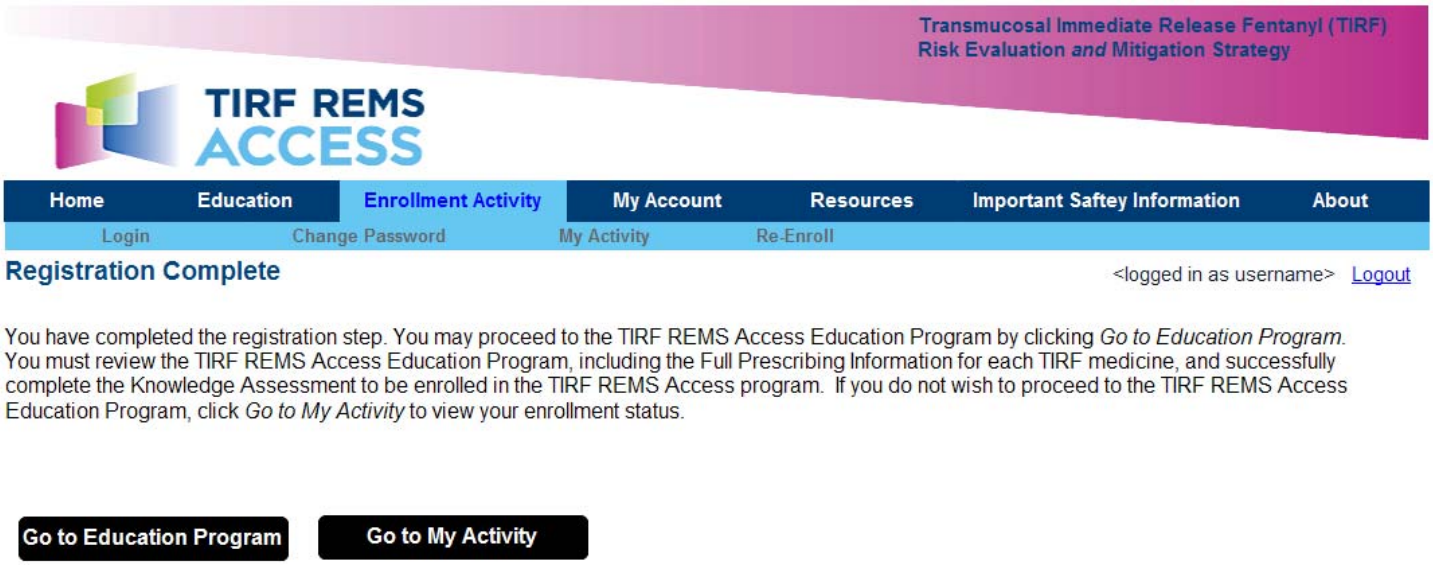
TIRF REMS Access Web Prototype

Inpatient Pharmacy Registration – Demographics



TIRF REMS Access Web Prototype

Registration Complete



Education and Assessment

See Education and Assessments sections starting on page 55

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TIRF REMS Access Web Prototype

Inpatient Pharmacy Enrollment and Attestation

Transmucosal Immediate Release Fentanyl (TIRF)
Risk Evaluation *and* Mitigation Strategy

TIRF REMS ACCESS

Home | Education | Enrollment Activity | My Account | Resources | Important Saftey Information | About

Login | Change Password | My Activity | Re-Enroll

Inpatient Pharmacy Enrollment

<logged in as username> Logout

Transmucosal Immediate Release Fentanyl REMS Access Program

The TIRF REMS Access Inpatient Pharmacy (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use) Enrollment Form

You may enroll in the TIRF REMS Access program for TIRF medicines by completing the following form and clicking the *Submit* button. You will receive enrollment confirmation via email or fax. Be sure to provide all the information requested.

Alternatively, you may click the *Print Form* button at the bottom of the page to print the enrollment form and fax it to the TIRF REMS Access program at **1-866-822-1487.**

Inpatient Pharmacy Registration Details

Authorized Pharmacist Details

First Name	Last Name	Title	Other	Phone Number	Fax Number	Email Address
John	Smith	RPh		(480) 555-1212	(480) 555-1111	john.smith@paincenter.com

Preferred Method of Communication: Fax

Inpatient Pharmacy Identifier Details

Pharmacy Zip Code: 85281

Pharmacy License Number

Pharmacy License Number	State Issued
12345-01	Arizona

DEA Registration Number

DEA Registration Number	Status
AH1234567	Valid

Edit Inpatient Pharmacy Registration Details

Inpatient Pharmacy Enrollment Details

Inpatient Pharmacy Details

Pharmacy Name	Address	Phone Number
Pharm1	123 Main St., Ste 104, Scottsdale, AZ 85281	(480) 555-1234

Edit Inpatient Pharmacy Enrollment Details

Web Page Continued on Next Page

TIRF REMS Access Web Prototype

Inpatient Authorized Pharmacist Attestation

By signing below, I affirm that I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients should be the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the health care facility that dispense to outpatients must also be enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access.
10. I understand that our pharmacy will not sell, loan or transfer TIRF medicines inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

Signature (Full First & Last Name typed): _____ **Date:** _____

☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Print Form | Submit

Error Message from Enrollment Page

Inpatient Pharmacy Attestation Submission - Invalid Identifiers

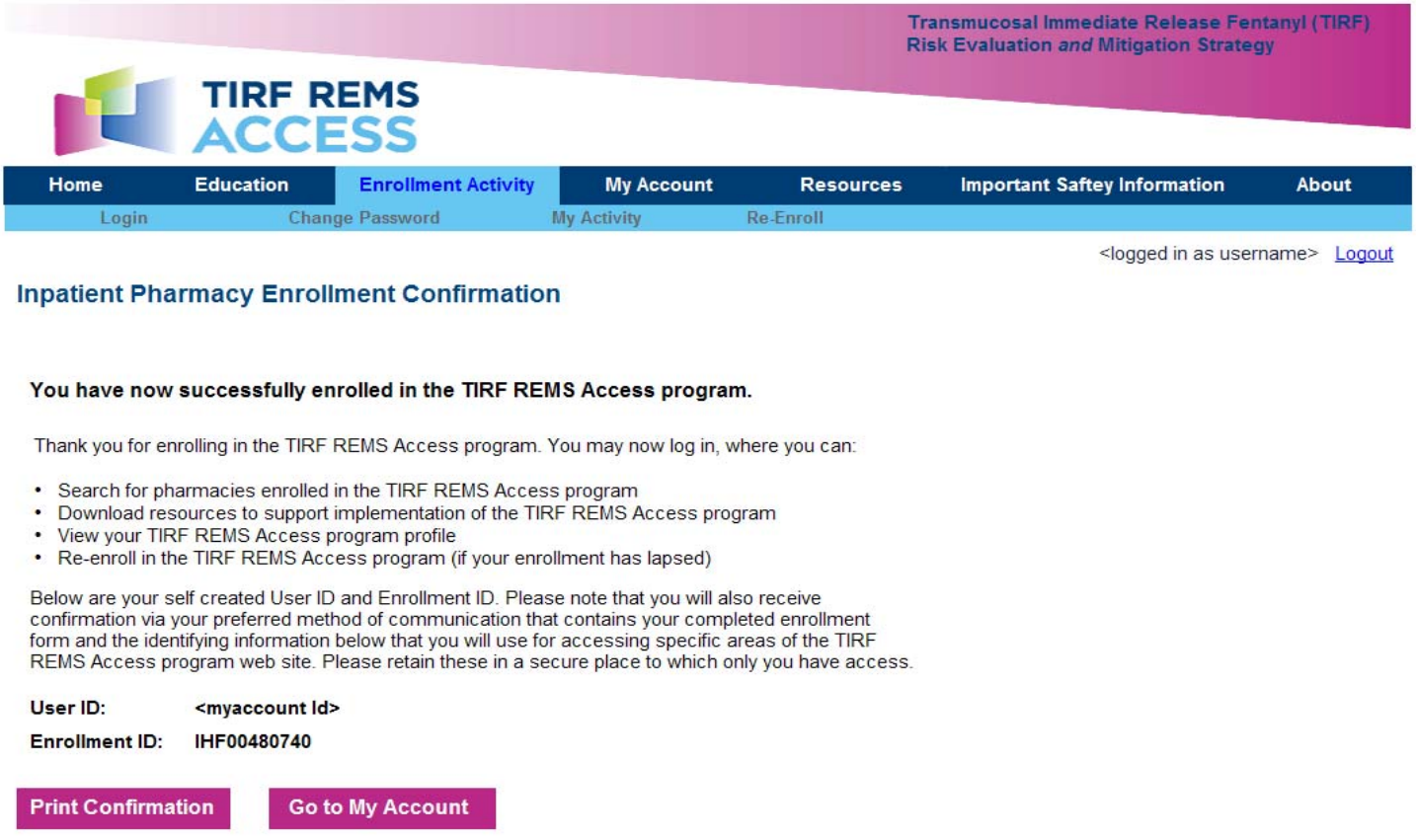
You are about to complete your attestation with one or more invalid identifiers.
You may select *Modify Identifiers* to correct the issue now or select *Continue* to complete your attestation.

As part of the TIRF REMS Access enrollment process all identifiers must be successfully validated for your enrollment in the program to be complete.

While your enrollment is incomplete, you will not be a valid pharmacy in the TIRF REMS Access program and your pharmacy cannot purchase or dispense TIRF medicines.

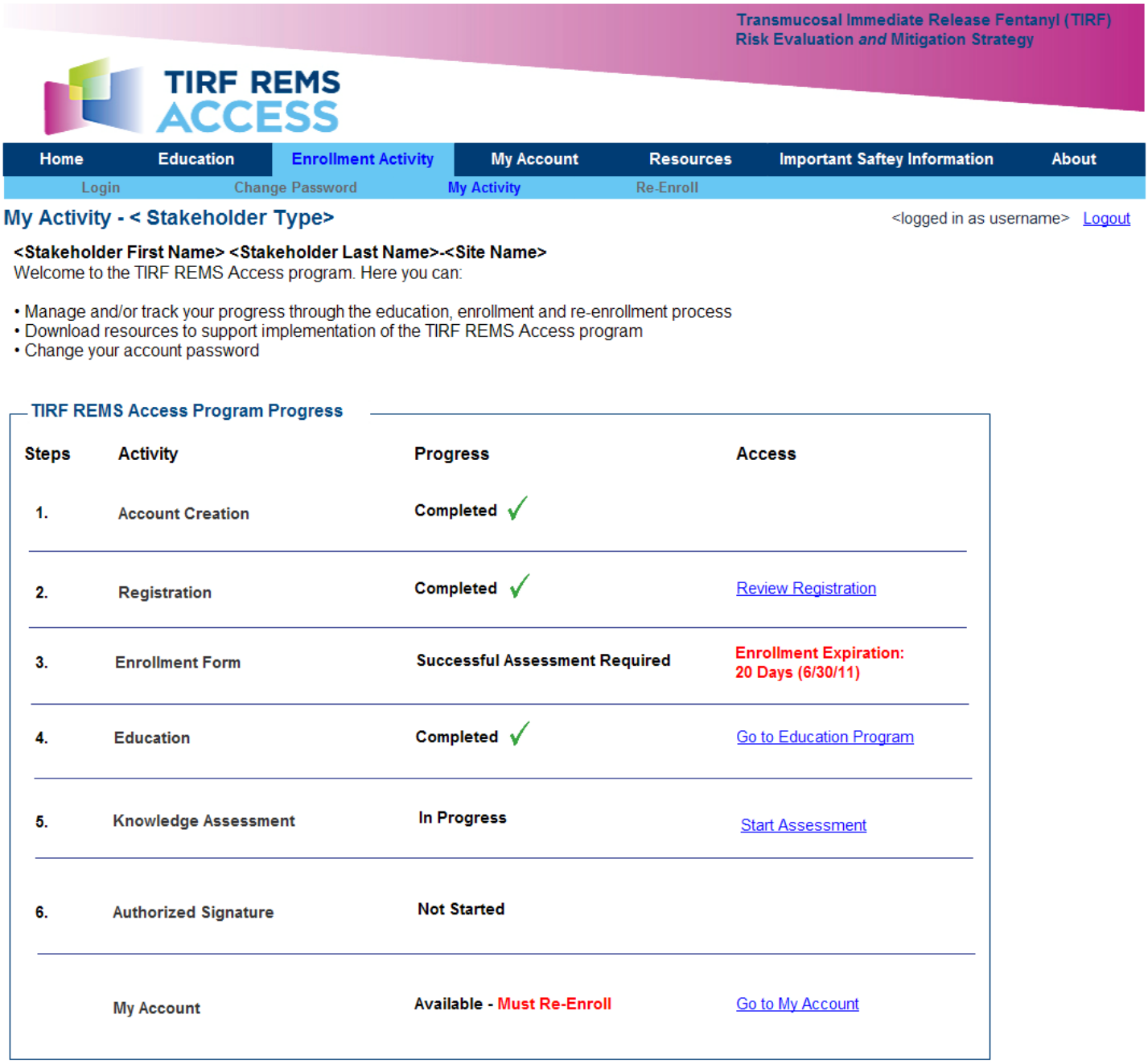
Modify Identifiers | Continue

Inpatient Pharmacy Enrollment Confirmation



TIRF REMS Access Web Prototype

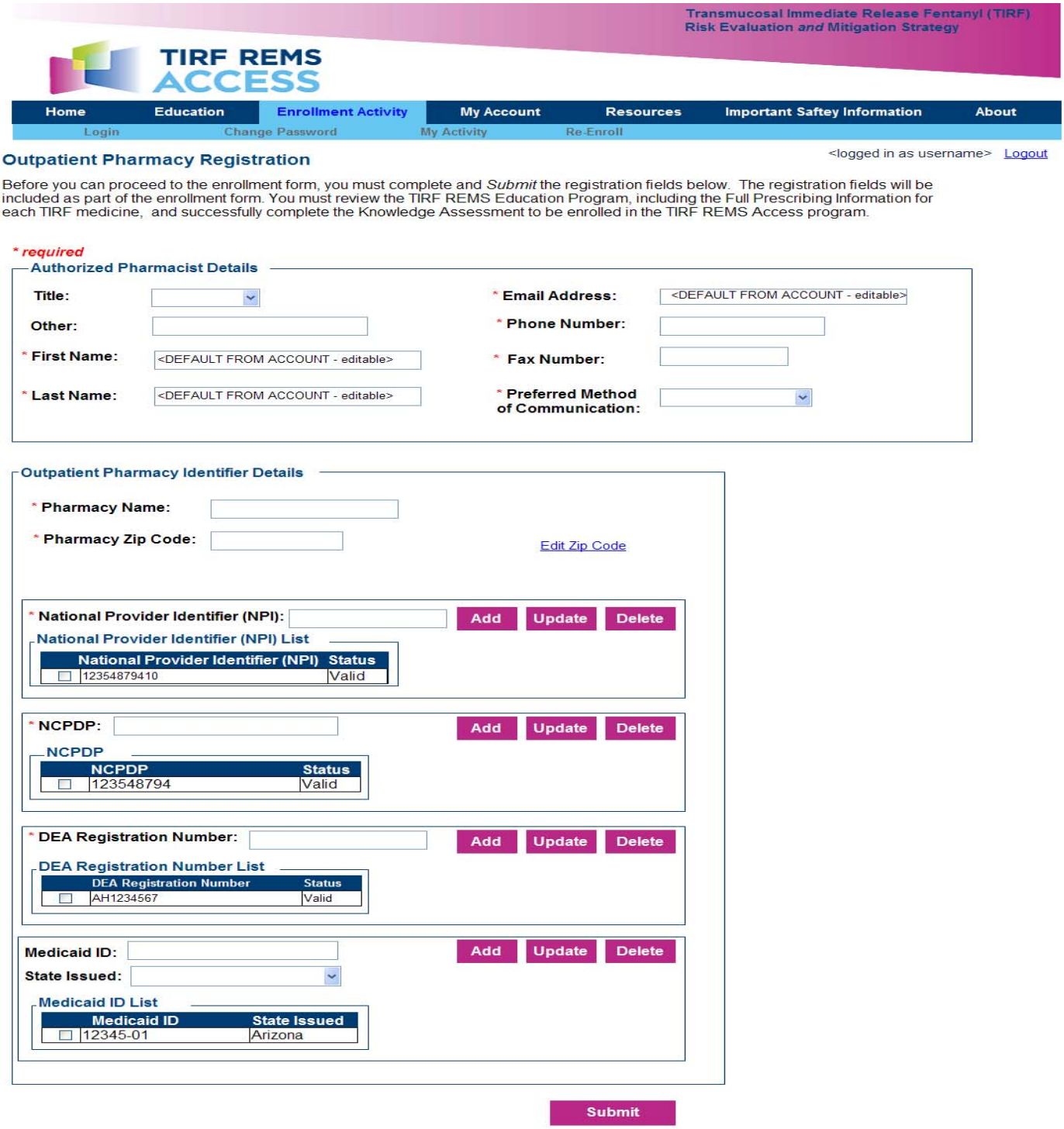
Inpatient Pharmacy Re-Enrollment



OUTPATIENT PHARMACY ENROLLMENT PROCESS

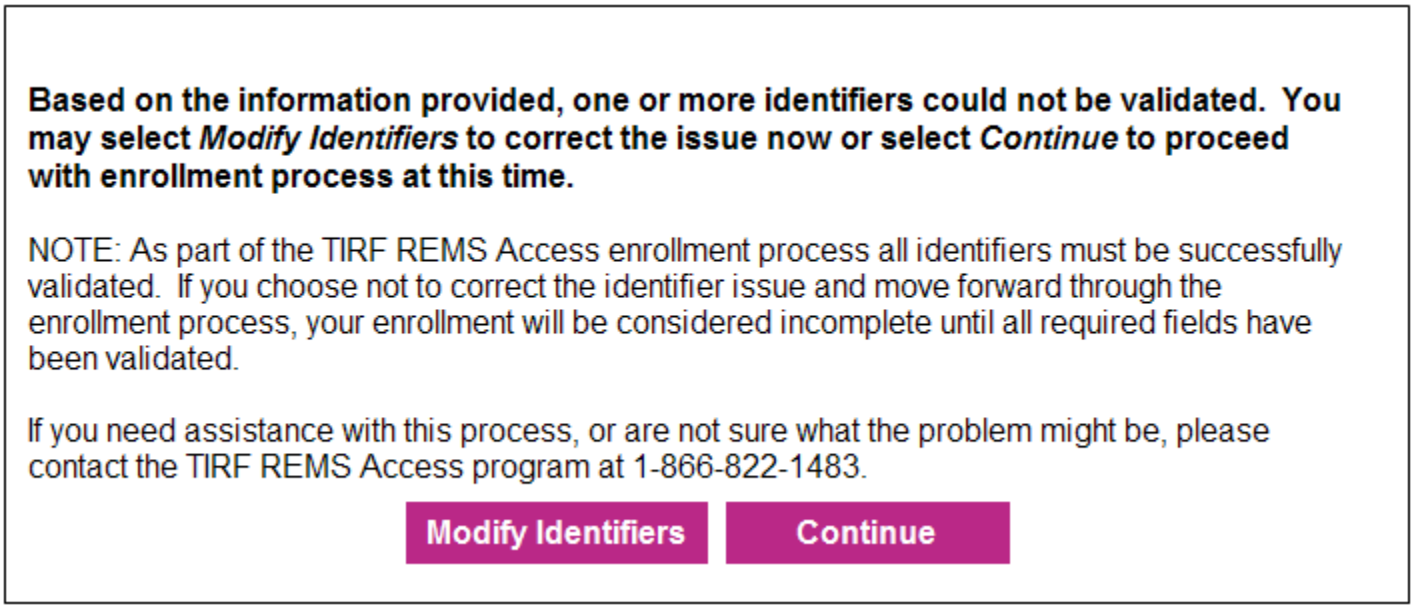
➔ See Enrollment Activity section on page 50 and follow for Outpatient

Outpatient Pharmacy Registration - Identifiers

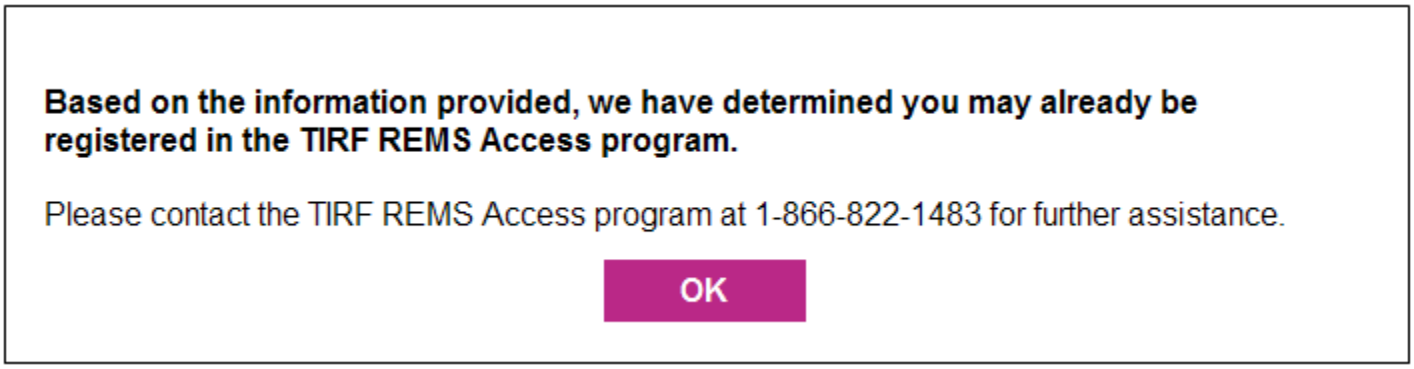


Outpatient Pharmacy Registration Warnings

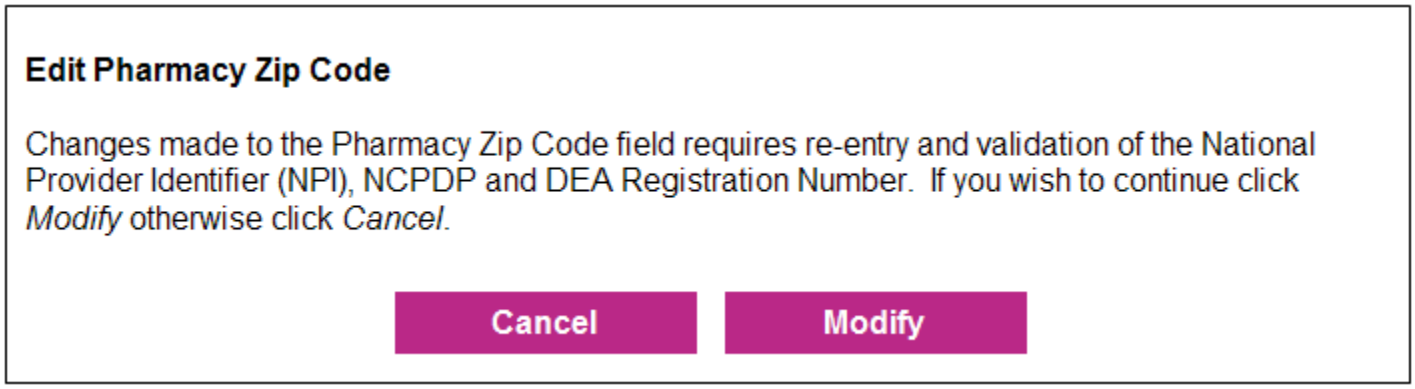
Outpatient Pharmacy Registration – Invalid Identifer Warning



Outpatient Pharmacy Registration – Duplicate Error

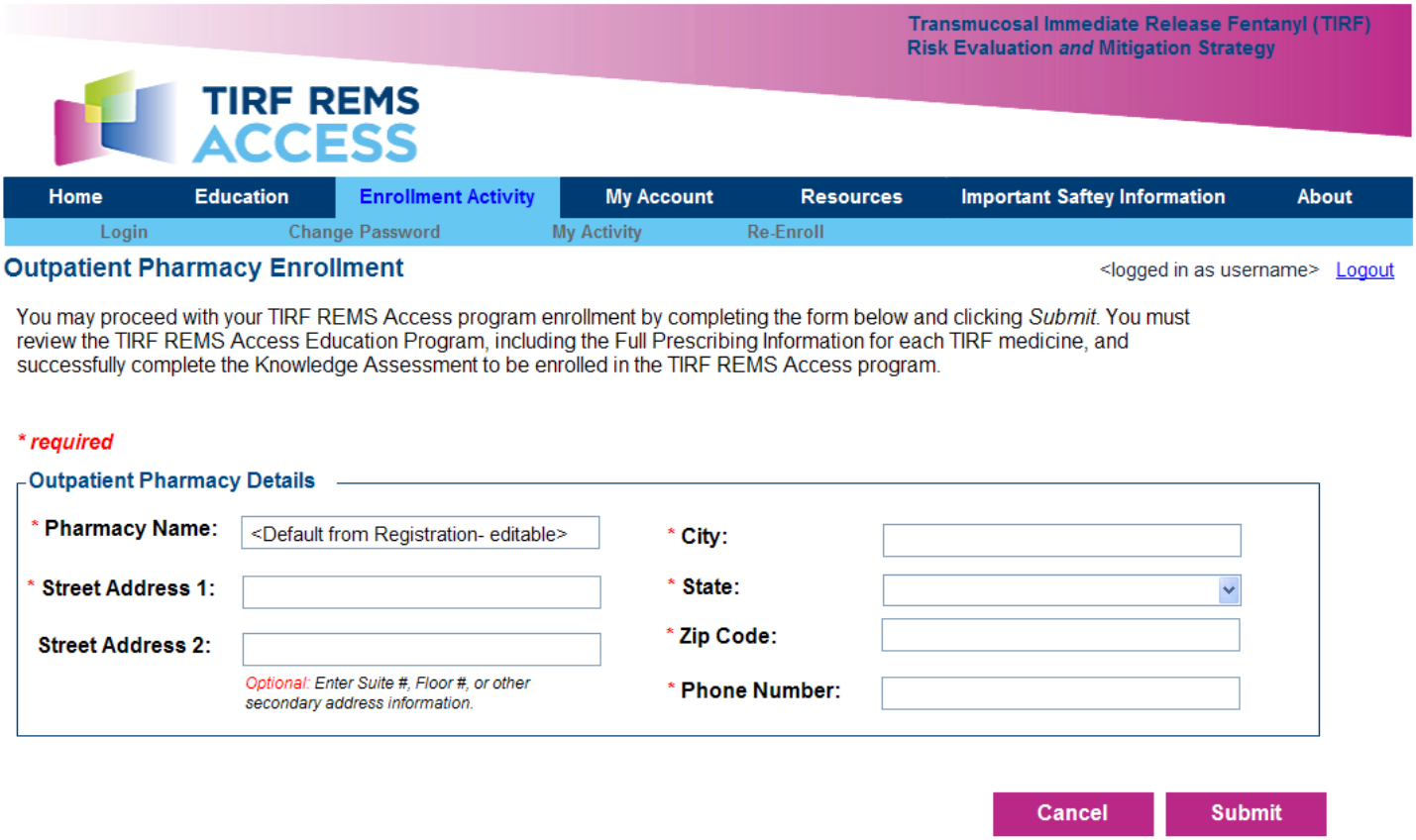


Outpatient Pharmacy Registration – Edit Pharmacy Zip Code



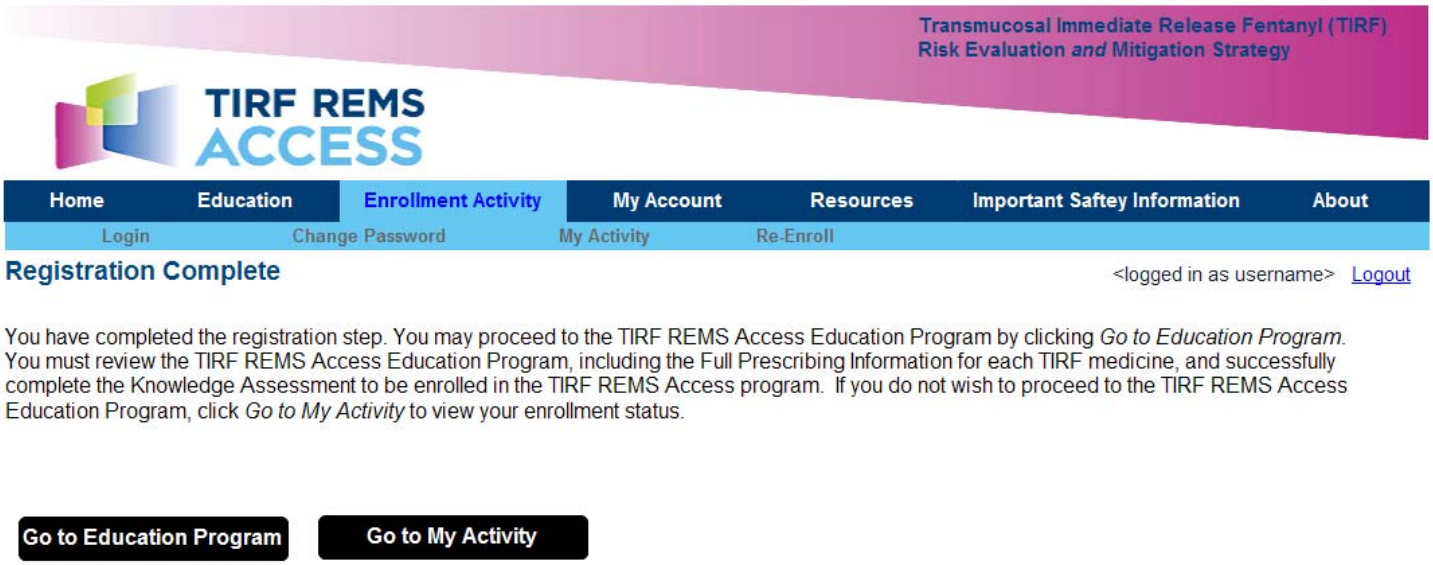
TIRF REMS Access Web Prototype

Outpatient Pharmacy Enrollment - Demographics



TIRF REMS Access Web Prototype

Registration Complete



Education and Assessment

See Education and Assessments sections starting on page 55

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TIRF REMS Access Web Prototype

Outpatient Pharmacy Enrollment Form and Attestation

Web Page Continued on Next Page

TIRF REMS Access Web Prototype

Outpatient Authorized Pharmacist Attestation

By signing below, I affirm that I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients must be the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

Signature (Full First & Last Name typed): _____ **Date:** _____

☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Print Form Submit

Web Page Continued on Next Page

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32,63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28, 51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30, 00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30,0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30, 55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30, 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access program to Providers via submission of all billing and reversal request. Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

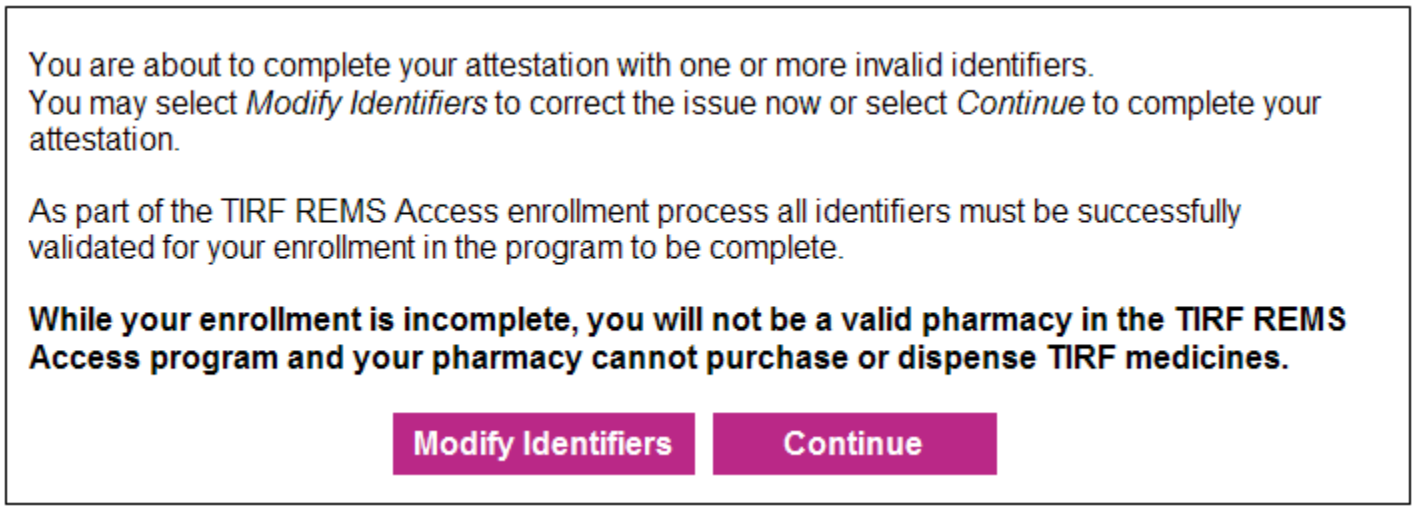
EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

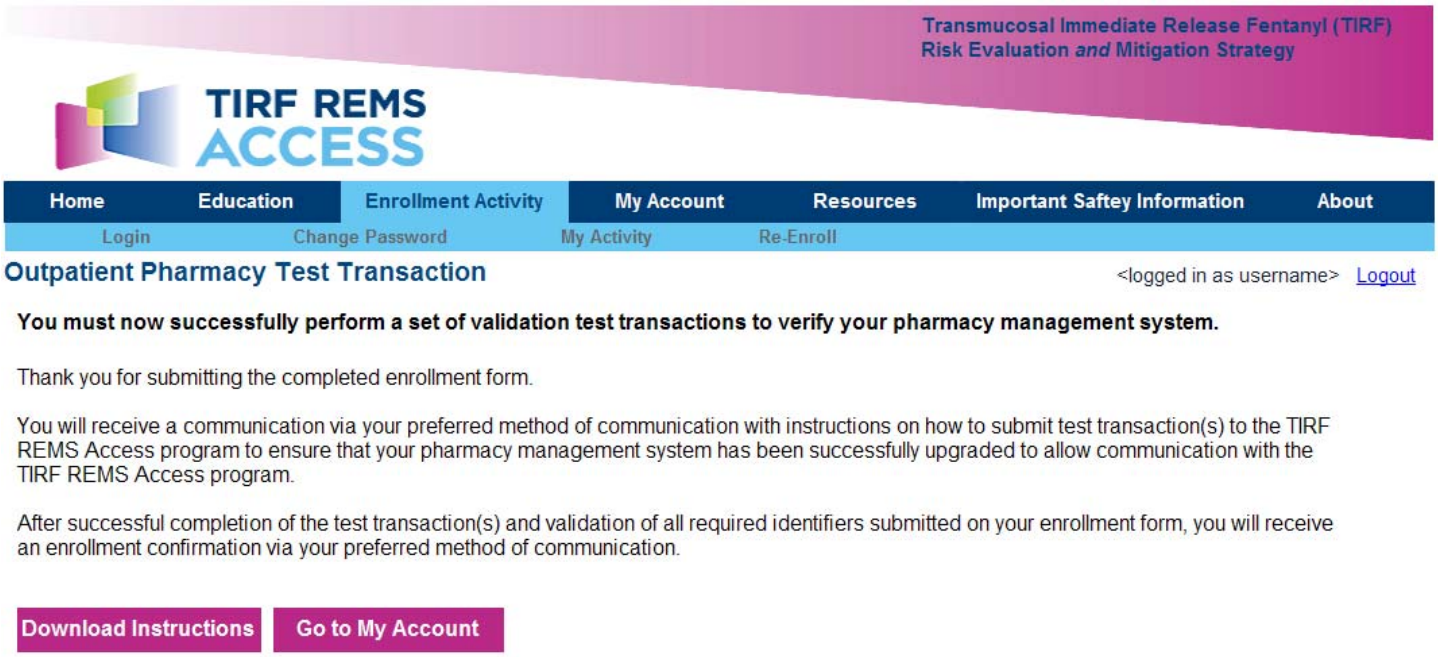
TIRF REMS Access Web Prototype

Error Message from Enrollment Page

Outpatient Pharmacy Attestation Submission - Invalid Identifiers

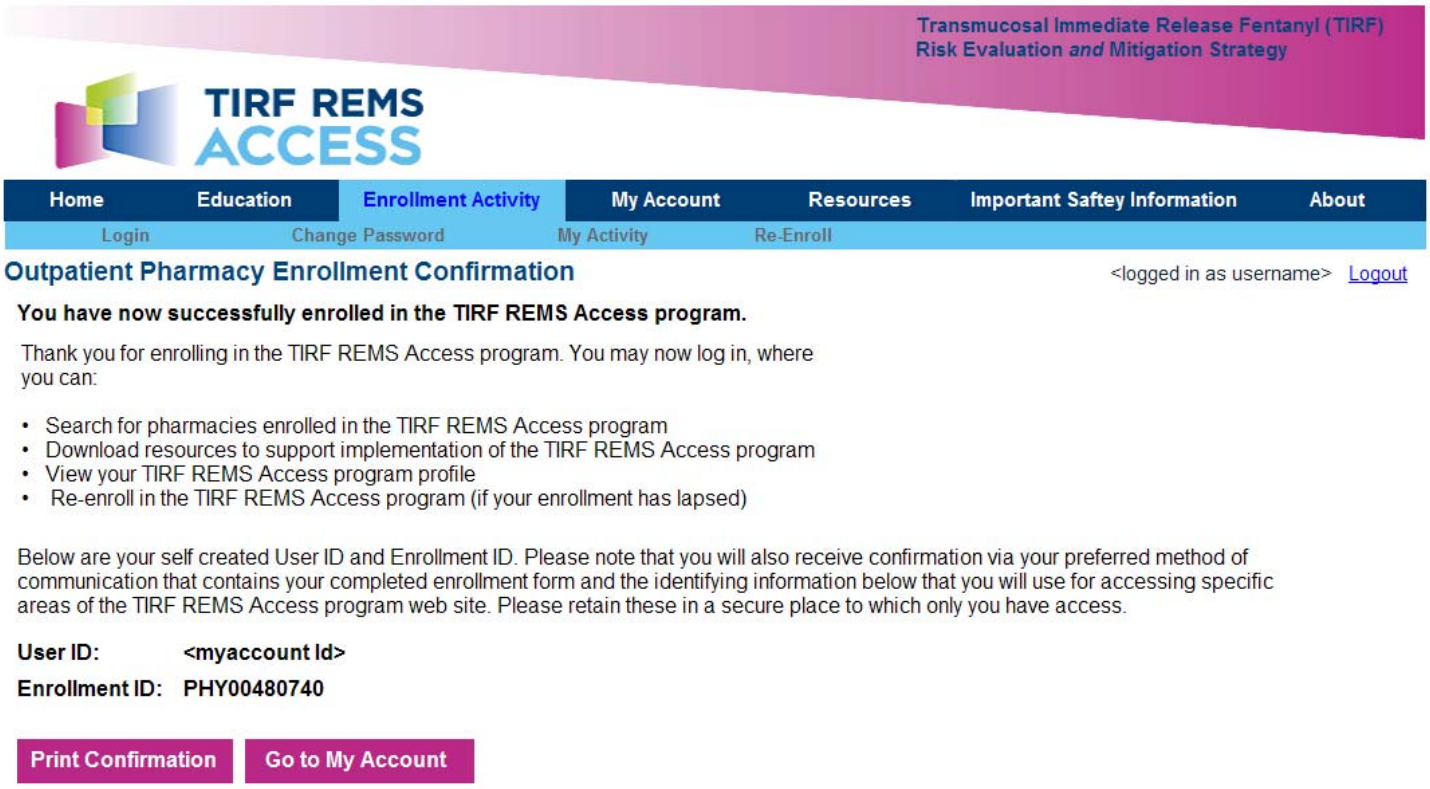


Outpatient Pharmacy Test Transaction



TIRF REMS Access Web Prototype

Outpatient Pharmacy Enrollment Confirmation



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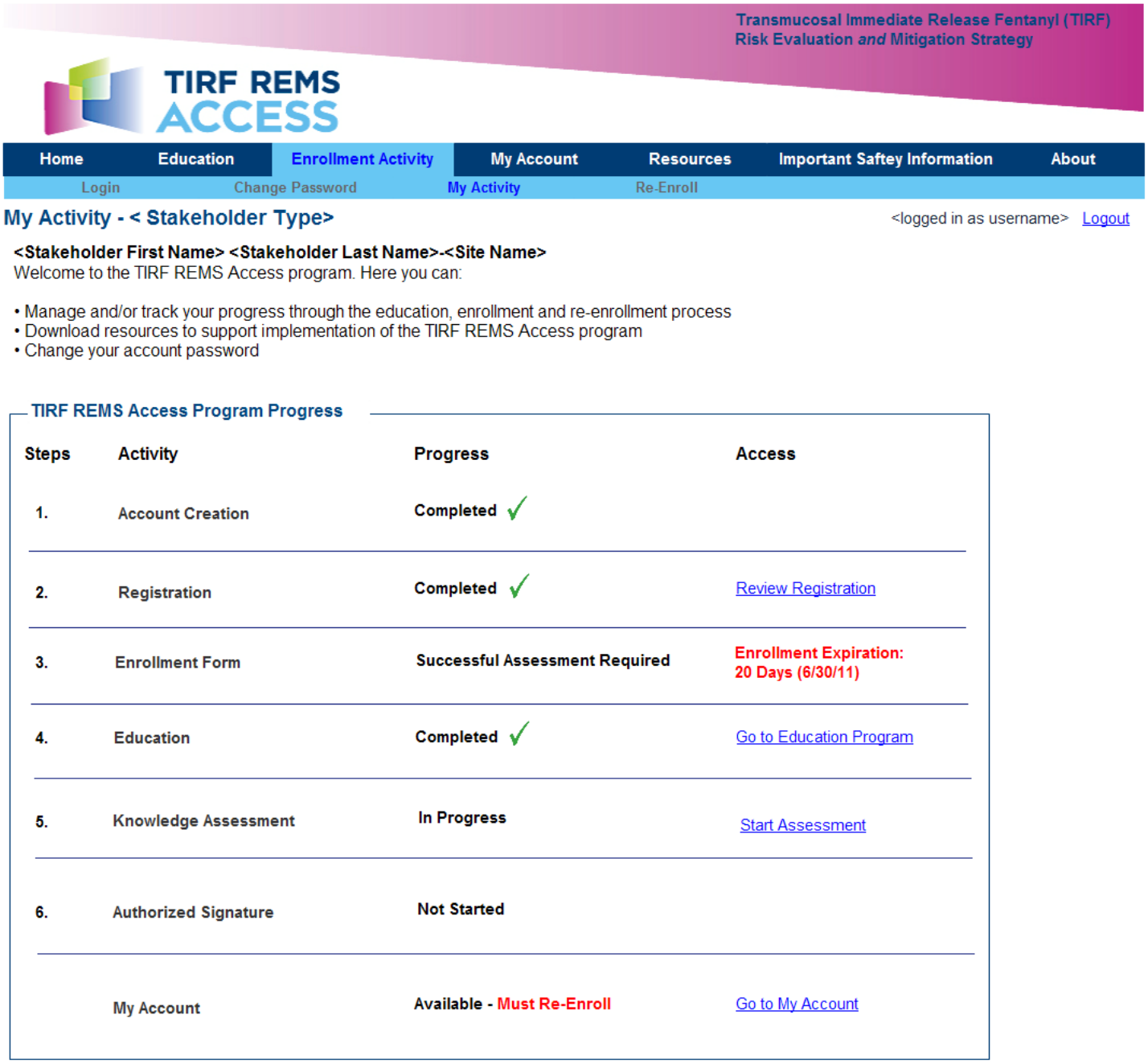
TIRF REMS Access Web Prototype

Outpatient Pharmacy Re-Enrollment

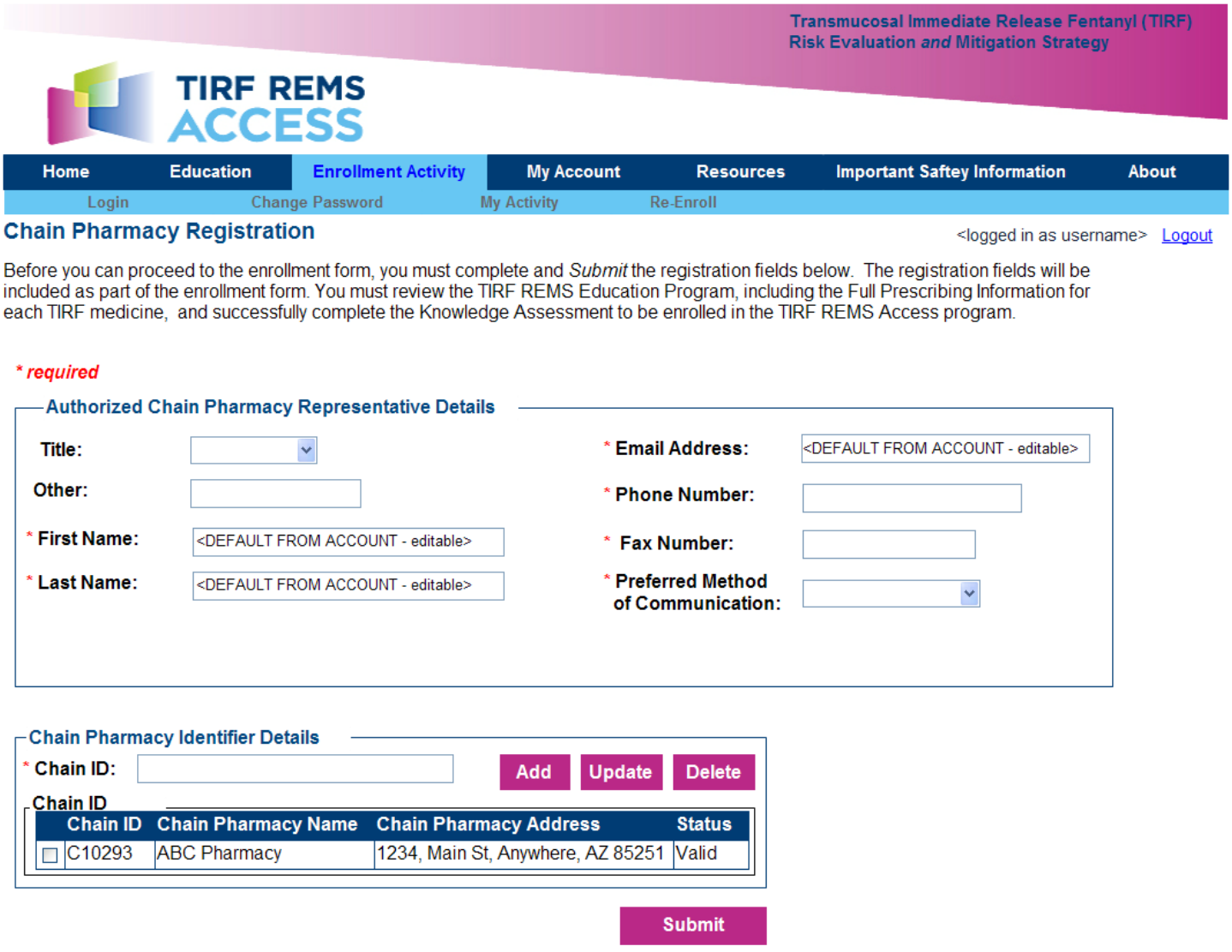


TIRF REMS Access Web Prototype

CHAIN PHARMACY ENROLLMENT PROCESS

➔ See Enrollment Activity section on page 50 and follow for Authorized Chain Pharmacy Representative

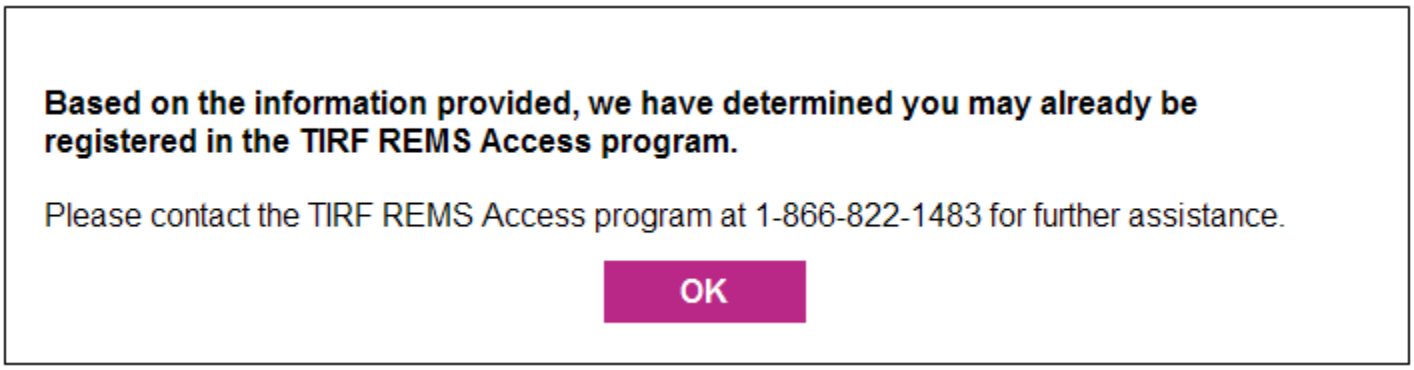
Chain Pharmacy Enrollment Registration - Identifiers



TIRF REMS Access Web Prototype

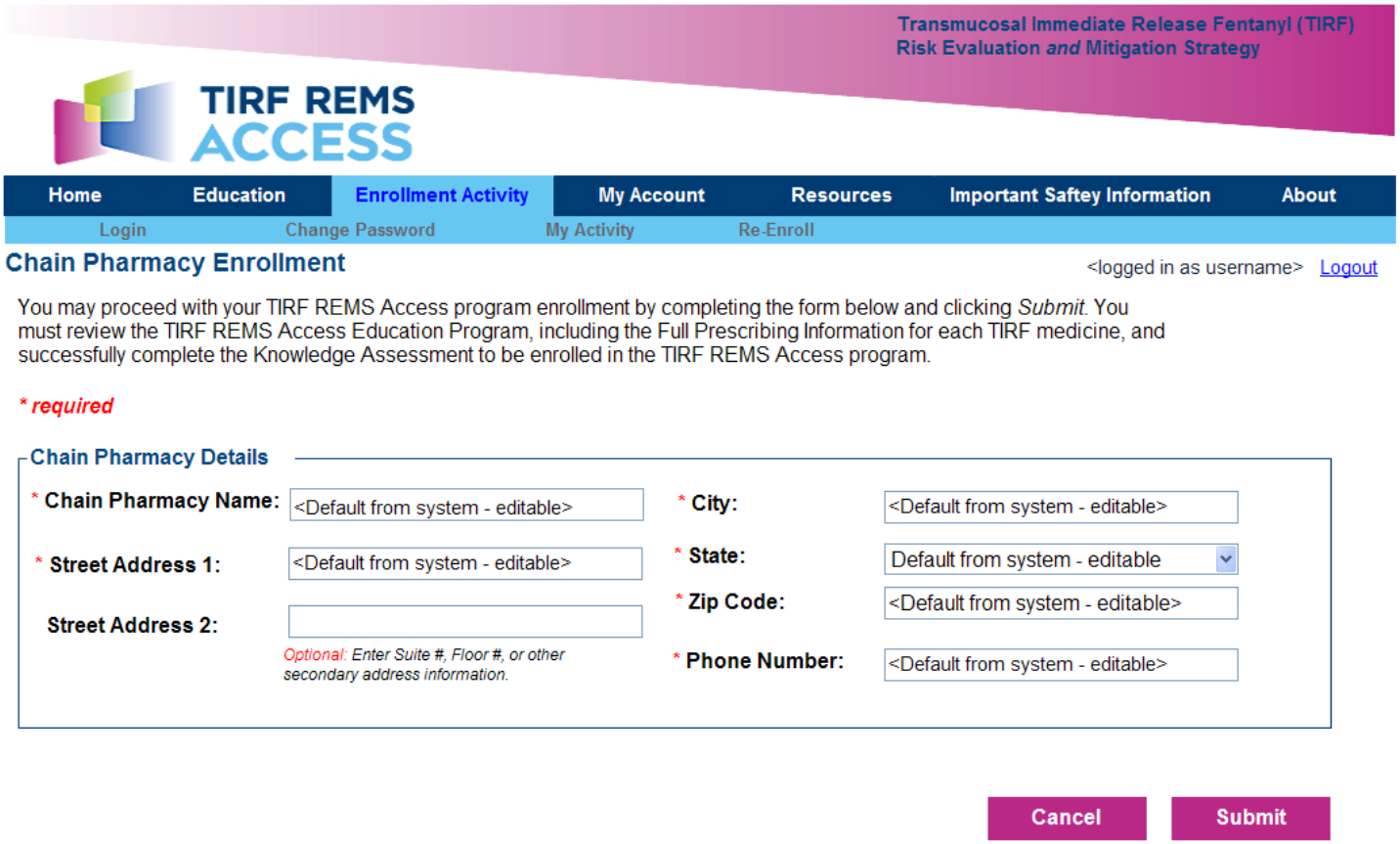
Chain Pharmacy Registration Warnings

Chain Pharmacy Rep Registration – Duplicate Error



TIRF REMS Access Web Prototype

Chain Pharmacy Registration Demographics



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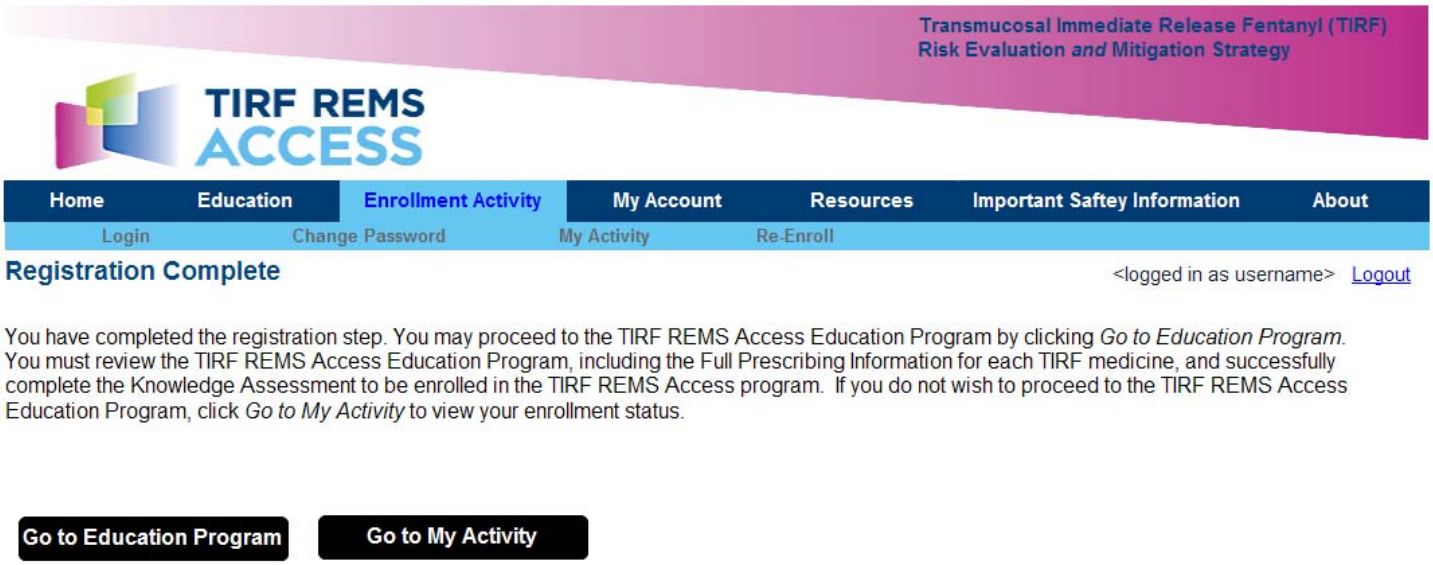
TIRF REMS Access Web Prototype

Registration Complete

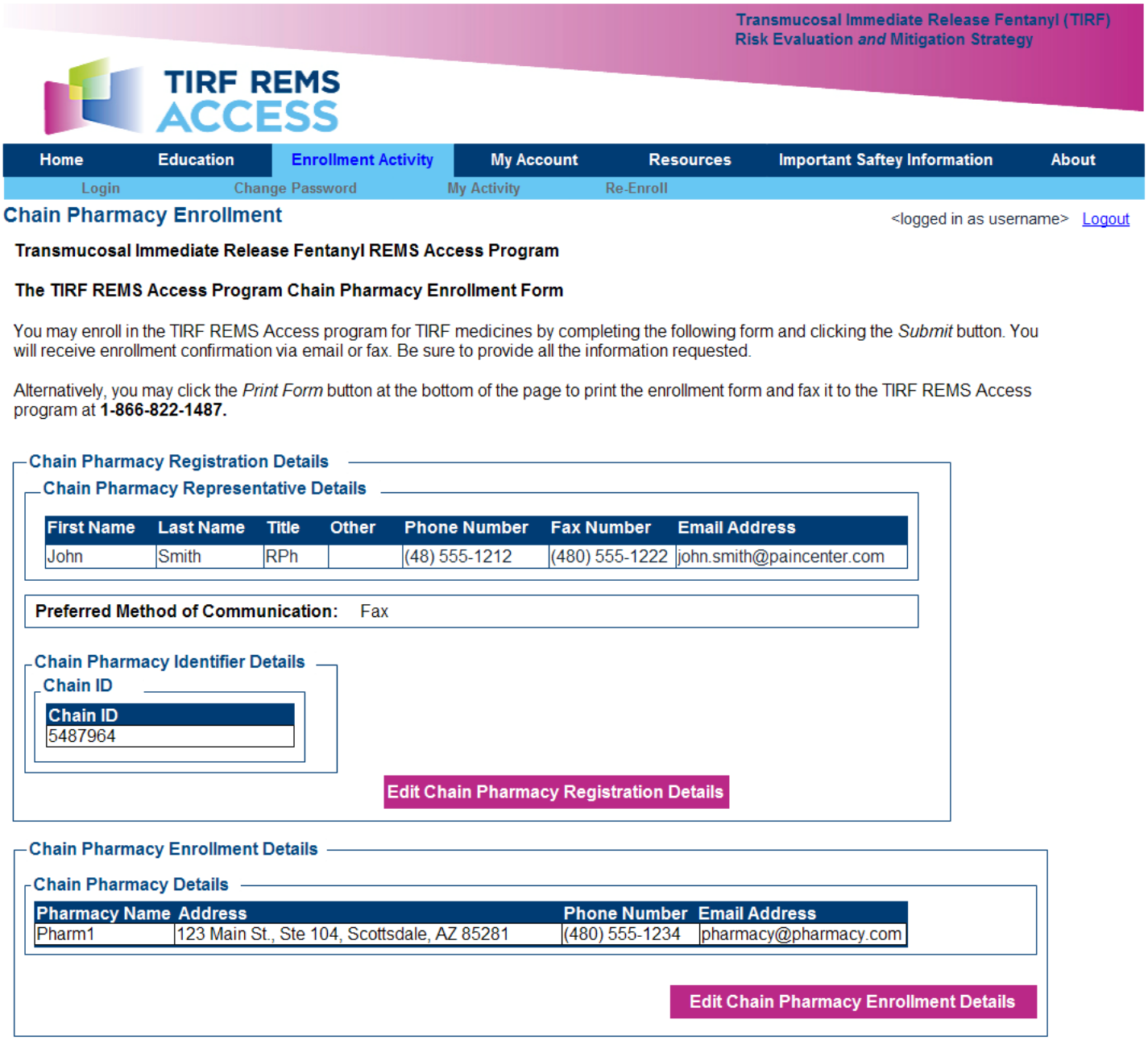


Education and Assessment

See Education and Assessments sections starting on page 55

TIRF REMS Access Web Prototype

Chain Pharmacy Enrollment and Attestation



Web Page Continued on Next Page

TIRF REMS Access Web Prototype

Authorized Chain Pharmacy Representative Attestation

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I undertsand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific recommendations (refer to the 'List of the TIRF Medicines available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients must be the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

Signature (Full First & Last Name typed): _____ **Date:** _____

☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Print Form Submit

Web Page Continued on Next Page

TIRF REMS Access Web Prototype

The TIRF REMS Access Program Additional Terms and Conditions

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Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32,63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28, 51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30, 00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30,0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30, 55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30, 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access program to Providers via submission of all billing and reversal request. Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

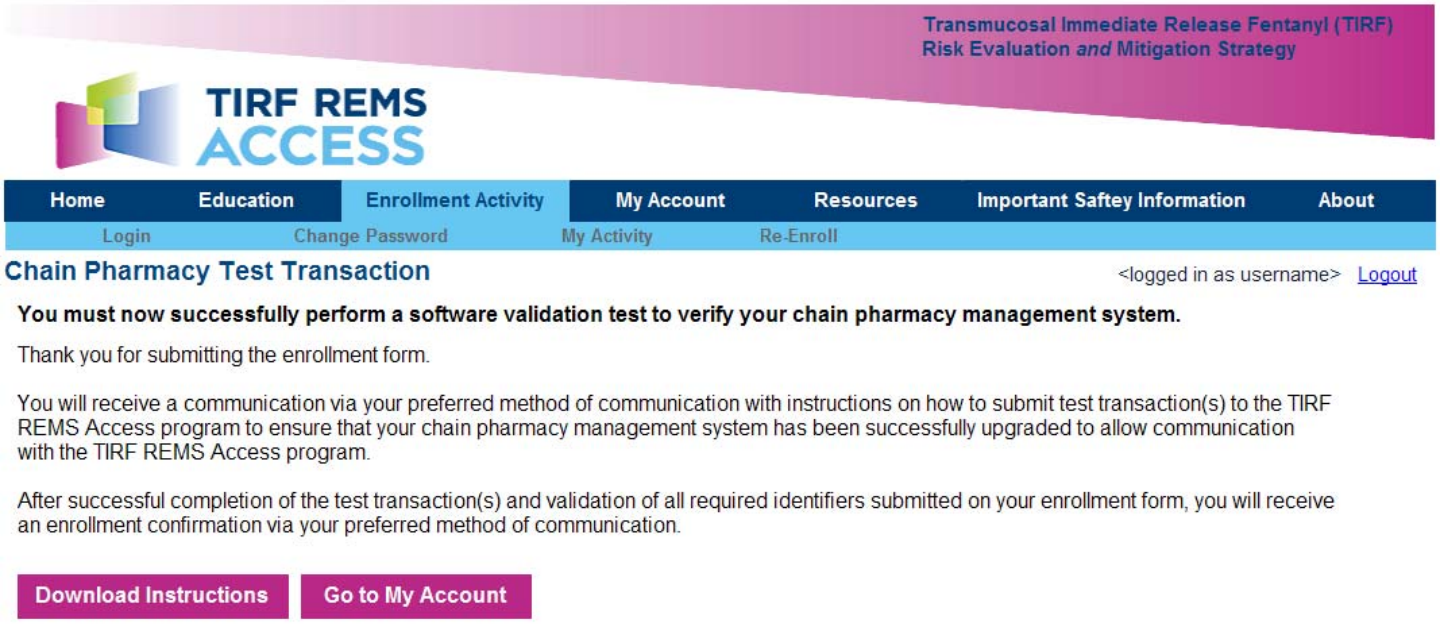
EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

TIRF REMS Access Web Prototype

Error Message from Enrollment Page

Chain Pharmacy Test Transaction



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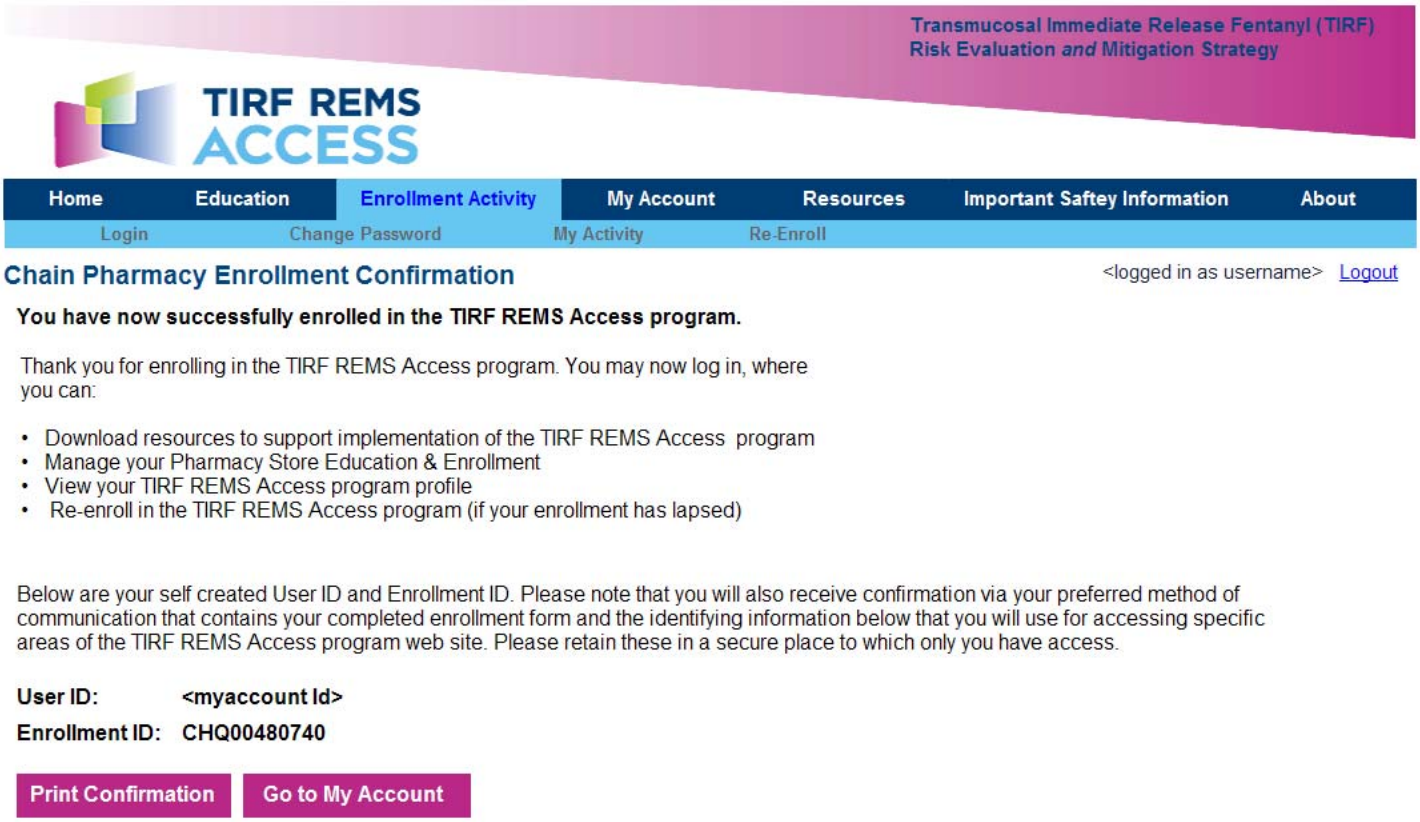
TIRF REMS Access Web Prototype

Chain Enrollment Confirmation



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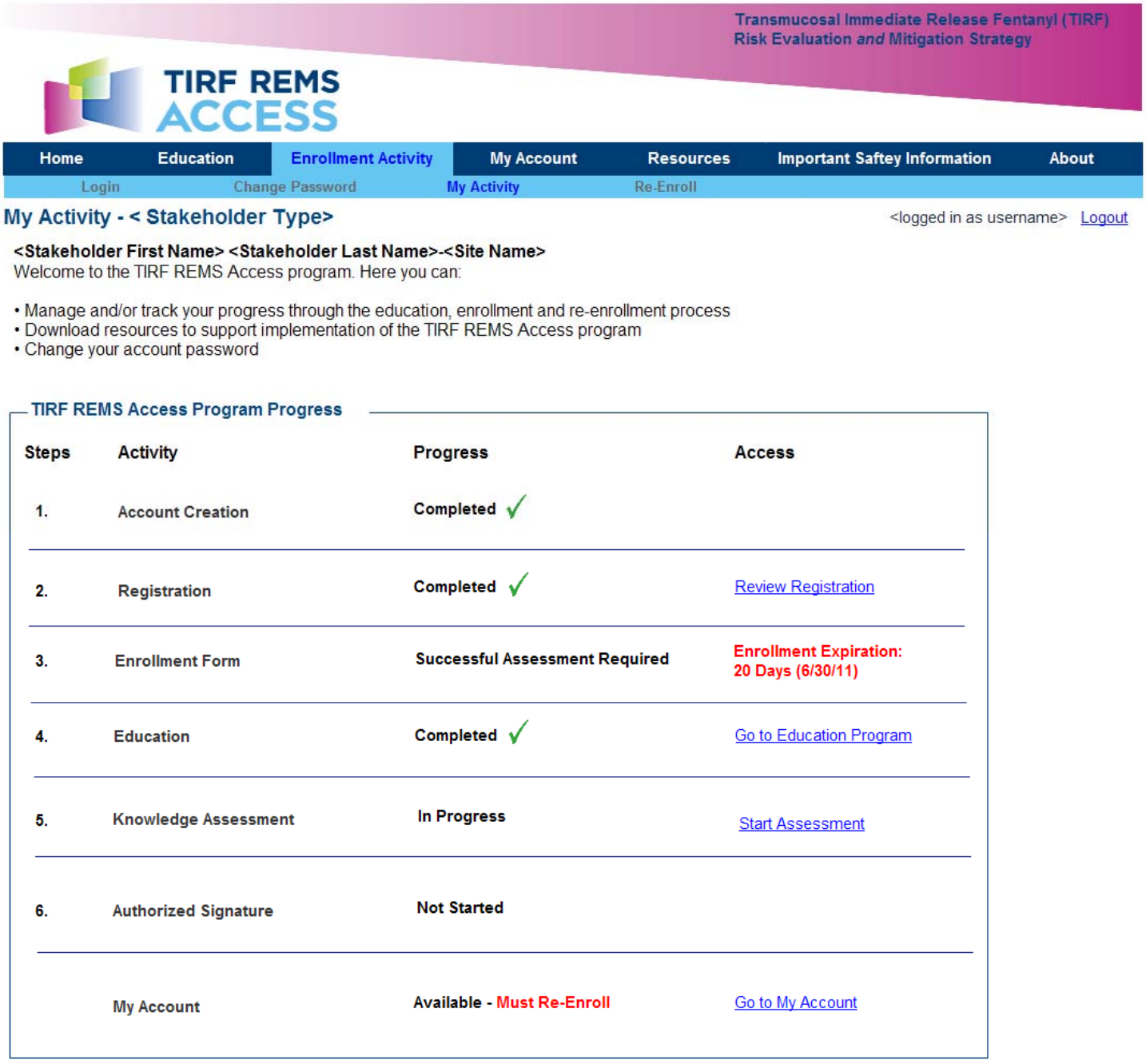
TIRF REMS Access Web Prototype

Chain Pharmacy Re-Enrollment

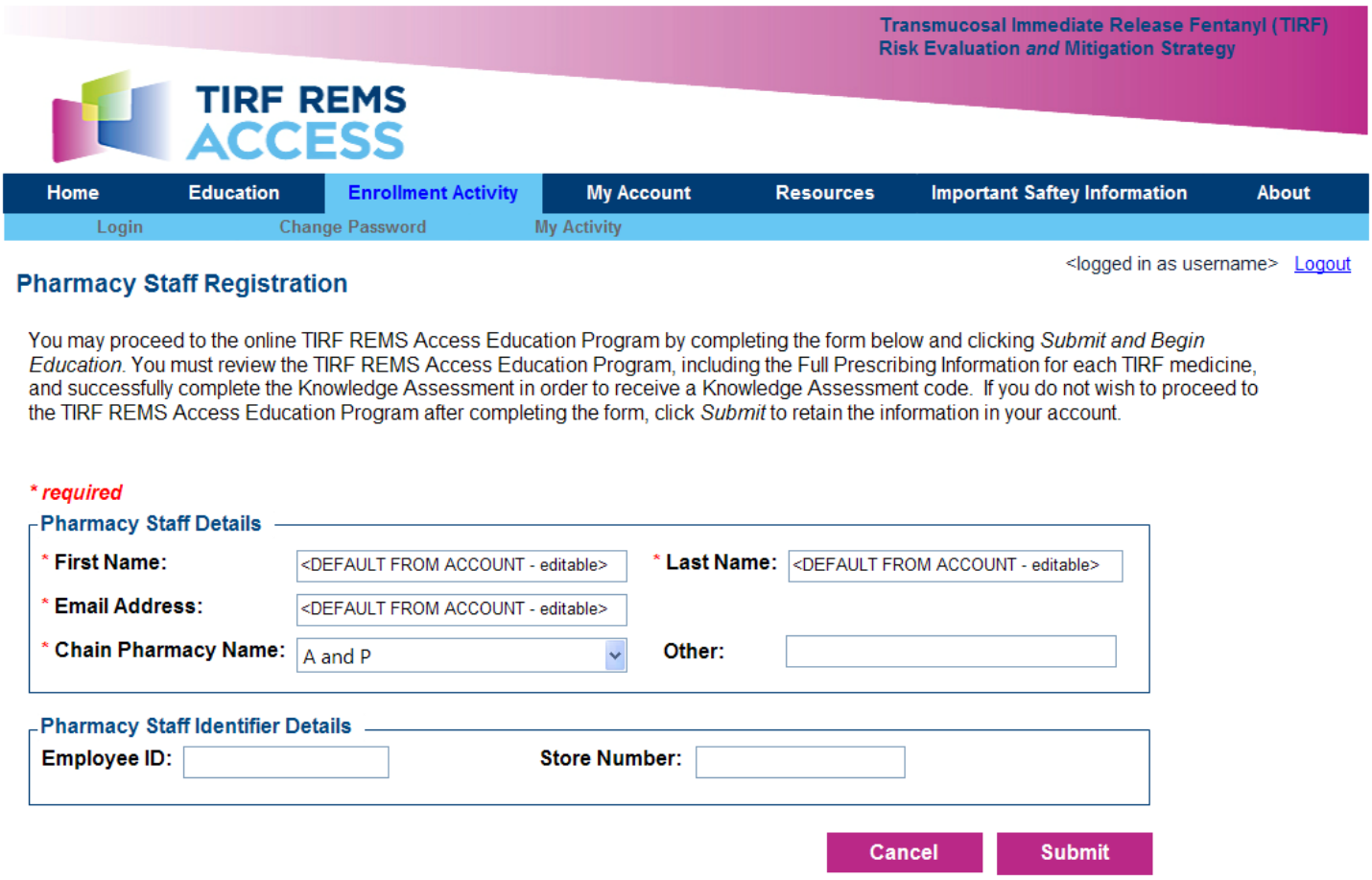


TIRF REMS Access Web Prototype

PHARMACY STAFF REGISTRATION PROCESS

➔ See Enrollment Activity section on page 50 and follow for Pharmacy Staff

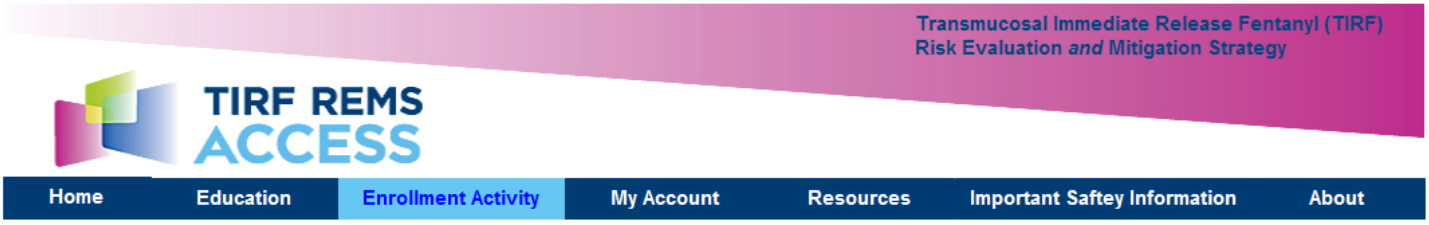
Pharmacy Staff Registration



Education and Assessment

See Education and Assessments sections starting on page 55

Pharmacy Staff Assessment Results - Correct



<logged in as username> Logout

Knowledge Assessment

You have now completed the assessment.

Congratulations!

You answered all the questions correctly and have passed the assessment.

Your Knowledge Assessment code is displayed below.

Knowledge Assessment Results

Question #	Your Answer
1	D
2	A
3	D
4	A
5	D
6	B
7	C
8	D
9	D
10	D
11	B

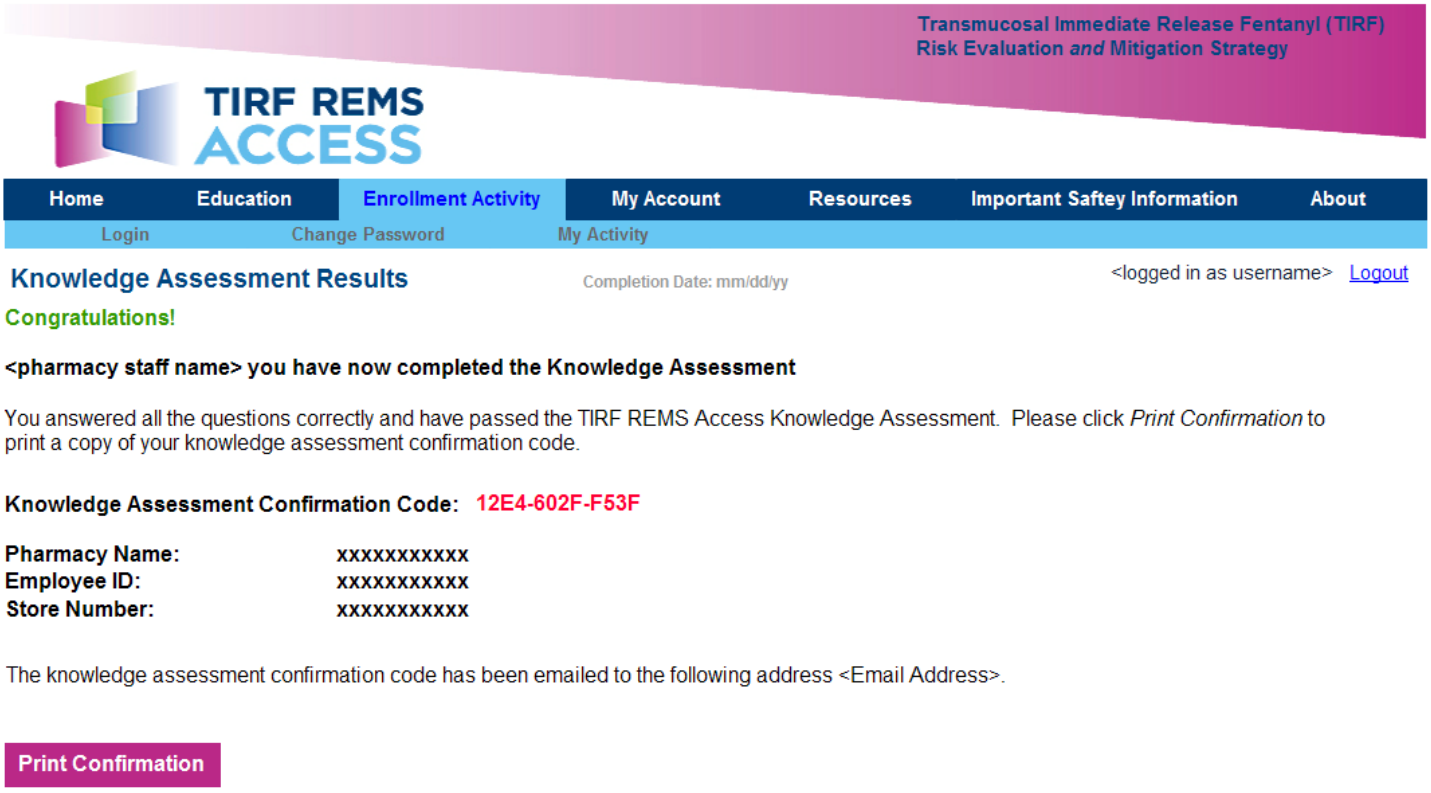
Knowledge Assessment Confirmation Code: 12E3-64B5-570A

Your knowledge assessment confirmation code has been emailed to the following address: xxx.xxxx@xxxxxxxx.com

Print Confirmation

TIRF REMS Access Web Prototype

Pharmacy Staff Knowledge Assessment Confirmation



TIRF REMS Access Web Prototype

MY ACCOUNT - PRESCRIBER

Prescriber Home

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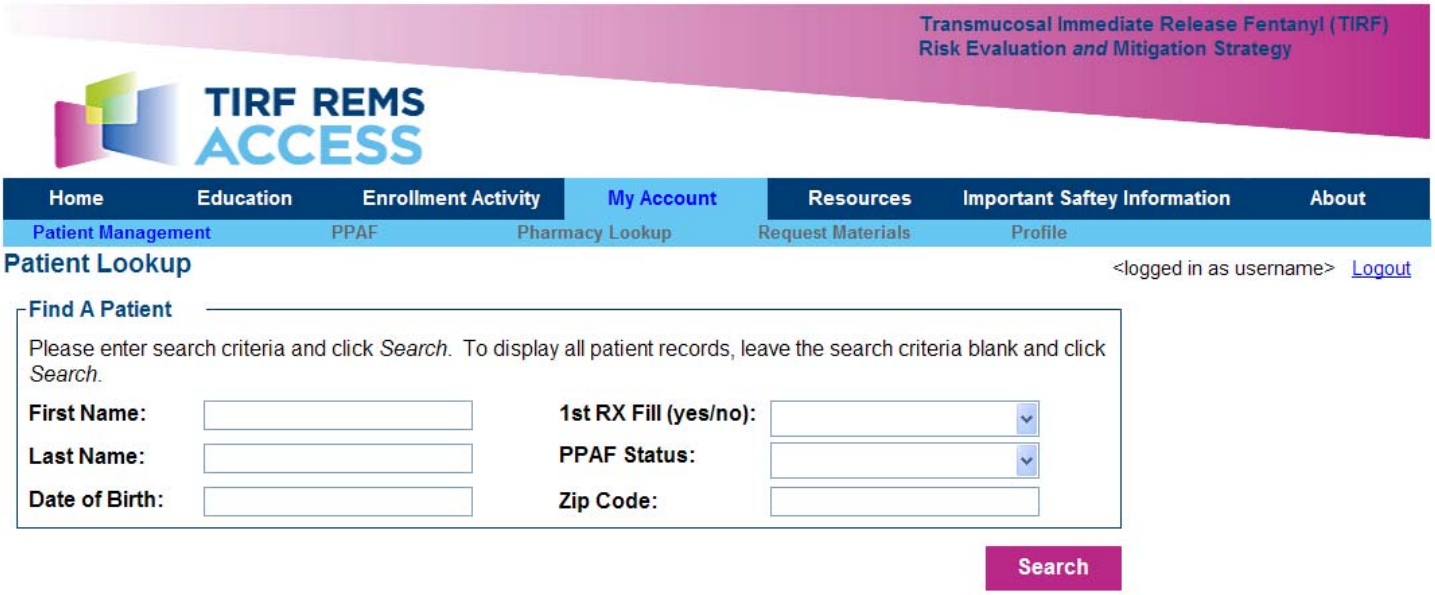
TIRF REMS Access Web Prototype

Patient Management



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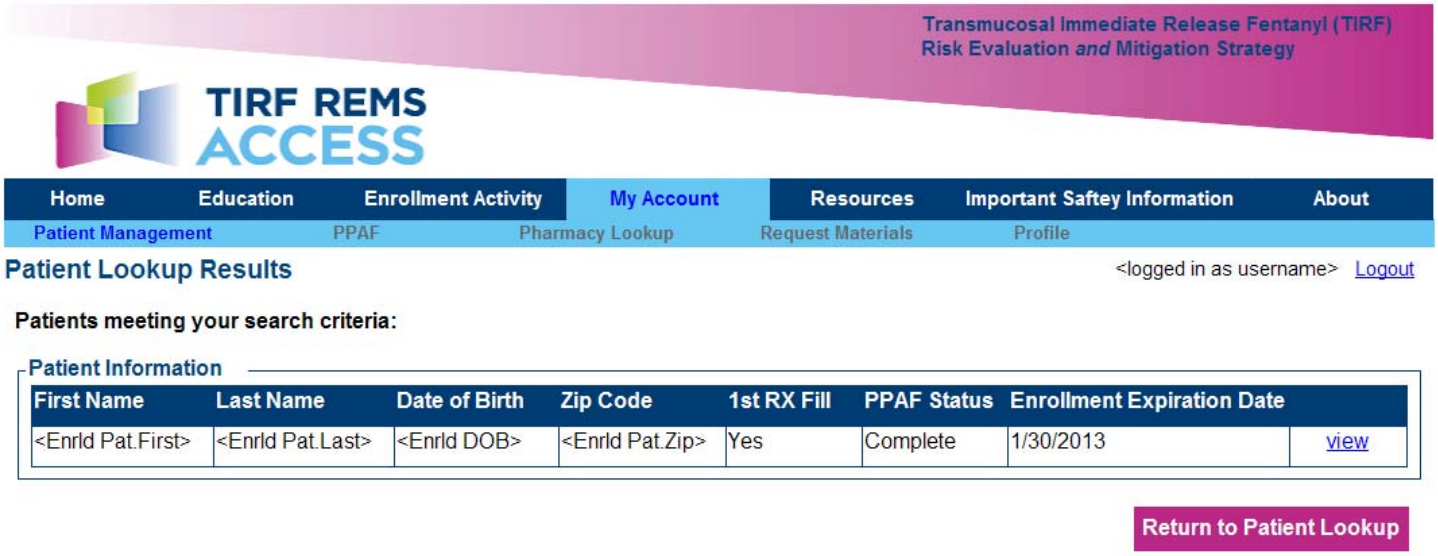
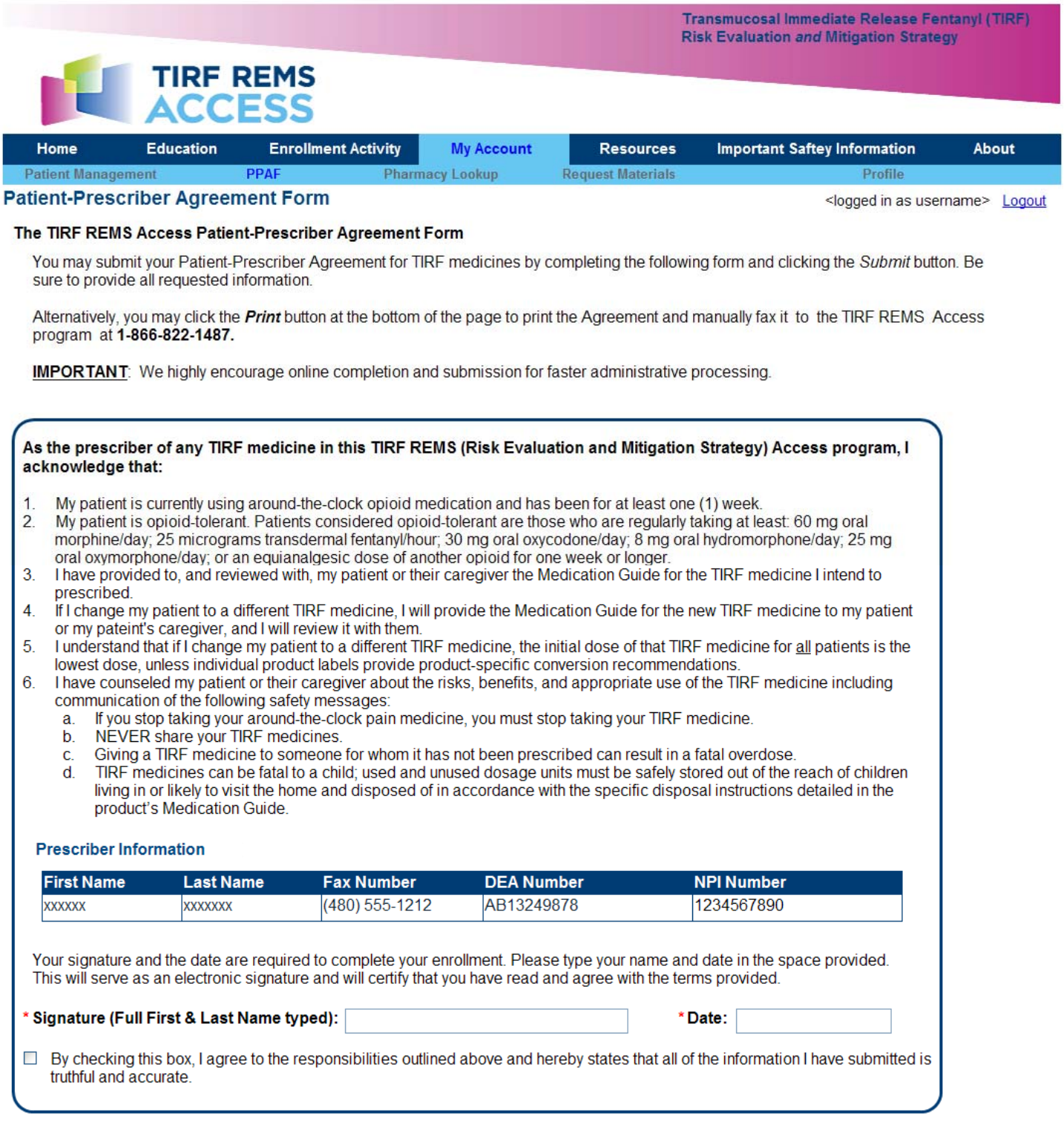
TIRF REMS Access Web Prototype

Patient Management Results



TIRF REMS Access Web Prototype

Patient Prescriber Agreement Form



Web Page Continued on Next Page

TIRF REMS Access Web Prototype

As the patient being prescribed a TIRF Medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

Web Page Continued on Next Page

TIRF REMS Access Web Prototype

** required*

Patient:

*** Patient First Name:** <Patient First Name>

*** Patient Last Name:** <Patient Last Name>

*** Date of Birth:** <Patient DOB>

*** Phone Number:** <Patient Phone>

*** State:**

*** Zip Code:** <Patient Zip Code>

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

*** Signature (Full First & Last Name Typed):** *** Date:** *MM/DD/YYYY*

☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Patient Representative: (if required)

*** First Name:** <Patient Rep First Name>

*** Last Name:** <Patient Rep Last Name

*** Relationship to Patient:** <Relationship>

Your signature and the date are required to complete your enrollment. Please type your name and date in the space provided. This will serve as an electronic signature and will certify that you have read and agree with the terms provided.

*** Signature (Full First & Last Name Typed):** *** Date:** *MM/DD/YYYY*

☐ By checking this box, I agree to the responsibilities outlined above and hereby state that all of the information I have submitted is truthful and accurate.

Please **print and sign two (2) copies** of PPA Form; one for the patient and one for the patient's file in the office. The form can be submitted either electronically or printed and faxed to the TIRF REMS Access call center (1-866-822-1487).

Print **Submit**

Web Page Continued on Next Page

TIRF REMS Access Web Prototype

Patient Privacy Notice for the TIRF REMS Access Program

I allow each of my doctors, pharmacists, and other healthcare providers to share personal- information, that can be used to identify myself. This includes information about my medical problems, diseases, treatment, lab and prescription information, name, address and telephone number. This information is my "Health Information".

This information may be given to the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Evaluate the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.

III. Provide me with educational information about the TIRF REMS Access program.

IV. Contact my health care providers to collect, enter and keep my Health Information in a secure TIRF REMS Access database.

V. Report to the FDA, about side effected from TIRF medicines and the TIRF REMS Access program effectiveness.

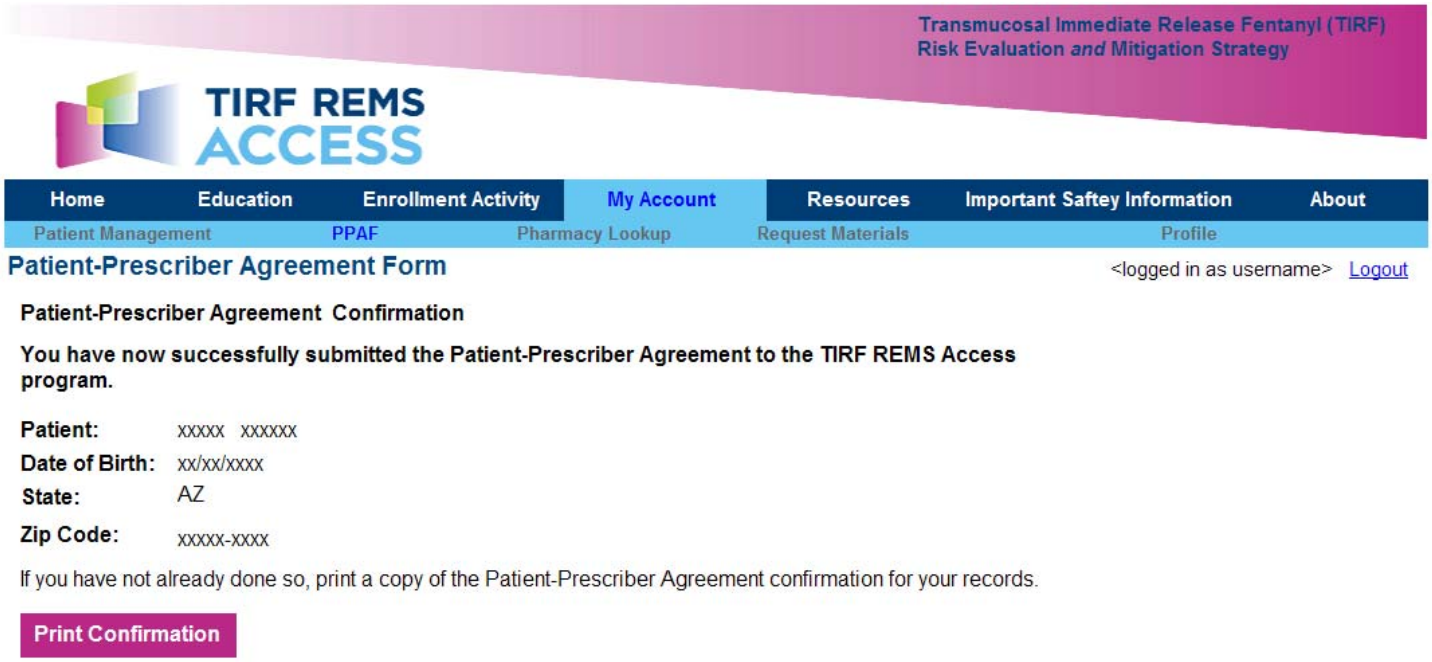
I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. The TIRF REMS Access program shall contact my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

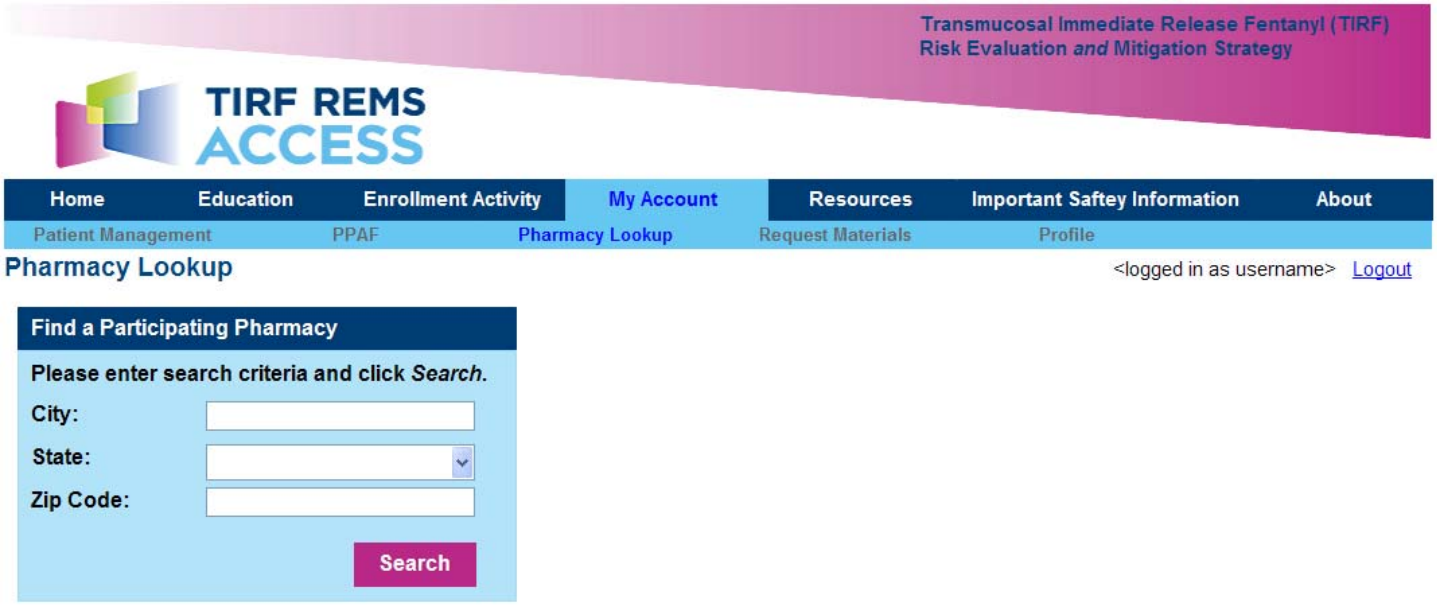
End of Web Pag

Patient Prescriber Agreement Confirmation



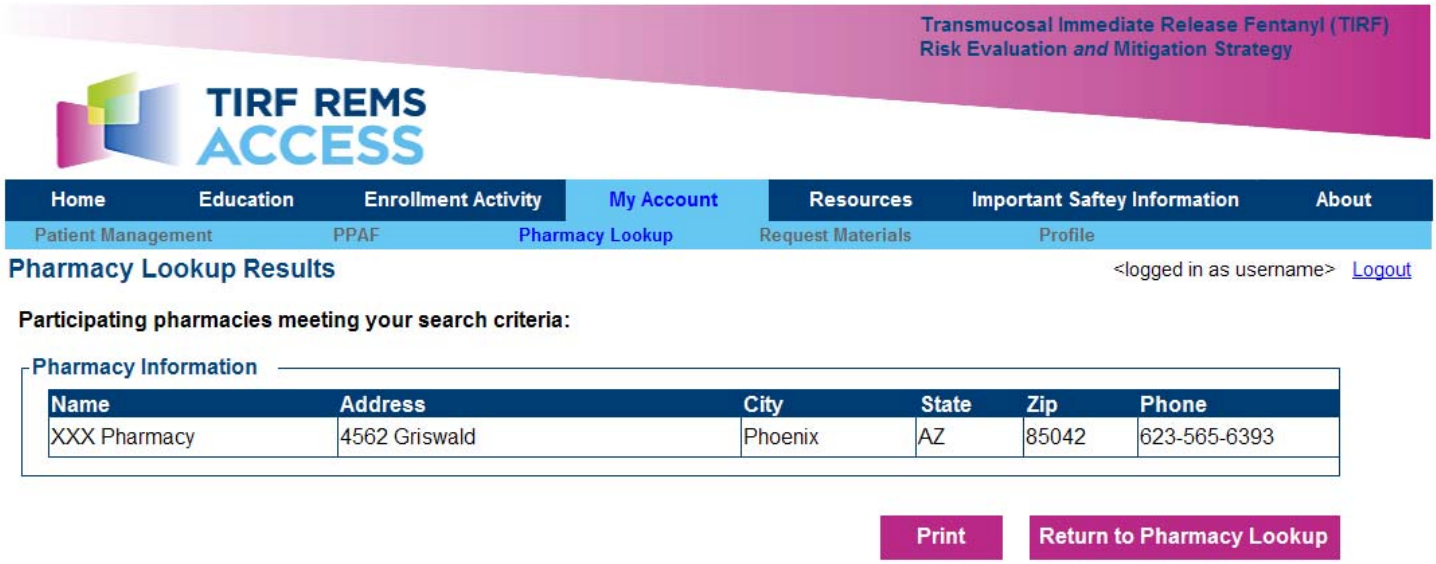
TIRF REMS Access Web Prototype

Pharmacy Lookup



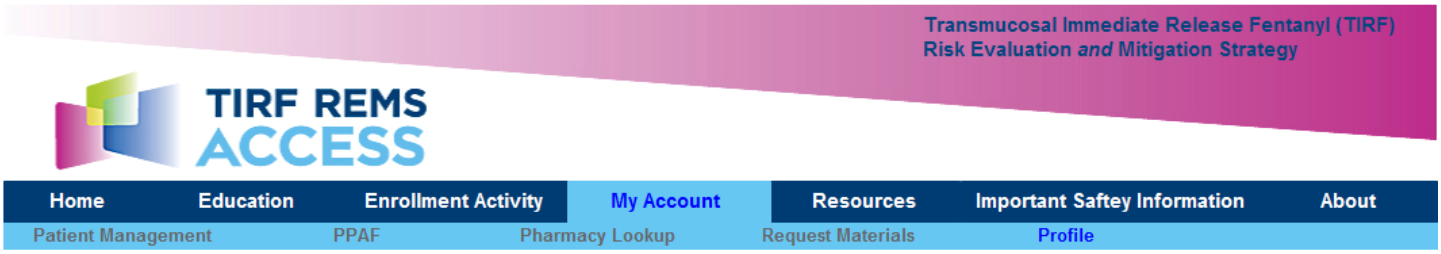
TIRF REMS Access Web Prototype

Pharmacy Lookup Results



TIRF REMS Access Web Prototype

Prescriber Profile



Prescriber Profile

<logged in as username> Logout

Your profile information is displayed below. If you wish to change additional profile Information, please call the TIRF REMS Access program at **1-866-822-1483**.

Enrollment Status

Enrollment ID	Enrollment Status	Enrollment Expiration
PRSxxxxxxxx	Enrolled	12/02/2011

Prescriber Details

Name	Credentials	Fax	Phone	Email
XXXXX XXXXX	M.D	XXX-XXX-XXXX (Primary Location fax)	XXX-XXX-XXXX (Primary Location phone)	XXX@XXX.com

Preferred Method of Communication: <preferred method>

Primary Practice Location Details

Site Name	Address	City	State	Zip	Fax	Phone
XXXXXXXX	##### XXXXX	XXXXX	XX	XXXXX	XXX-XXX-XXXX	XXX-XXX-XXXX

Secondary Practice Location Details

Site Name	Address	City	State	Zip	Fax	Phone
XXXXXXXX	##### XXXXX	XXXXX	XX	XXXXX	XXX-XXX-XXXX	XXX-XXX-XXXX

National Provider Identifier (NPI)

NPI
1234567890

DEA Number(s)

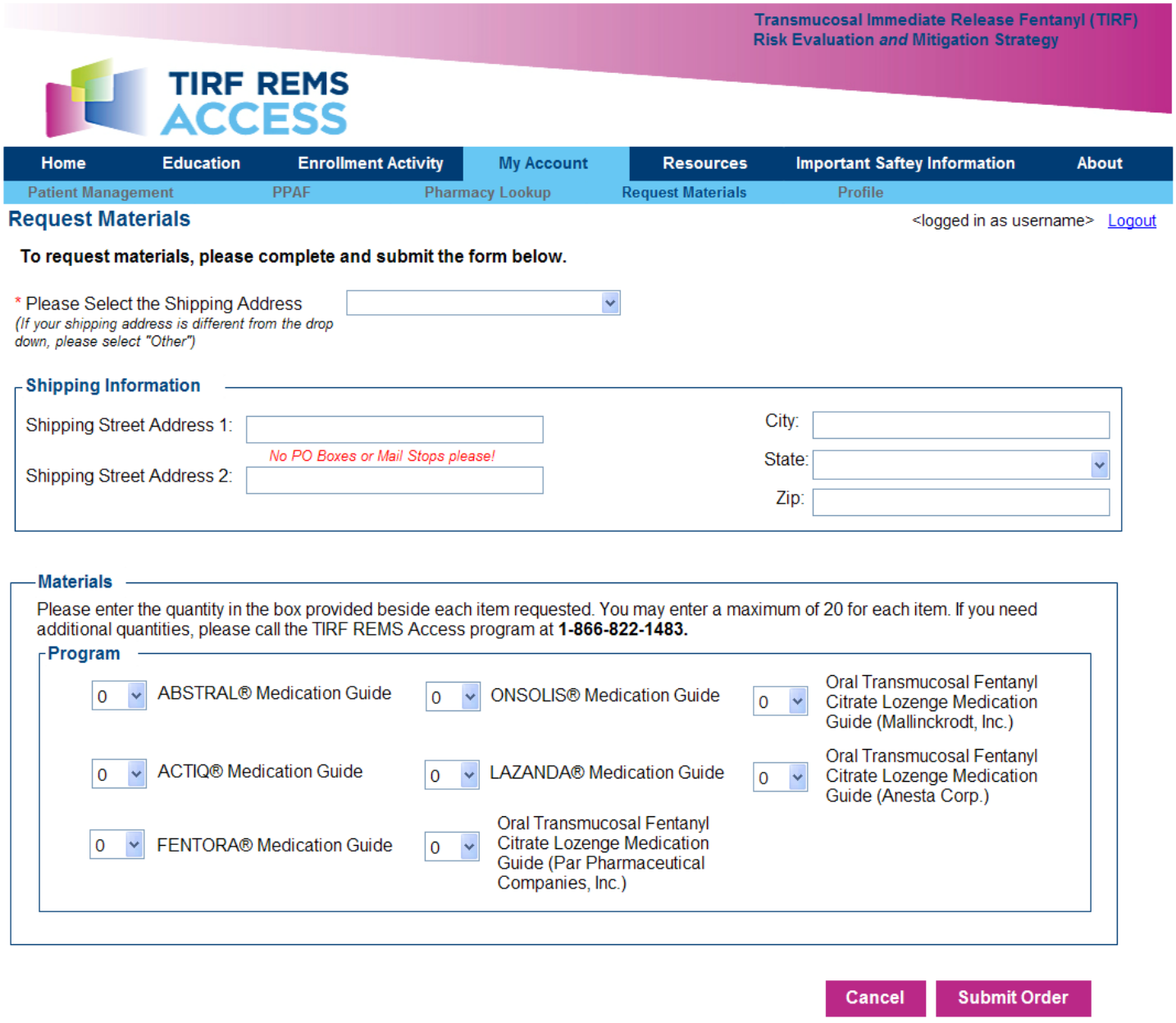
DEA Registration Number	Schedule II
AH1234567	Yes
AB987654	No

State License Number(s)

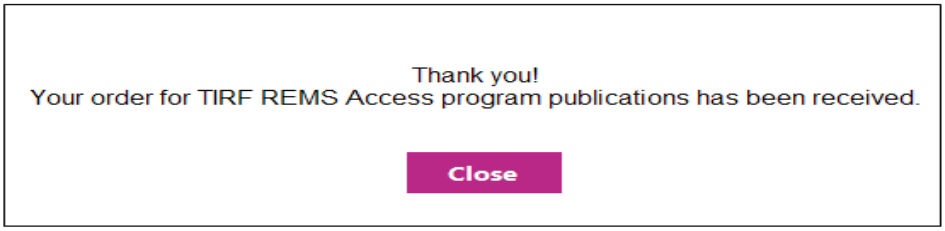
State License Number	State Issued
12345-05	AZ

TIRF REMS Access Web Prototype

Prescriber Request Materials



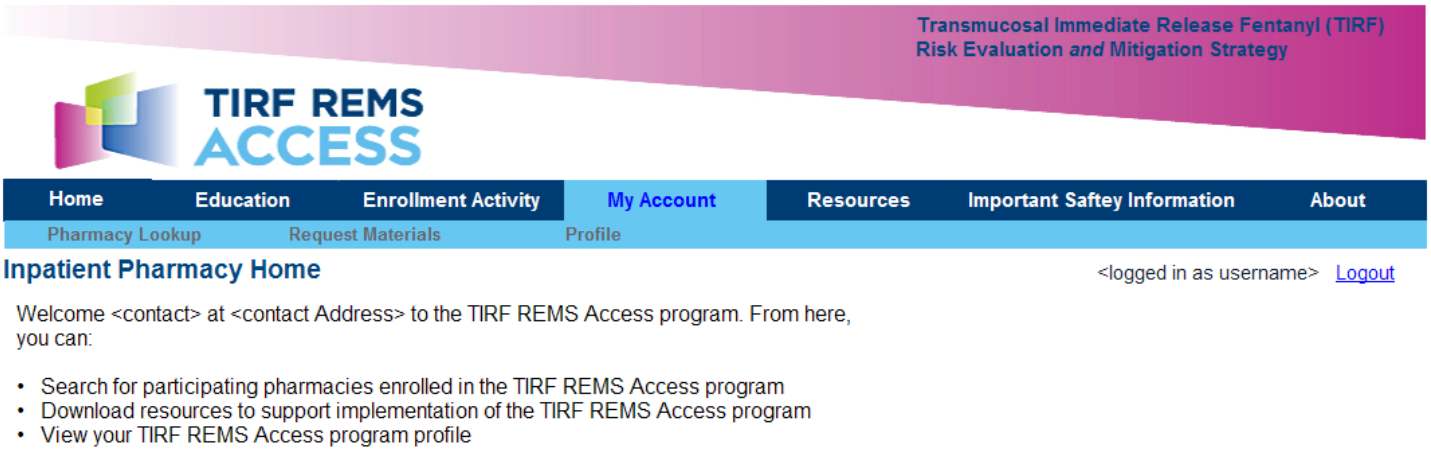
Request Material Confirmation



TIRF REMS Access Web Prototype

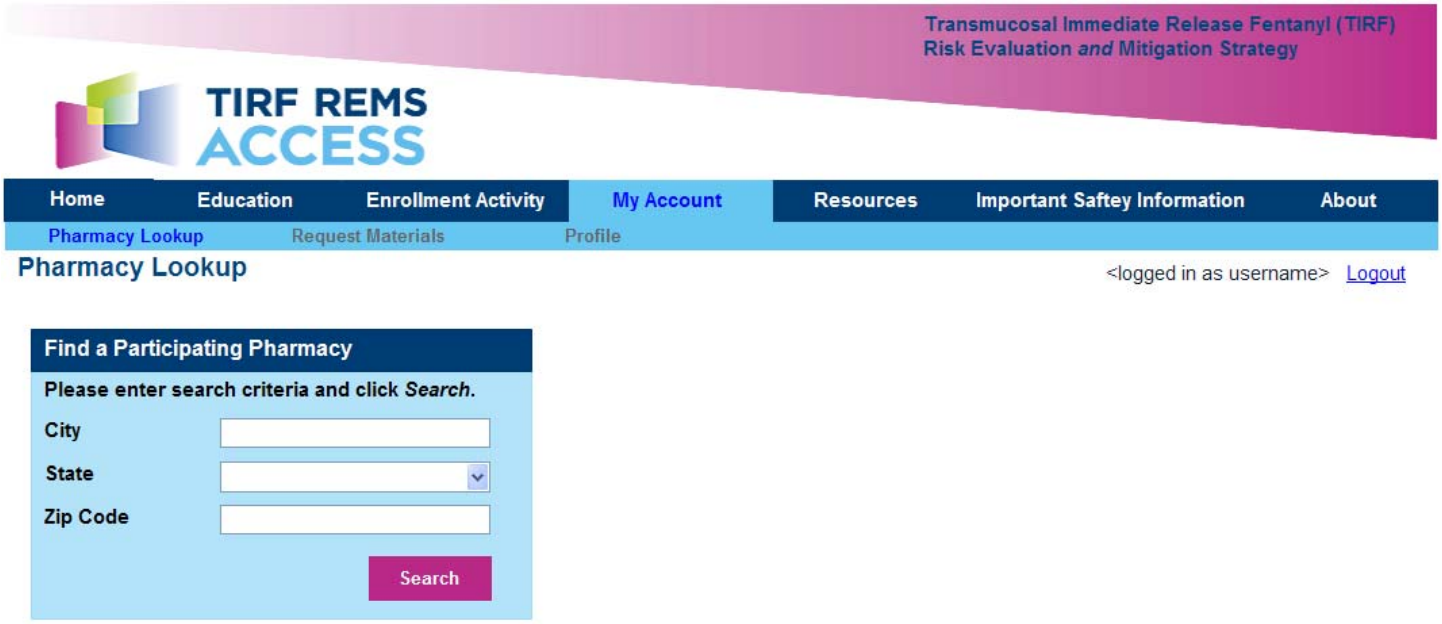
MY ACCOUNT – INPATIENT PHARMACY

Inpatient Pharmacy Home

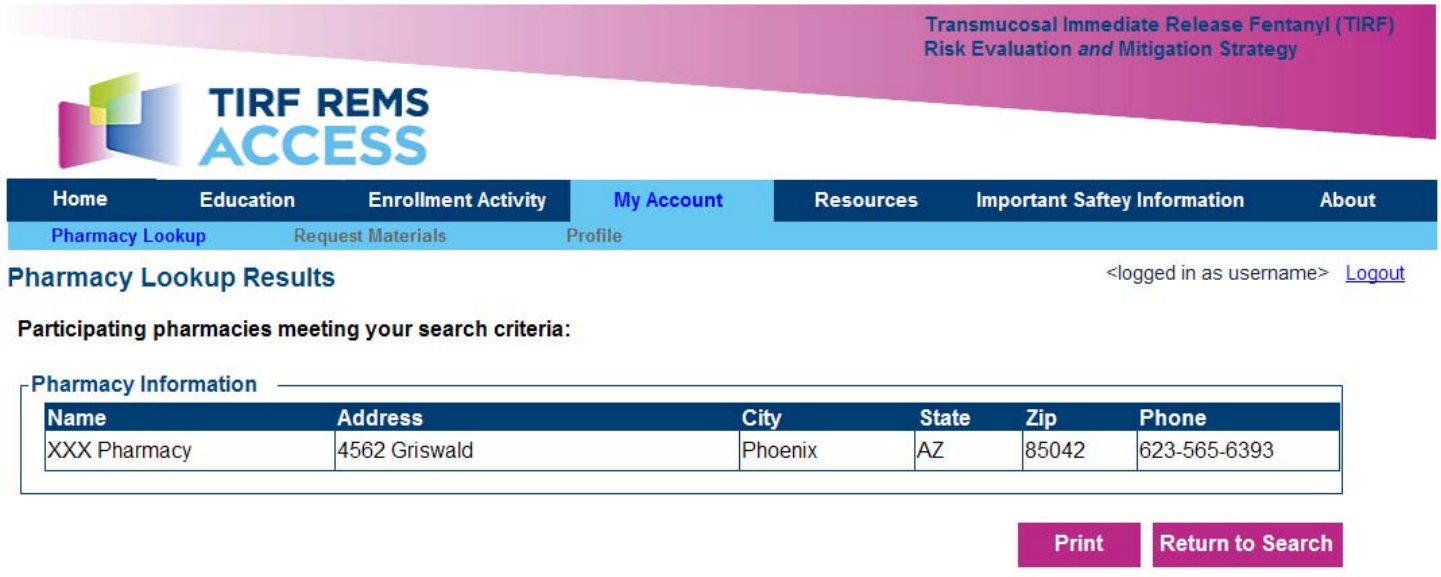


TIRF REMS Access Web Prototype

Inpatient Pharmacy Lookup



Inpatient Pharmacy Lookup Result



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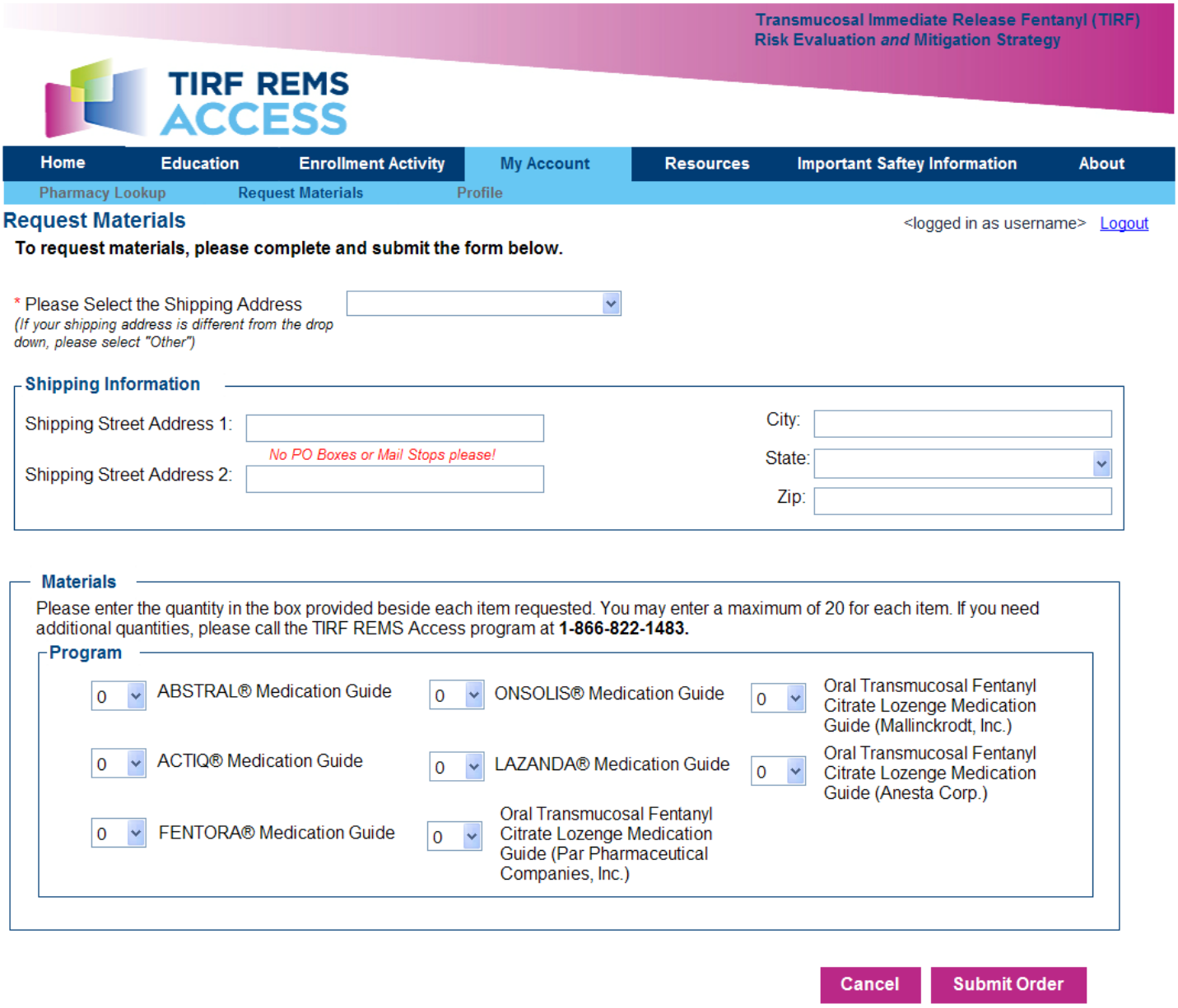
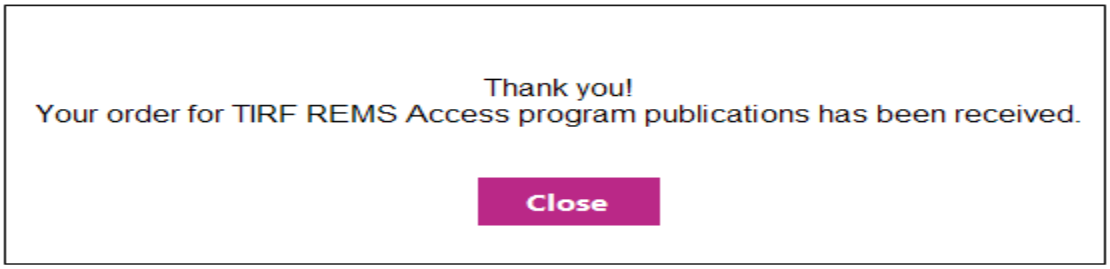
TIRF REMS Access Web Prototype

Inpatient Pharmacy Request Materials

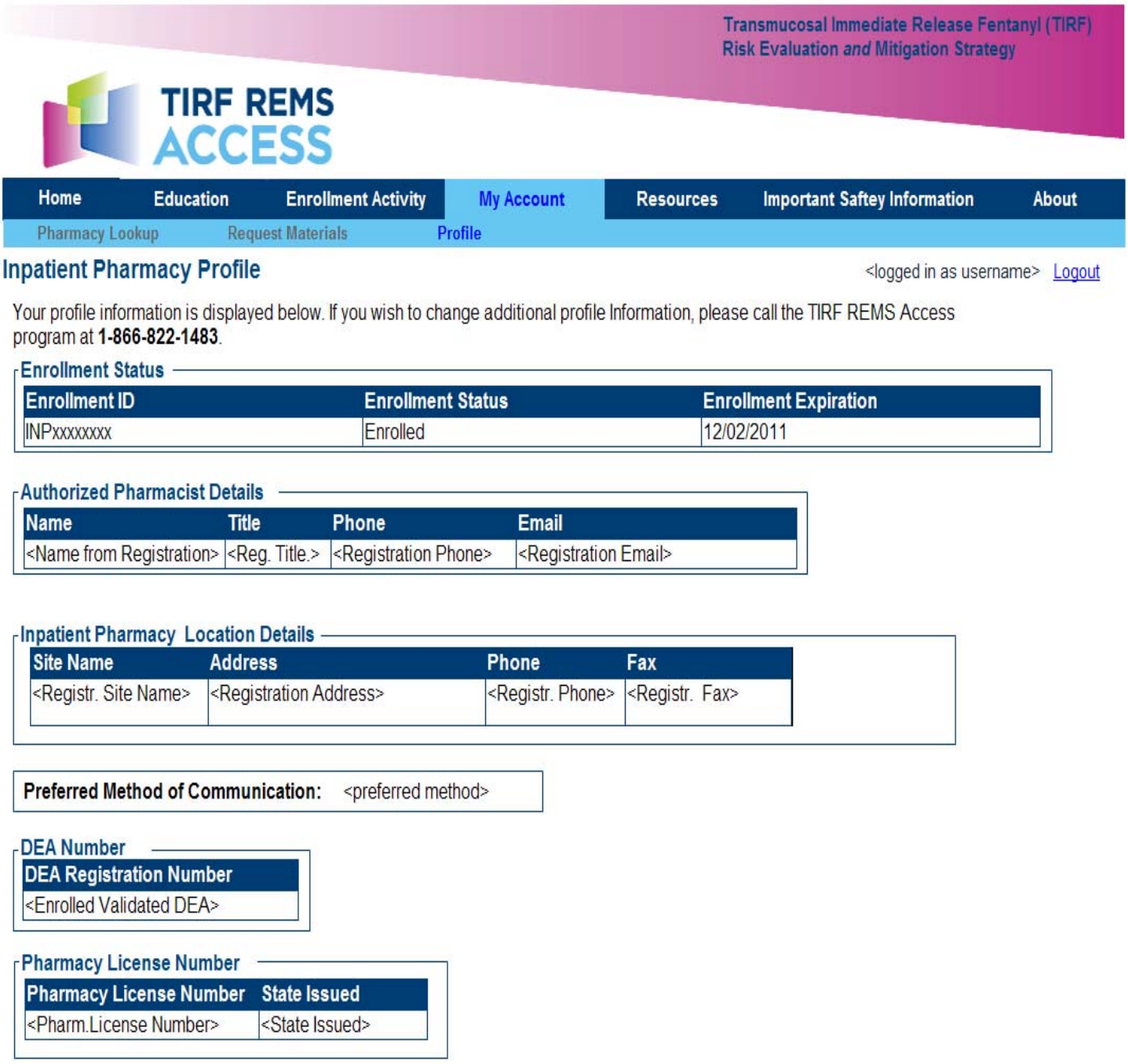


Request Material Confirmation



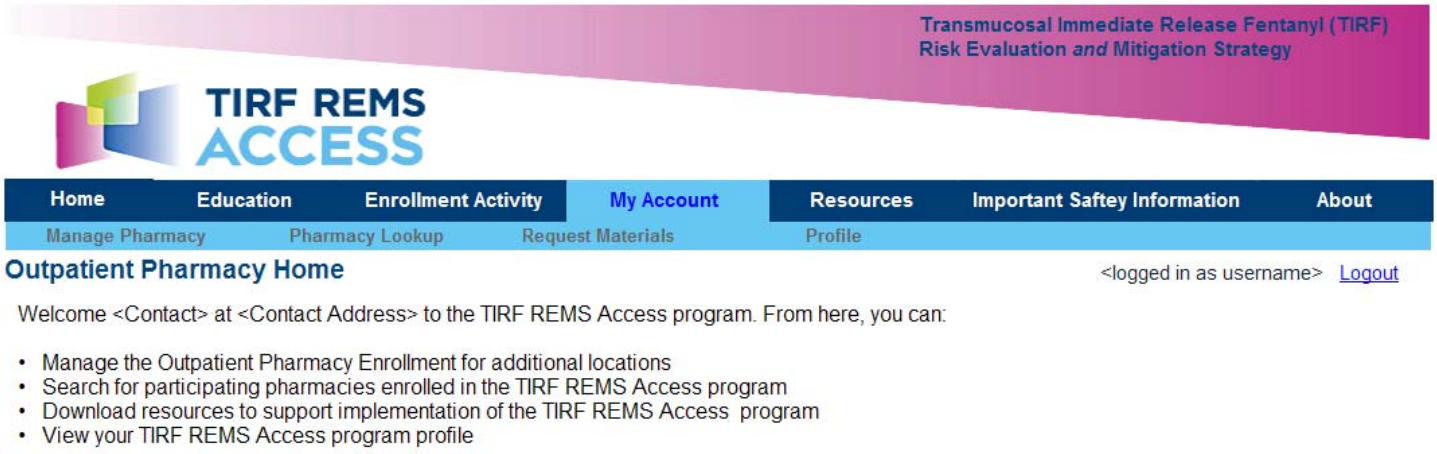
TIRF REMS Access Web Prototype

Inpatient Pharmacy Profile



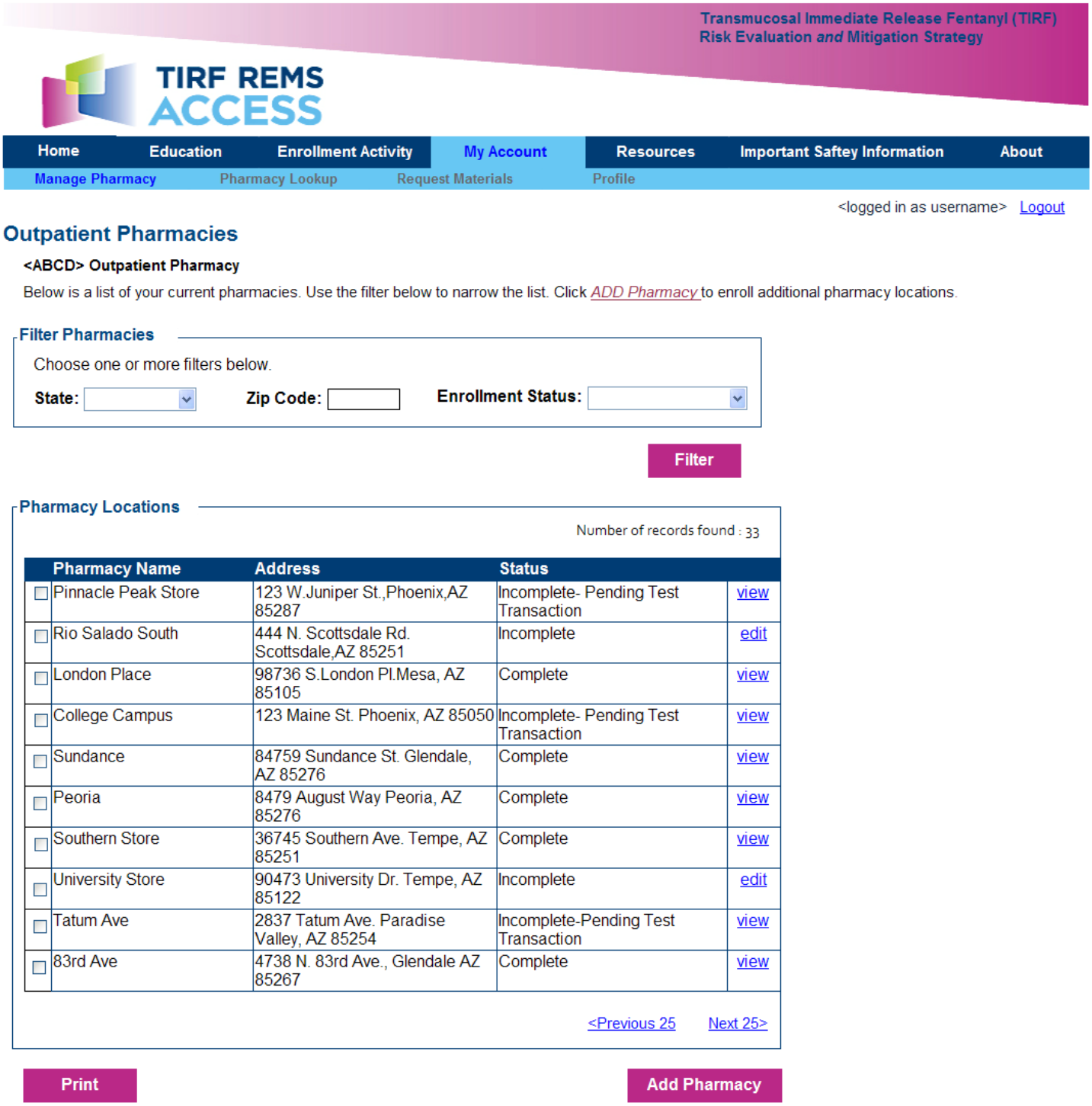
MY ACCOUNT – OUTPATIENT PHARMACY

Outpatient Pharmacy Home



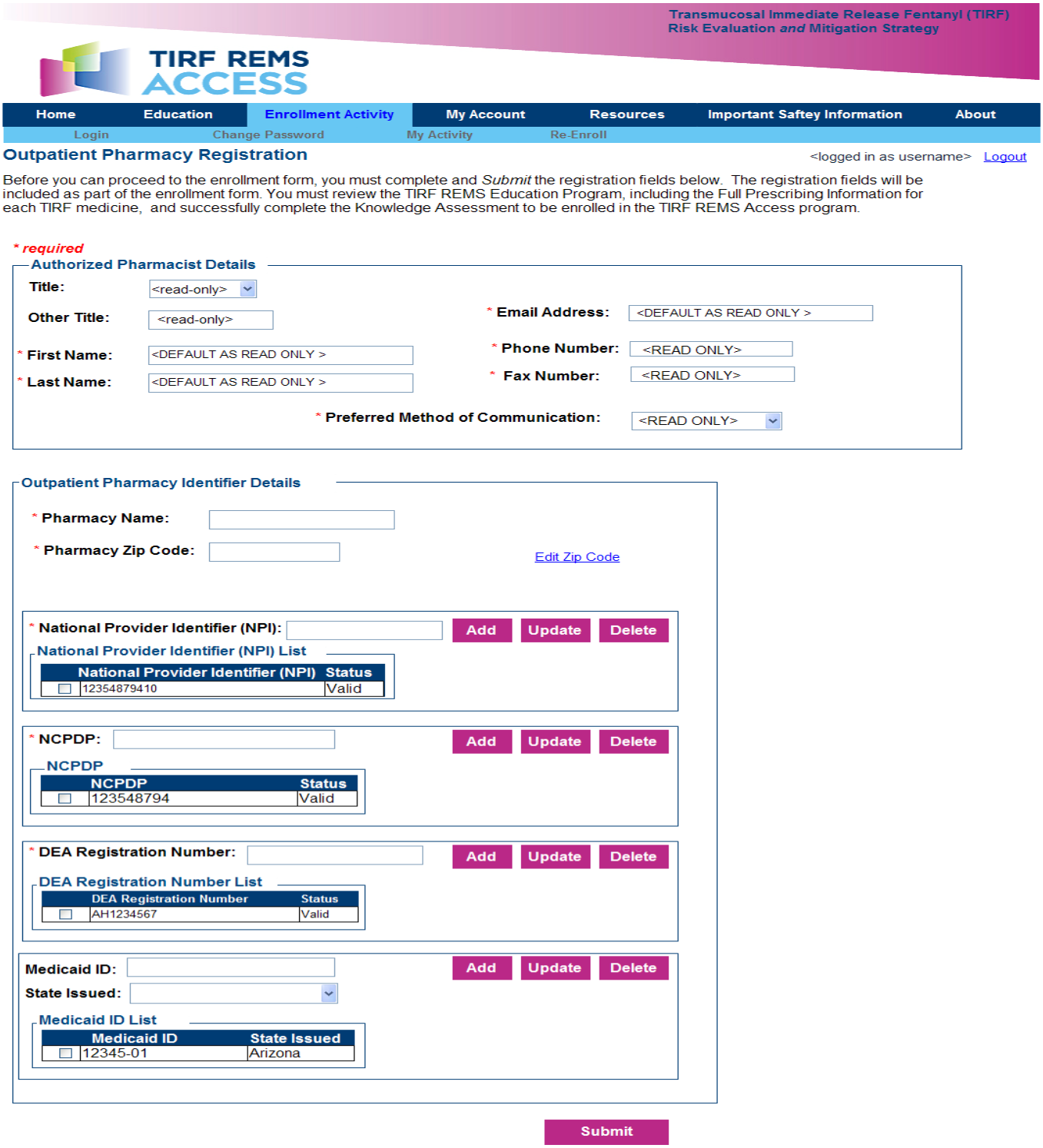
TIRF REMS Access Web Prototype

Outpatient Pharmacy – Manage Pharmacy



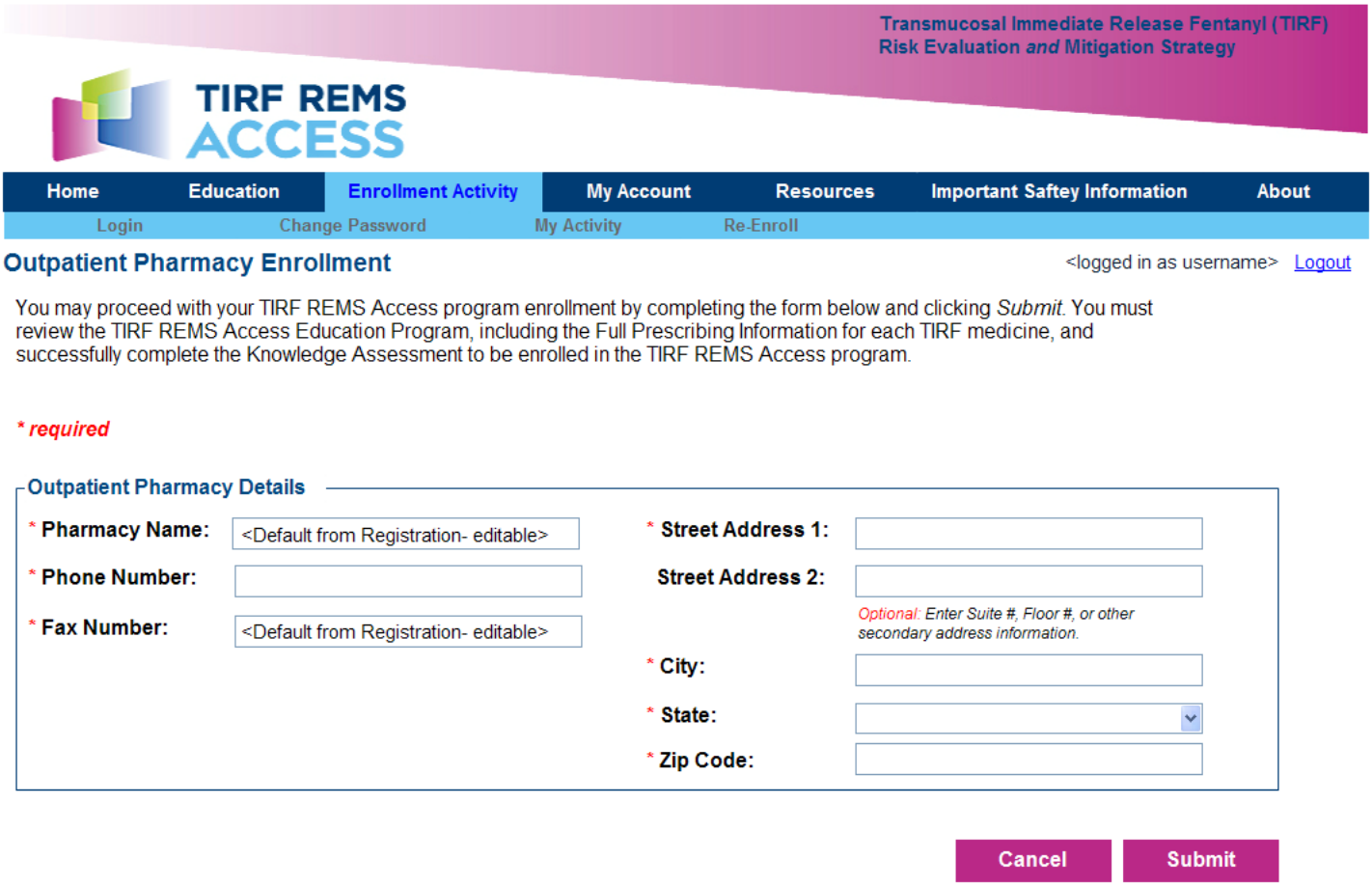
TIRF REMS Access Web Prototype

Outpatient Pharmacy – Add Pharmacy Registration Identifier



TIRF REMS Access Web Prototype

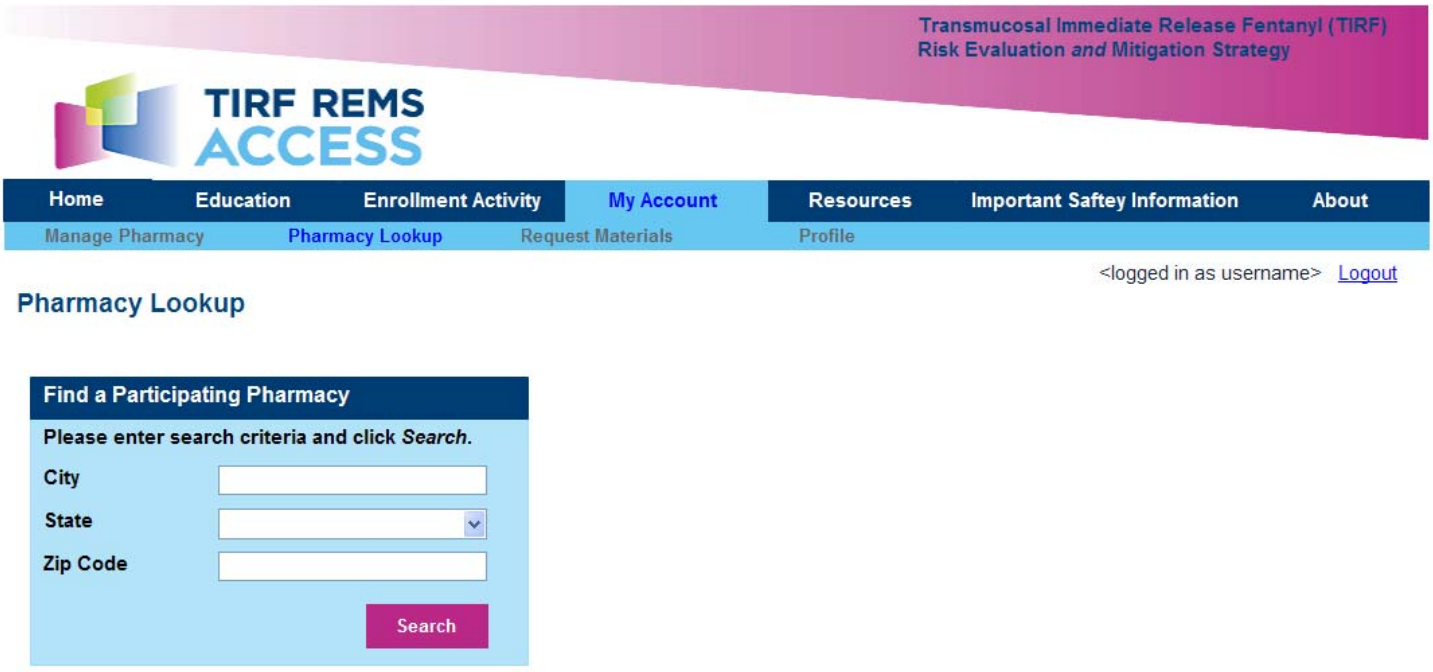
Outpatient Pharmacy – Add Pharmacy Enrollment Demographics



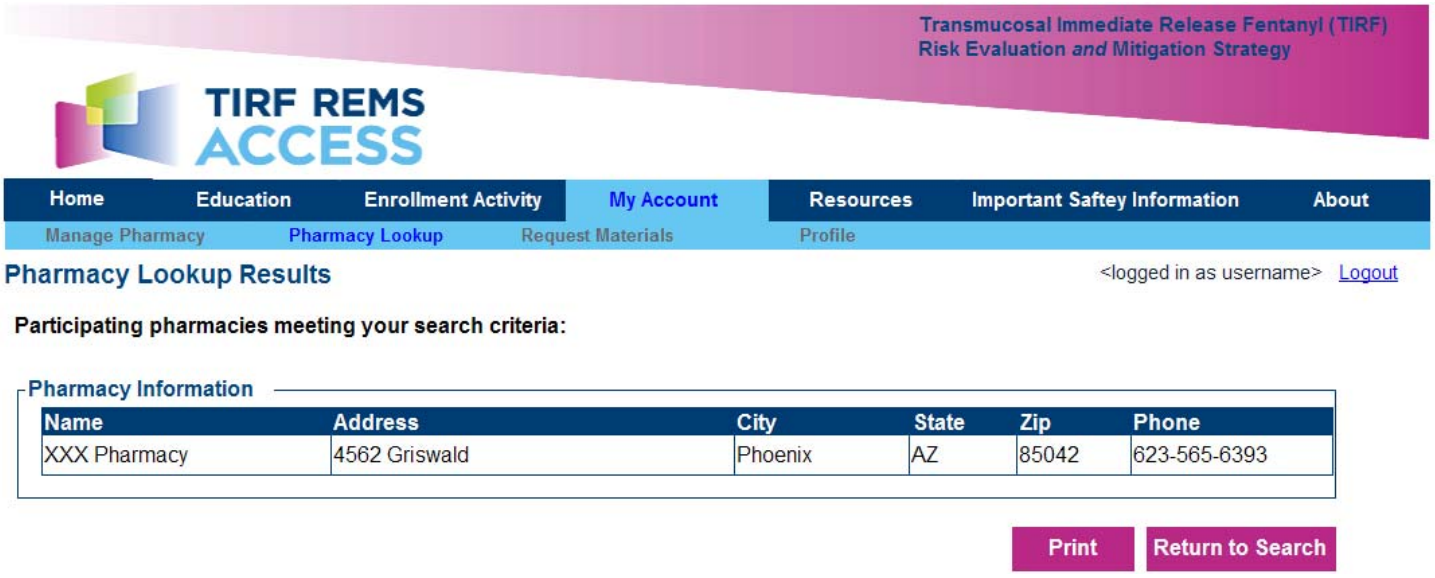
After clicking “Submit” , the system will navigate the user to the Outpatient Attestation and Signature page. See page # 109 for the remaining flow.

TIRF REMS Access Web Prototype

Pharmacy Lookup



Pharmacy Lookup Results



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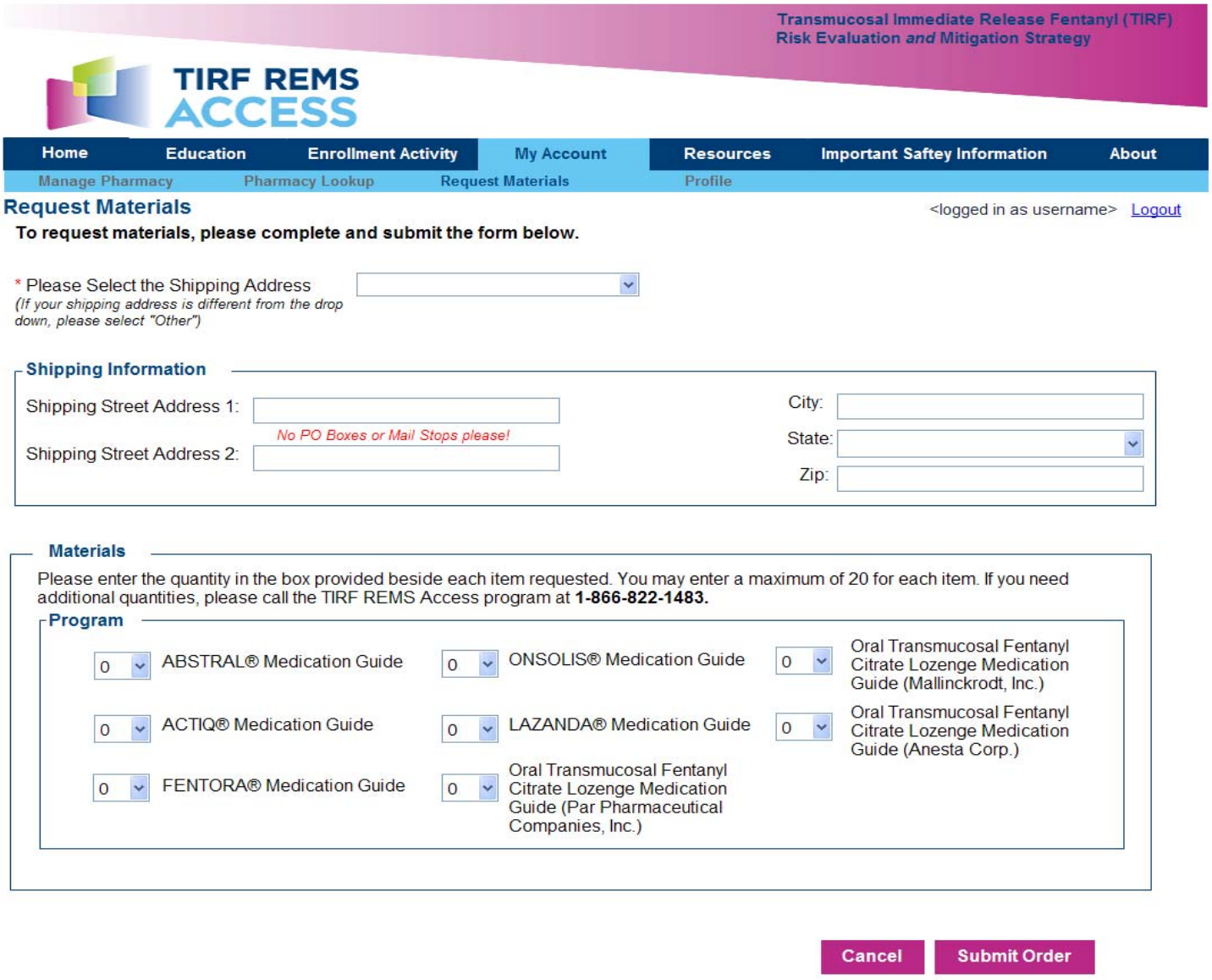
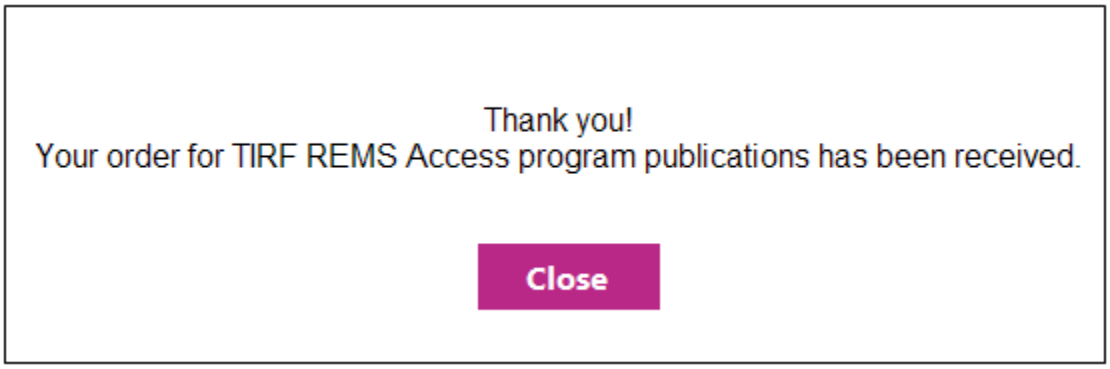
TIRF REMS Access Web Prototype

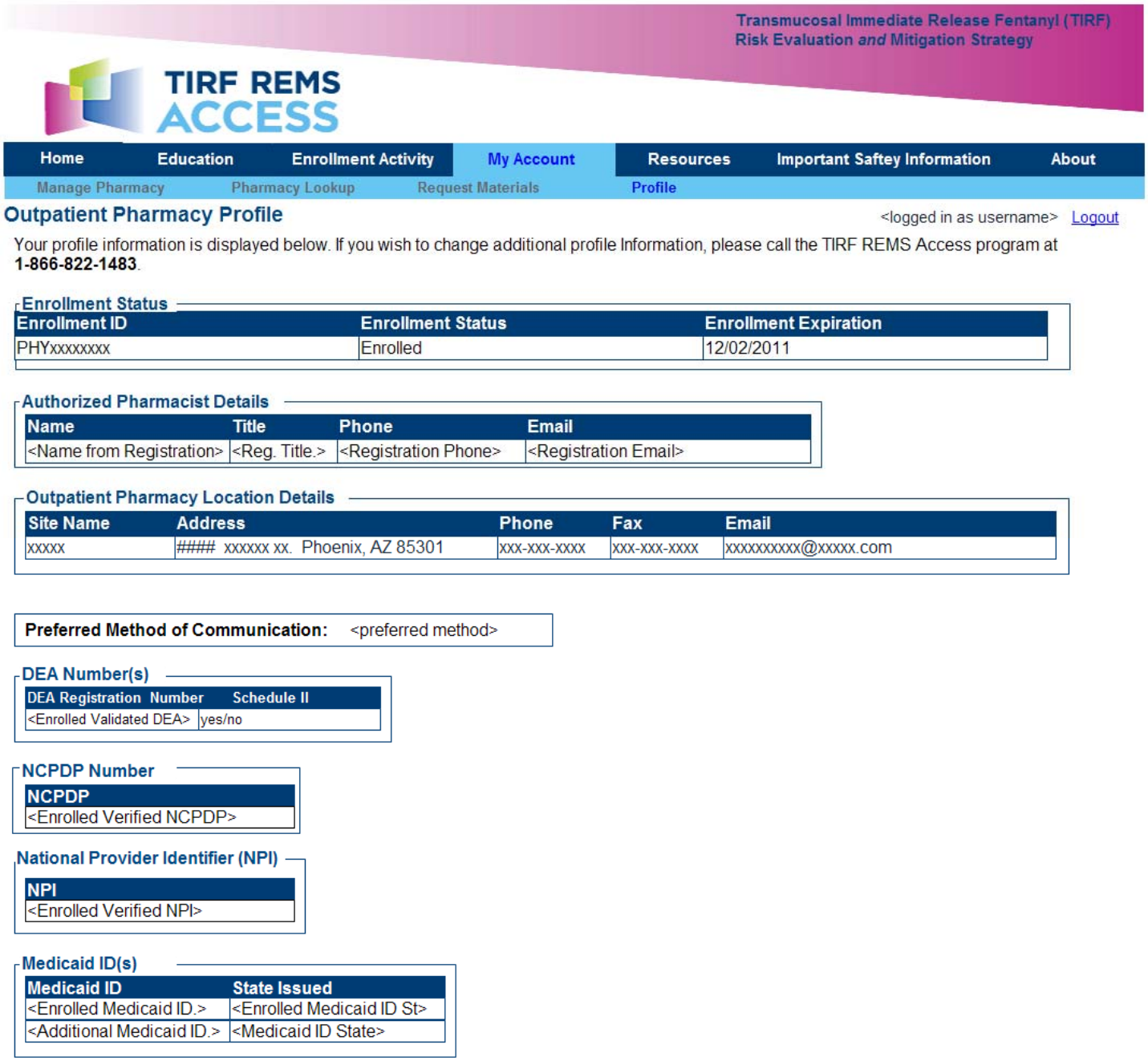
Outpatient Pharmacy Request Materials



Request Material Confirmation

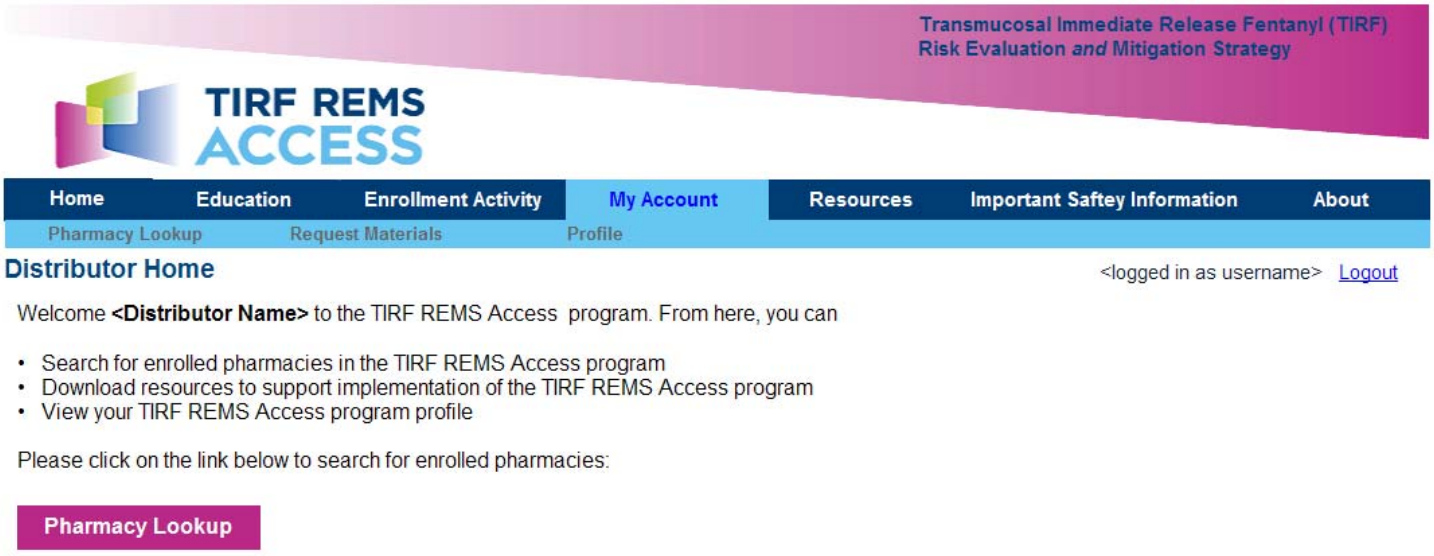


Outpatient Pharmacy Profile



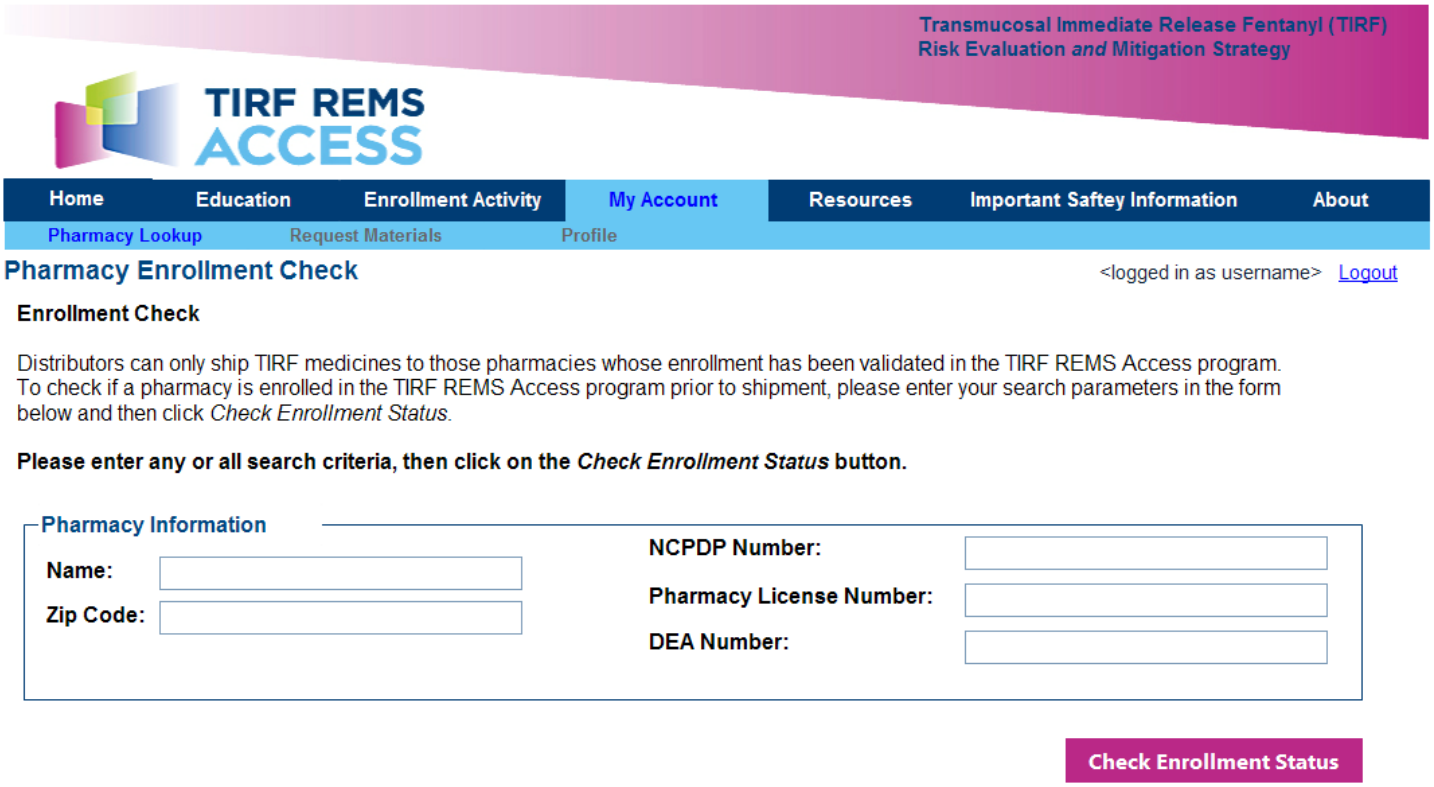
MY ACCOUNT - DISTRIBUTOR

Distributor Home



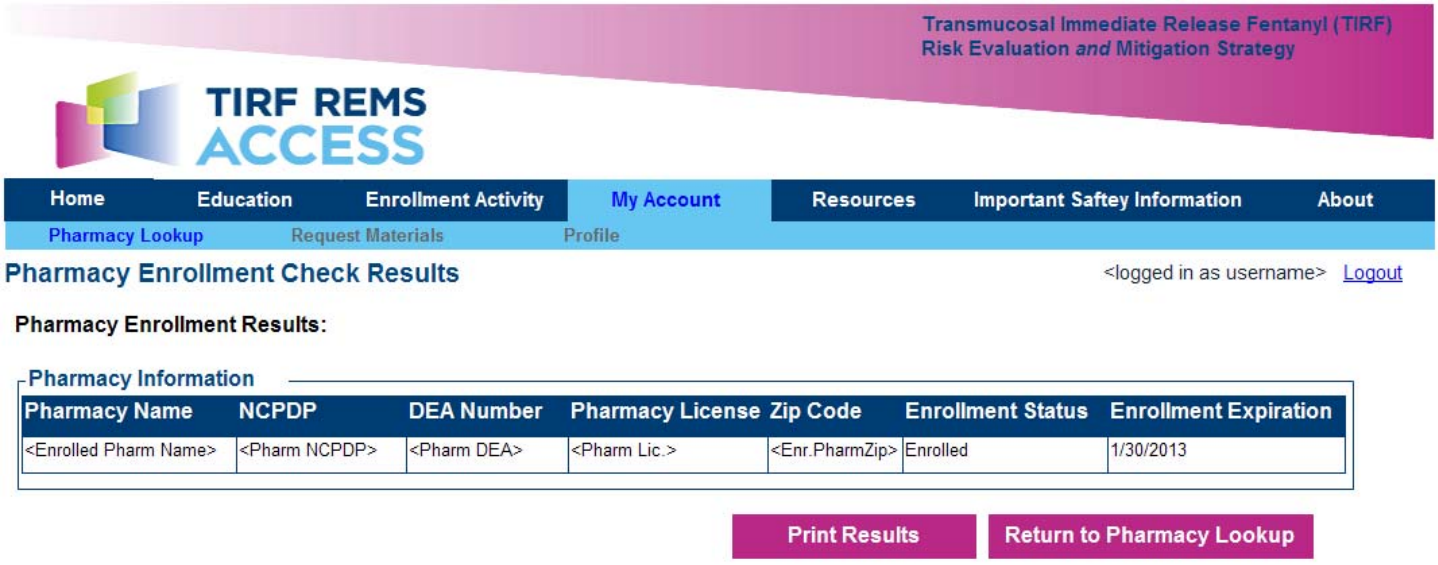
TIRF REMS Access Web Prototype

Pharmacy Enrollment Check



TIRF REMS Access Web Prototype

Pharmacy Enrollment Check Results



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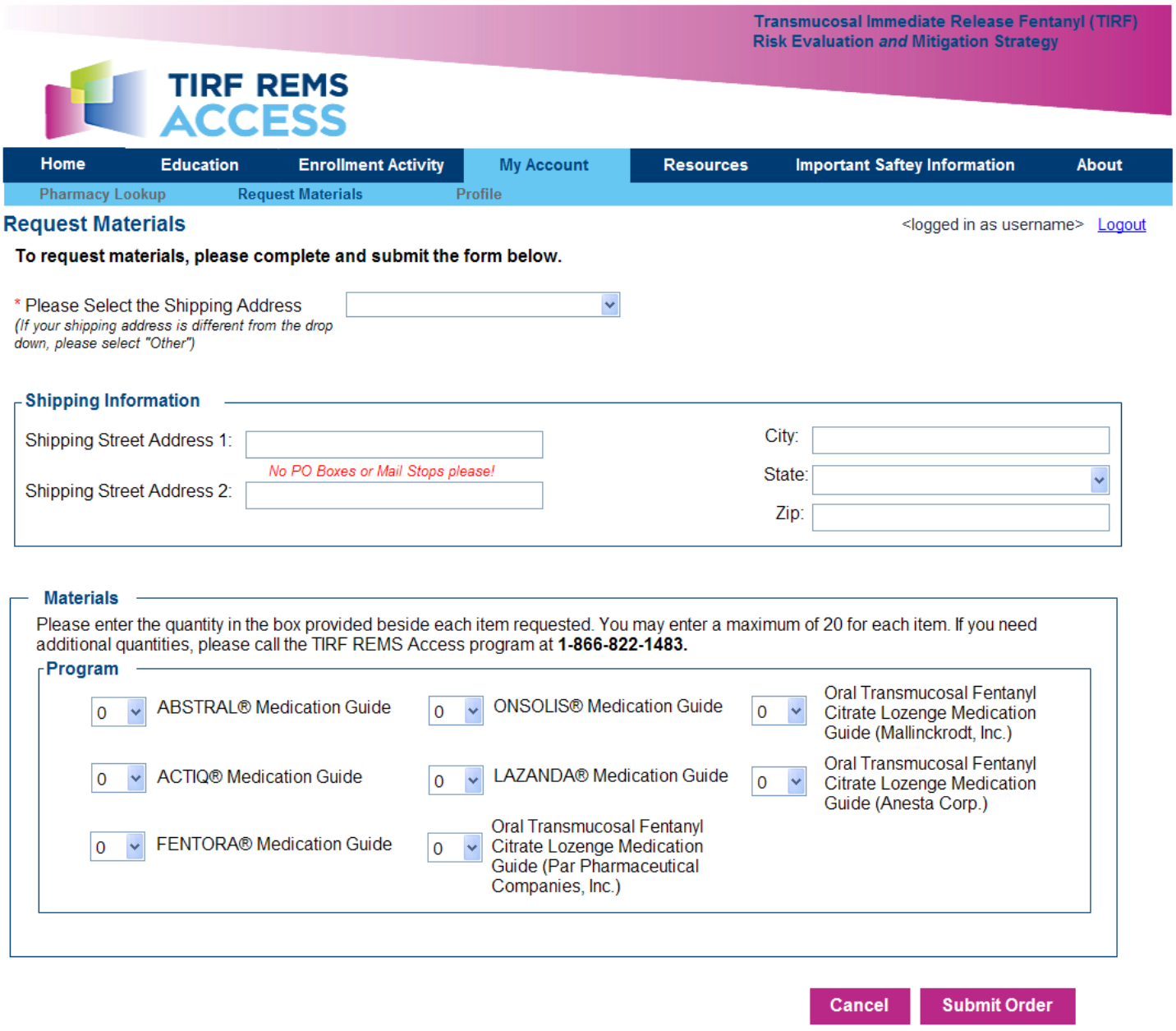
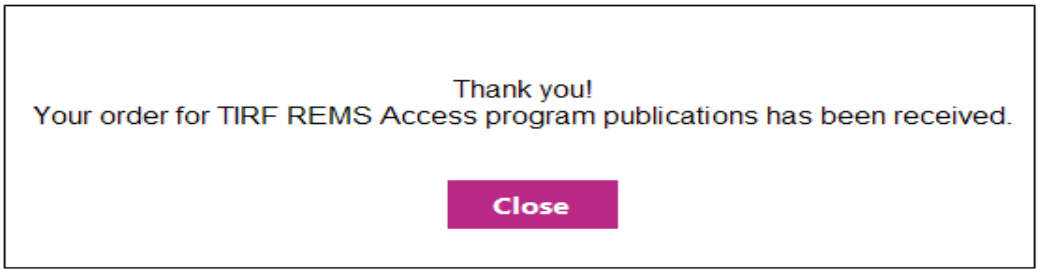
TIRF REMS Access Web Prototype

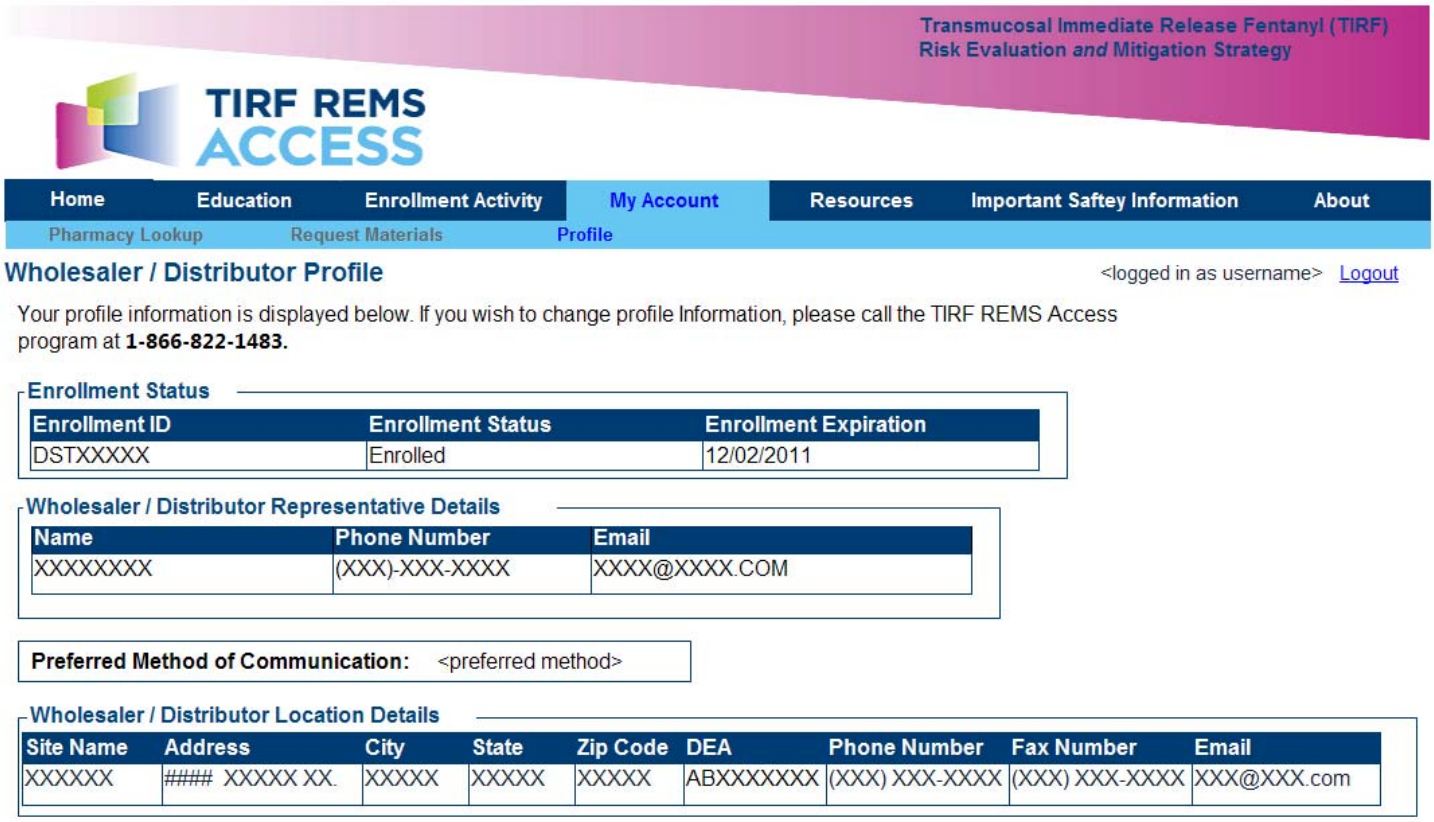
Distributor Request Materials



Request Materials Confirmation



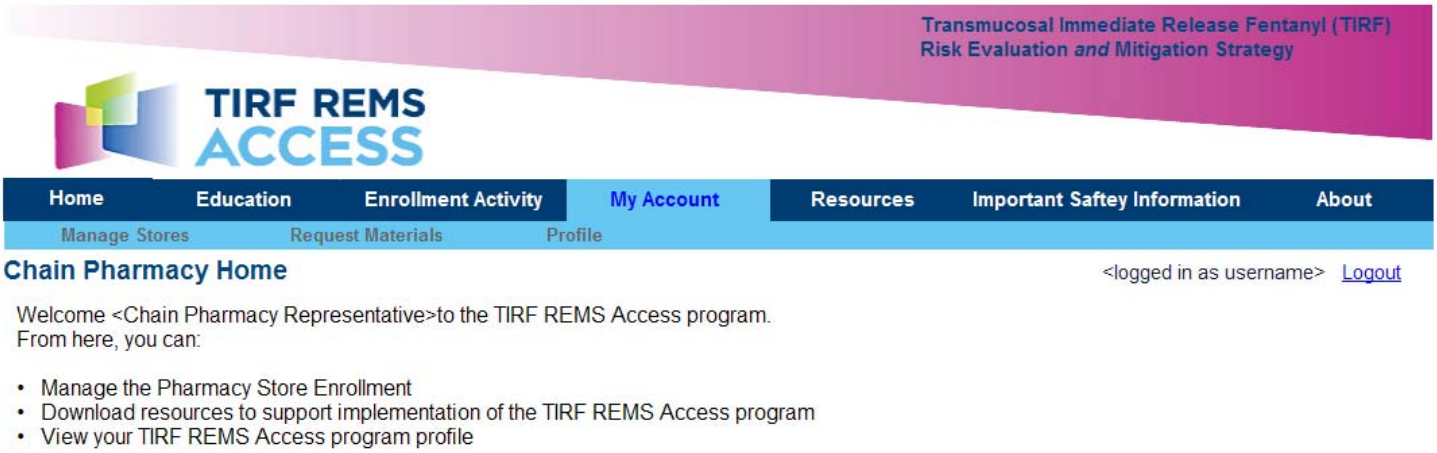
Distributor Profile



TIRF REMS Access Web Prototype

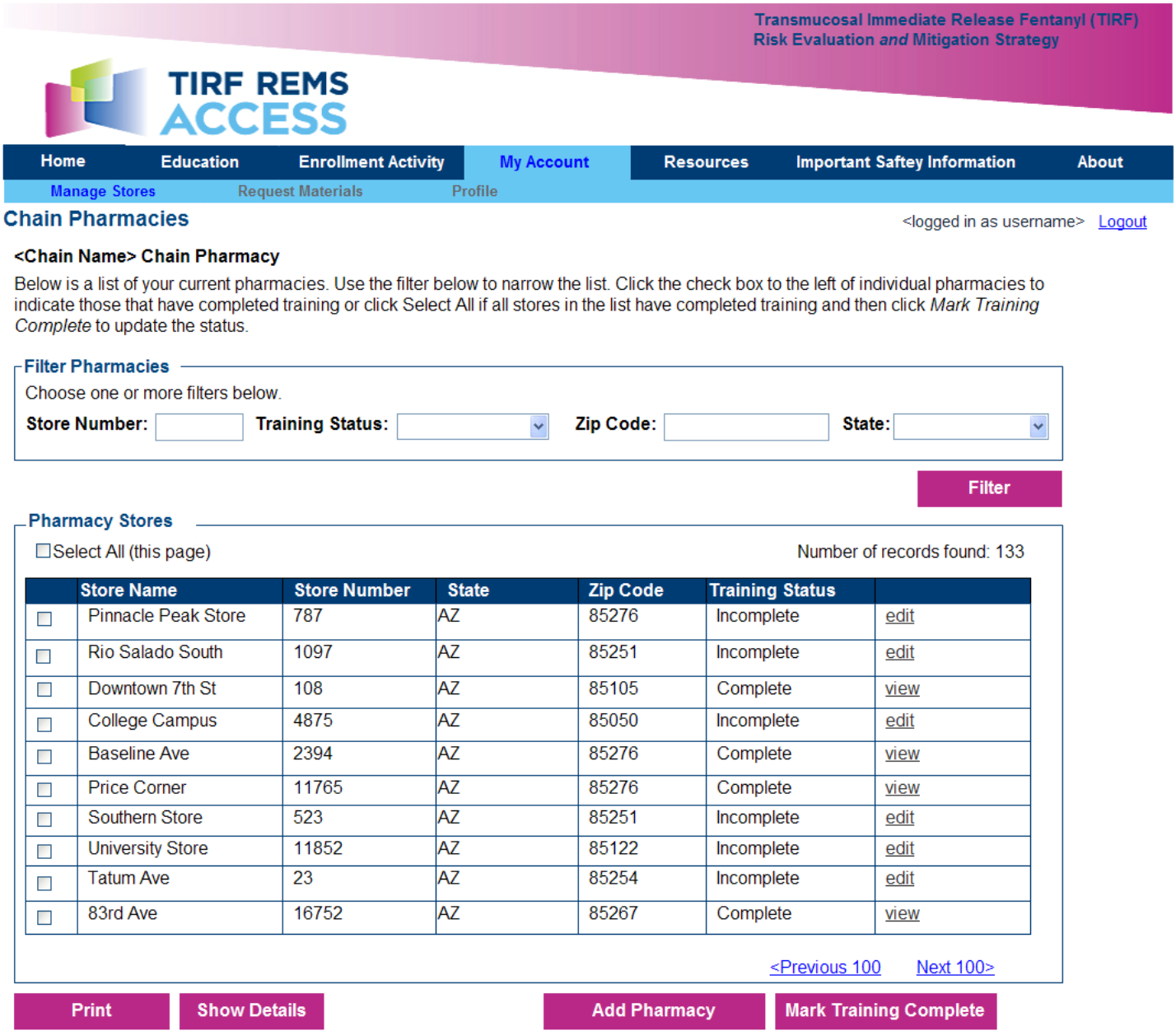
MY ACCOUNT – CHAIN PHARMACY

Chain Pharmacy Home



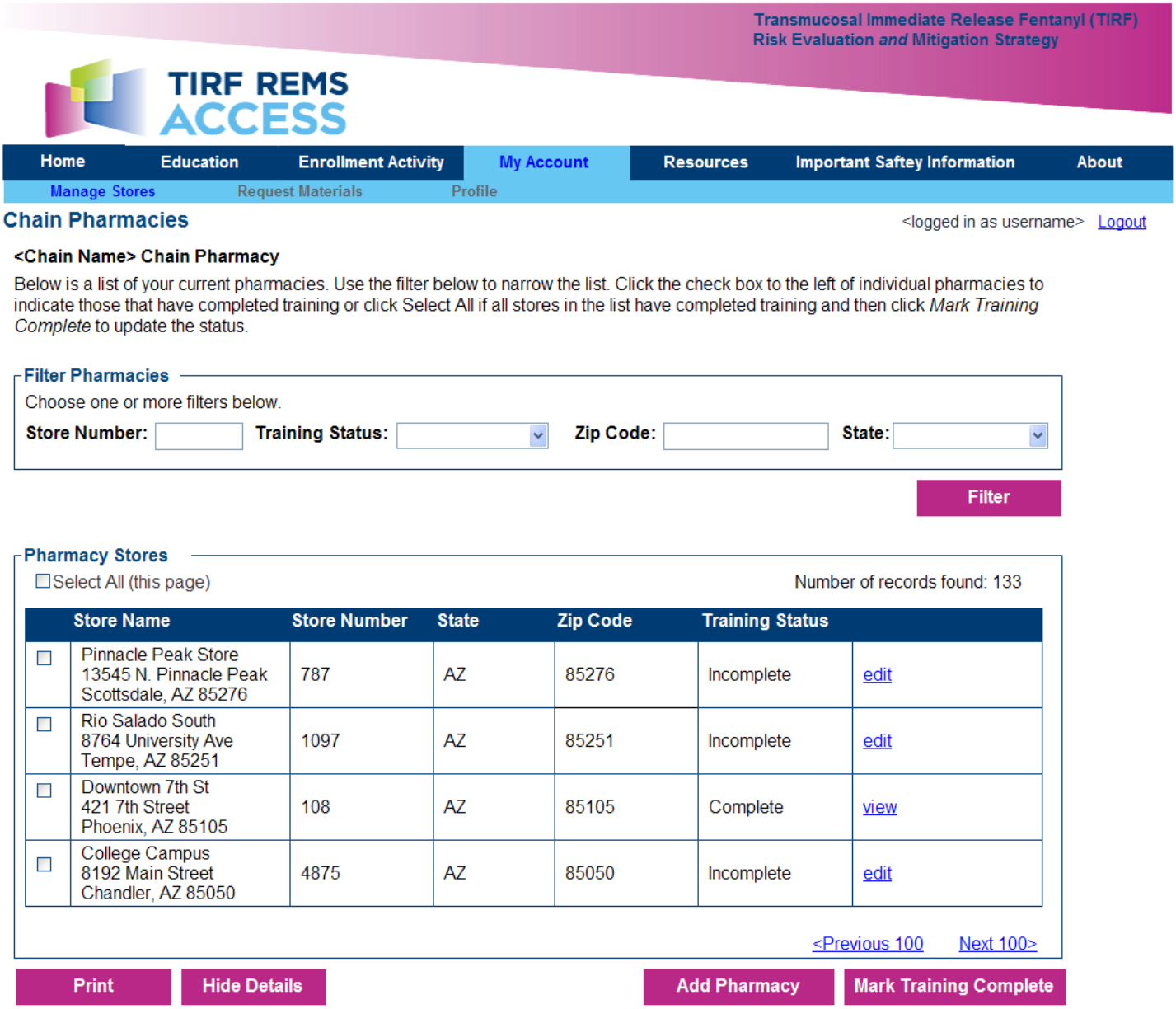
TIRF REMS Access Web Prototype

Manage Pharmacy Stores



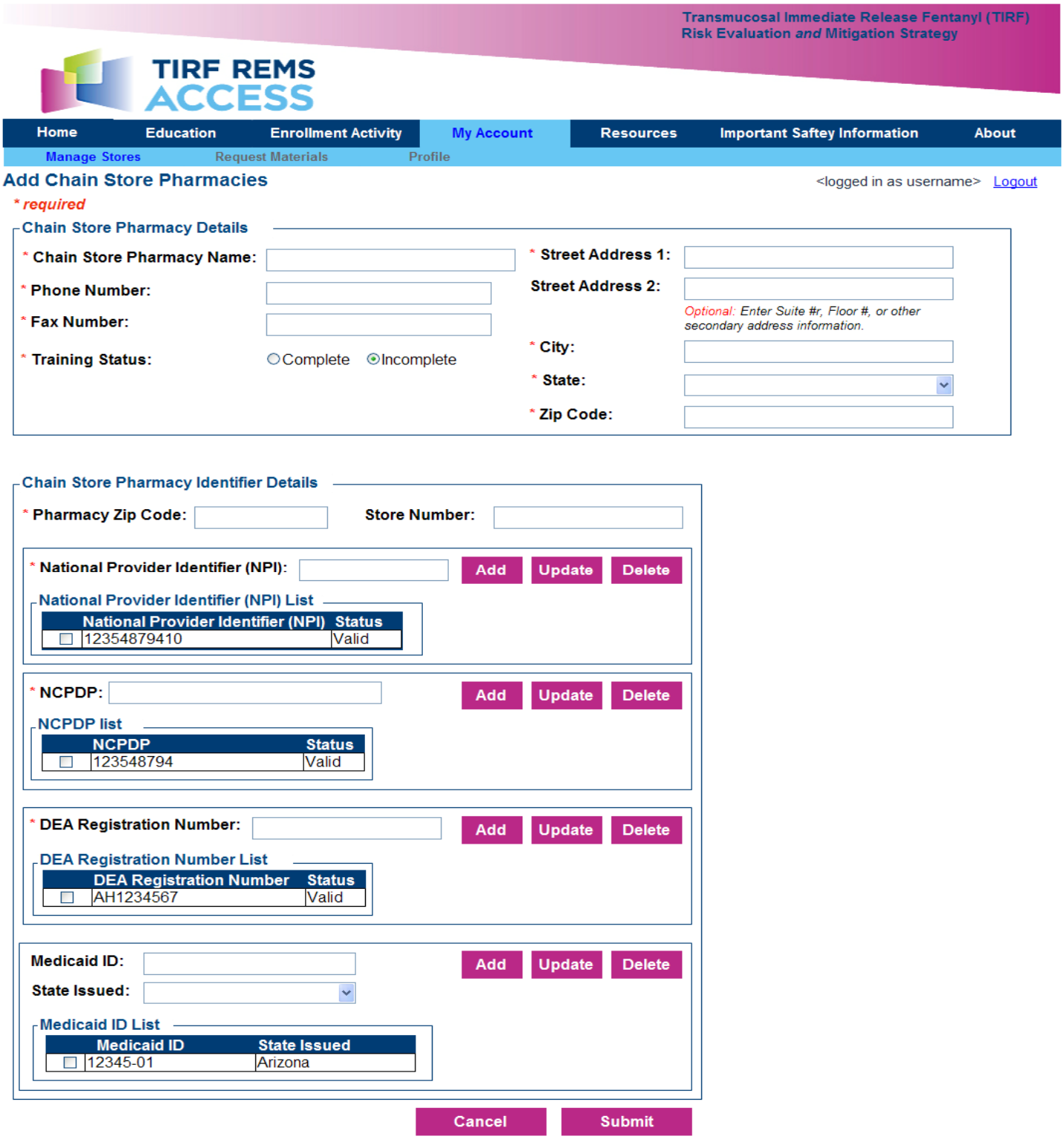
TIRF REMS Access Web Prototype

Manage Pharmacy Store Details



TIRF REMS Access Web Prototype

Add Pharmacy Stores



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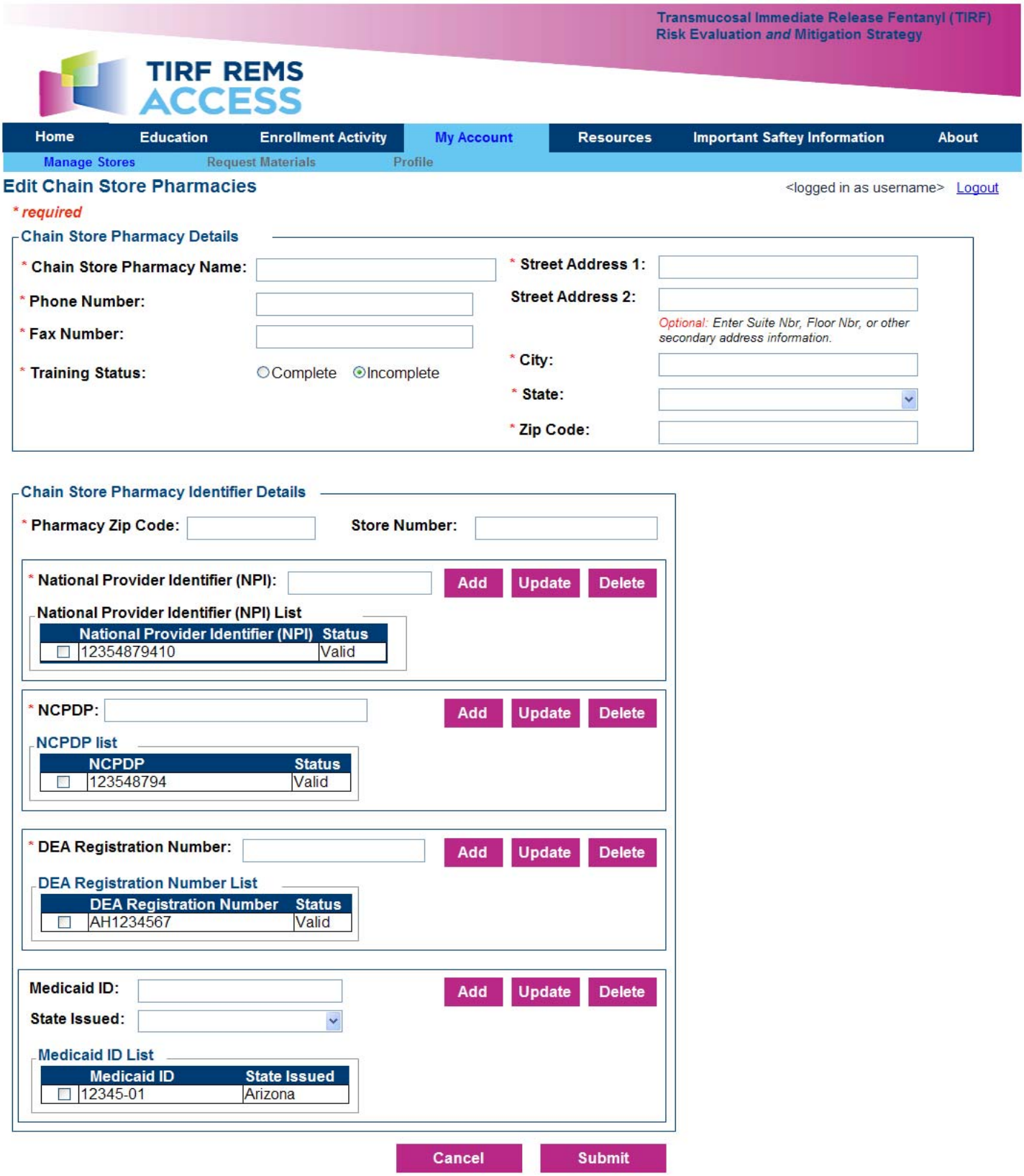
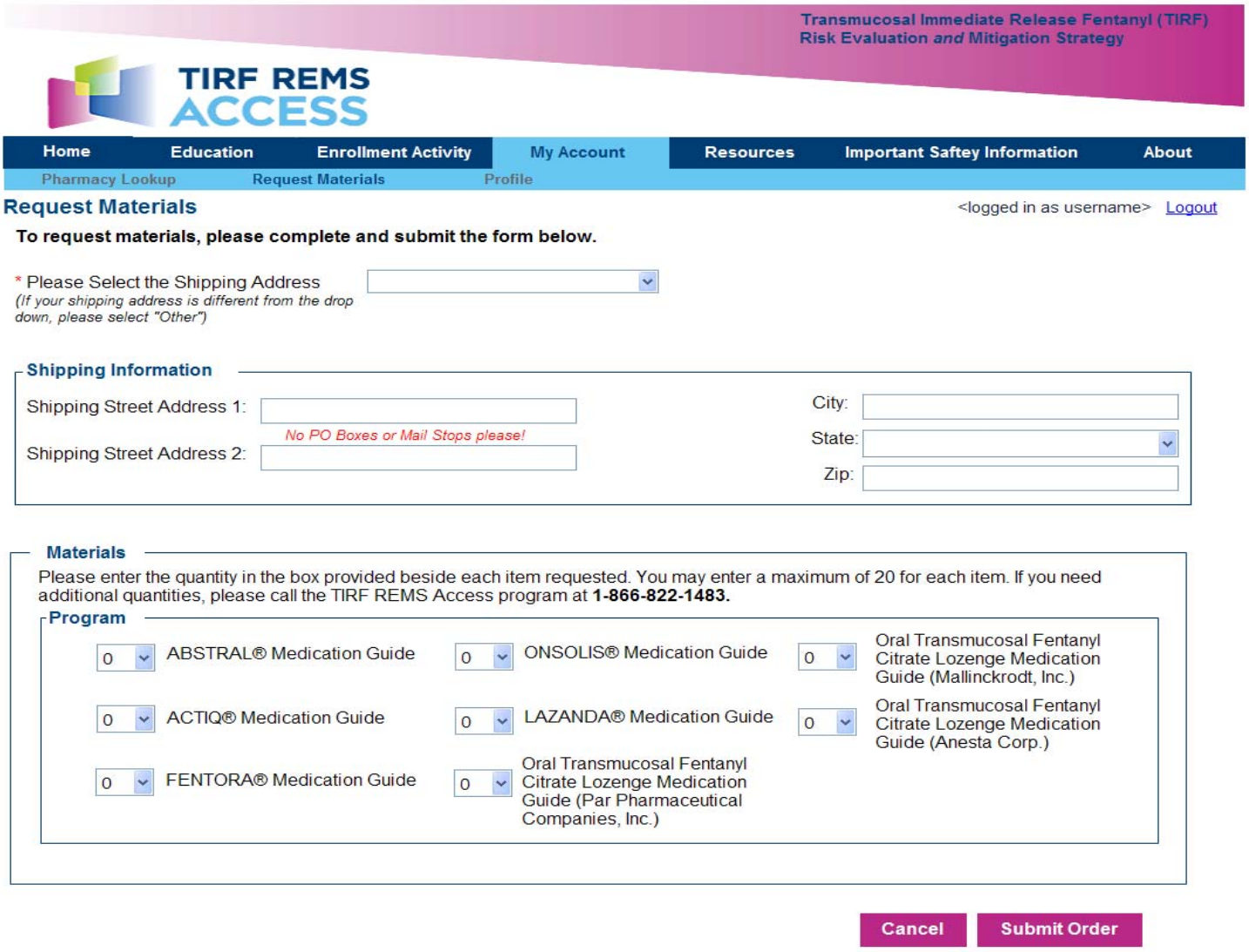
TIRF REMS Access Web Prototype

Edit Pharmacy Stores

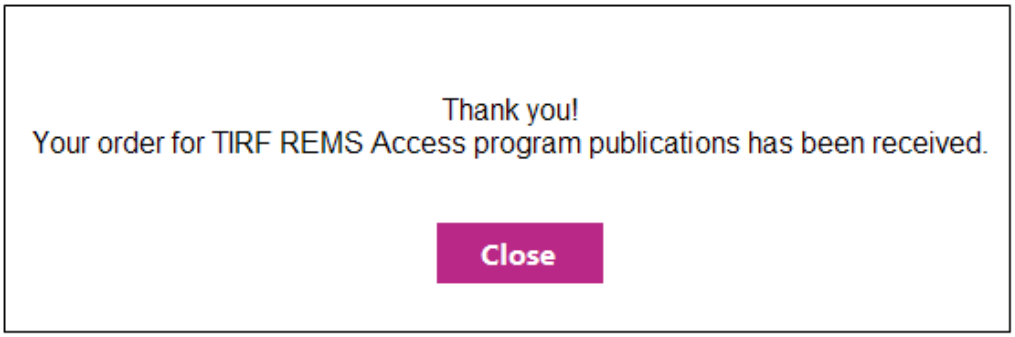


TIRF REMS Access Web Prototype

Chain Pharmacy Request Materials

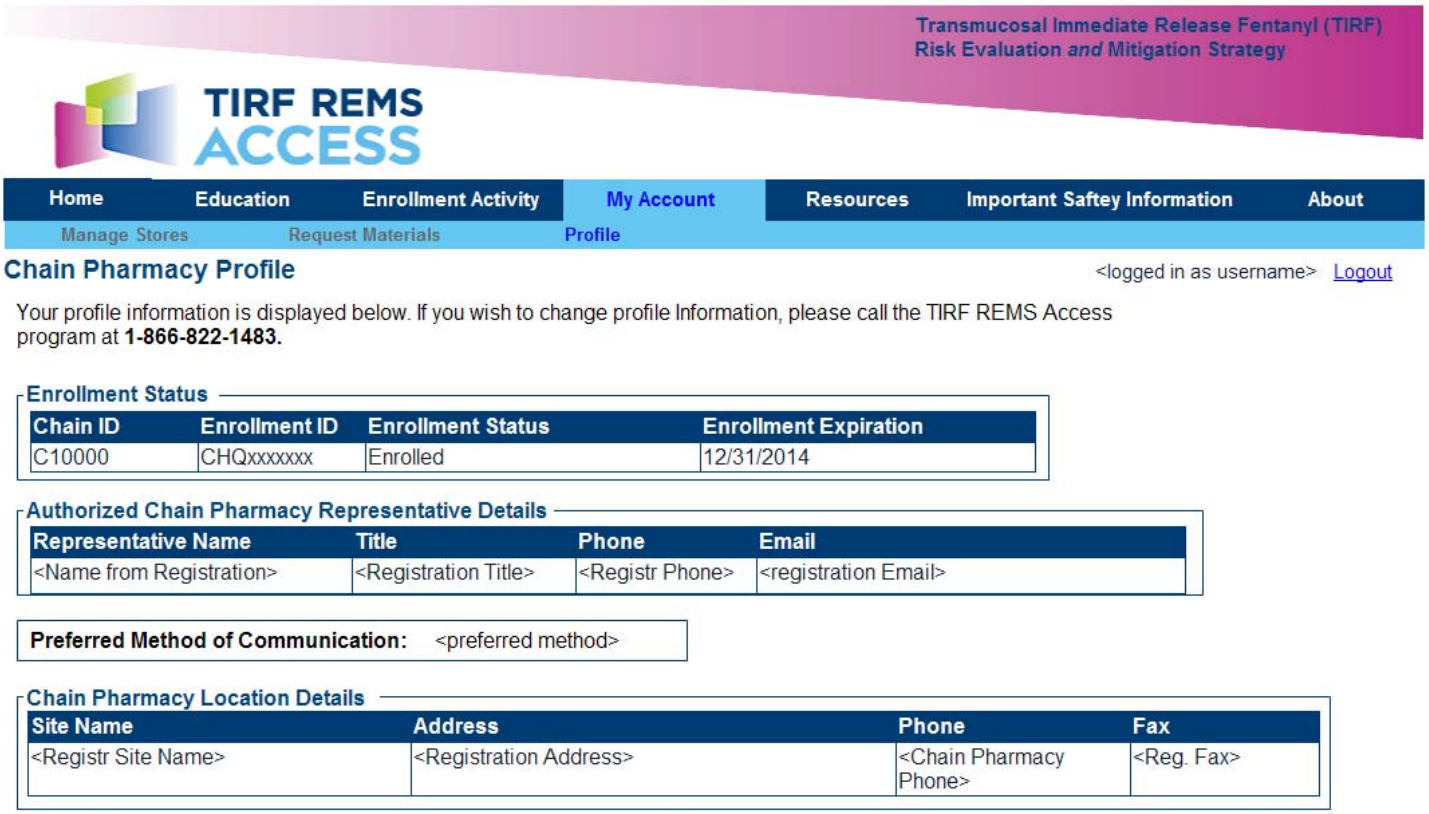


Request Material Confirmation



TIRF REMS Access Web Prototype

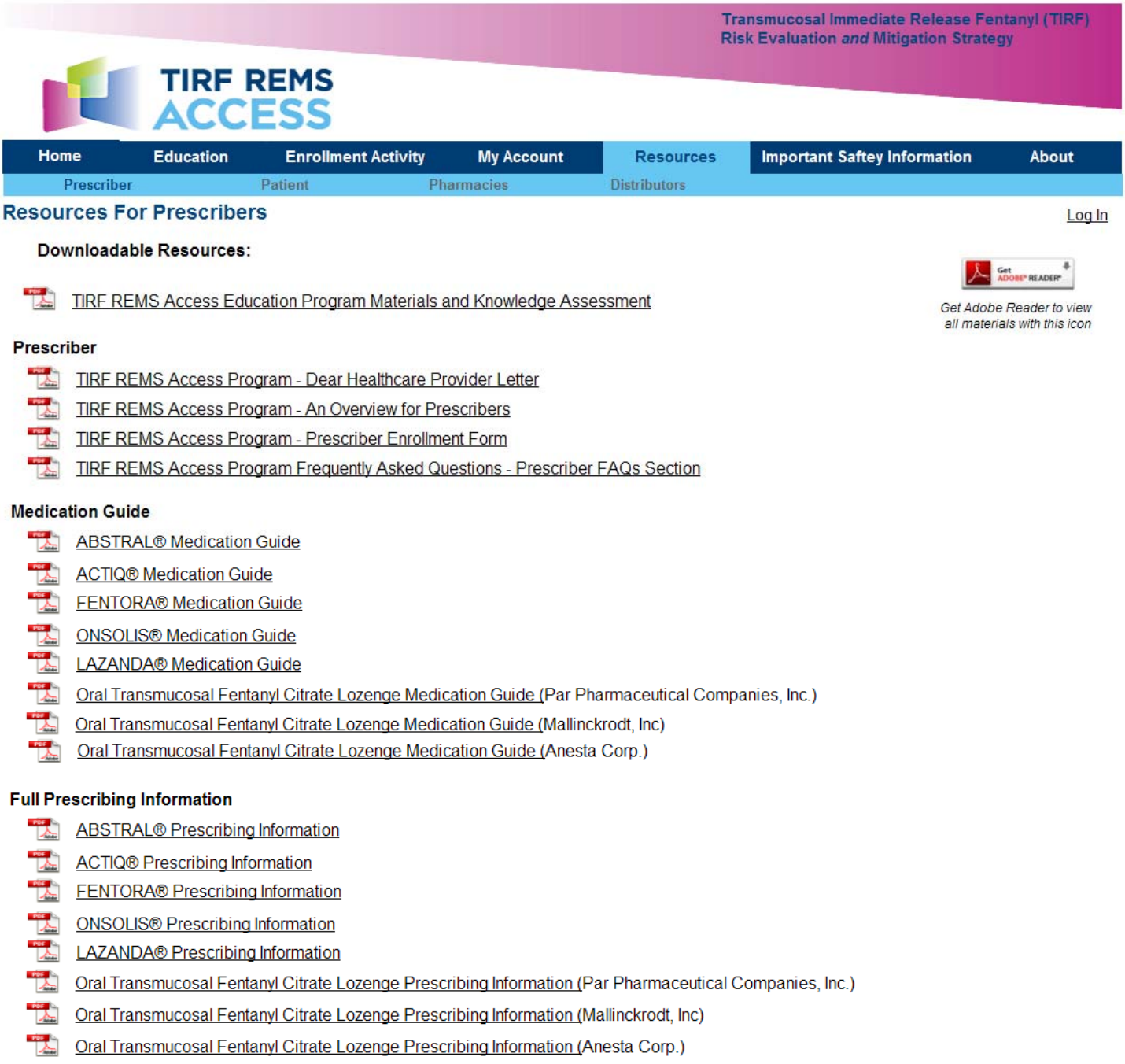
Chain Pharmacy Profile



TIRF REMS Access Web Prototype

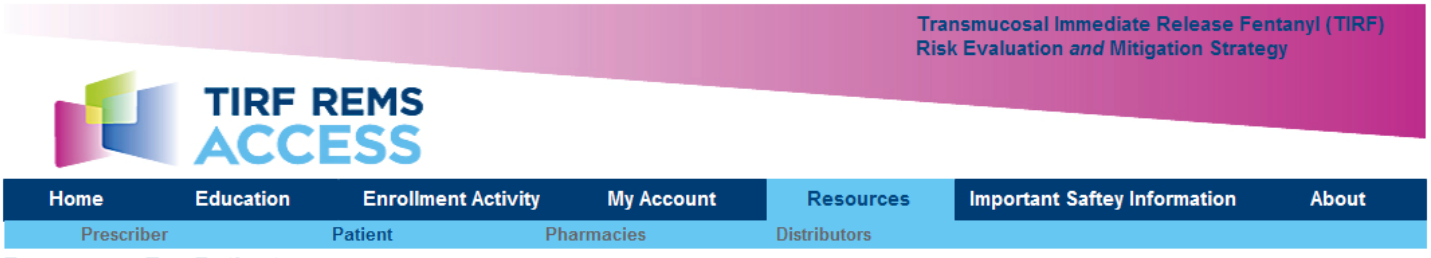
RESOURCES

Resources for Prescriber



TIRF REMS Access Web Prototype

Resources for Patients



Resources For Patients

Log In

The resources below will help you understand Fentanyl .

If you think that Fentanyl might be right for you, please contact your healthcare provider.

Get Adobe Reader to view all materials with this icon

Downloadable Resources:

Patients

- TIRF REMS Access Program - An Overview for Patients and Caregivers
- TIRF REMS Access Program - Patient-Prescriber Agreement Form
- TIRF REMS Access Program Frequently Asked Questions - Patient FAQs Section

Medication Guide

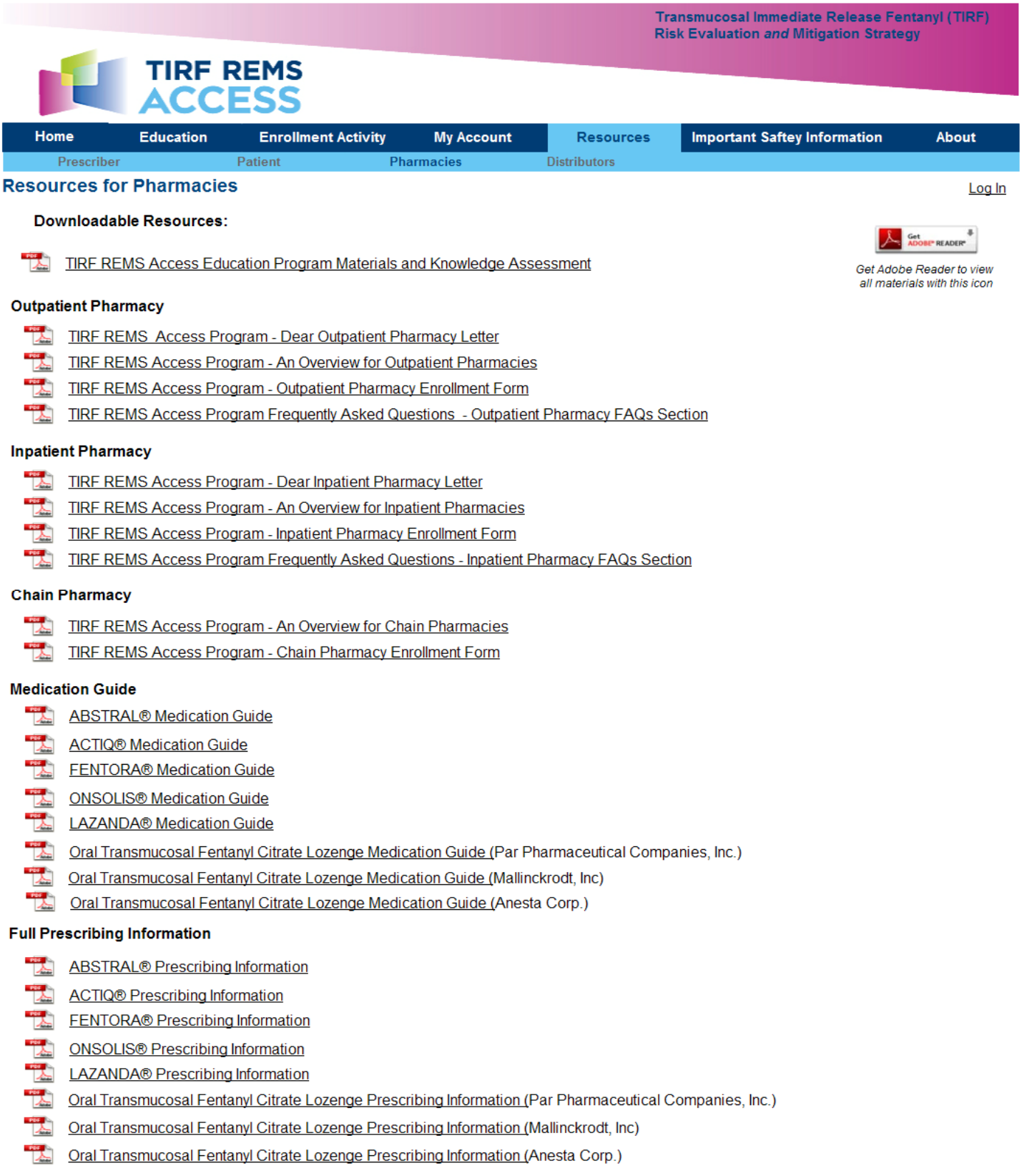
- ABSTRAL® Medication Guide
- ACTIQ® Medication Guide
- FENTORA® Medication Guide
- ONSOLIS® Medication Guide
- LAZANDA® Medication Guide
- Oral Transmucosal Fentanyl Citrate Lozenge Medication Guide (Par Pharmaceutical Companies, Inc.)
- Oral Transmucosal Fentanyl Citrate Lozenge Medication Guide (Mallinckrodt, Inc)
- Oral Transmucosal Fentanyl Citrate Lozenge Medication Guide (Anesta Corp.)

Full Prescribing Information

- ABSTRAL® Prescribing Information
- ACTIQ® Prescribing Information
- FENTORA® Prescribing Information
- ONSOLIS® Prescribing Information
- LAZANDA® Prescribing Information
- Oral Transmucosal Fentanyl Citrate Lozenge Prescribing Information (Par Pharmaceutical Companies, Inc.)
- Oral Transmucosal Fentanyl Citrate Lozenge Prescribing Information (Mallinckrodt, Inc)
- Oral Transmucosal Fentanyl Citrate Lozenge Prescribing Information (Anesta Corp.)

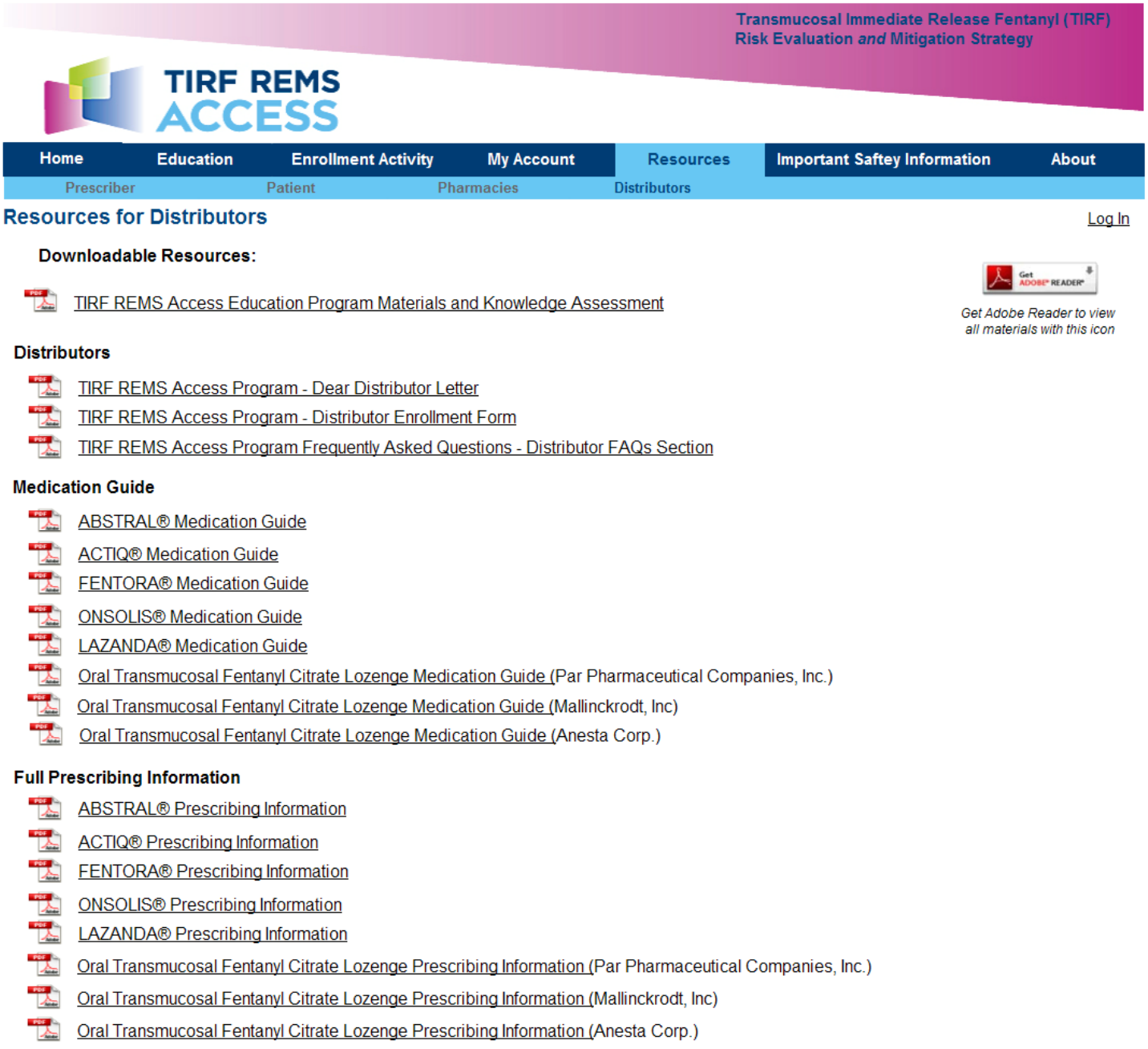
TIRF REMS Access Web Prototype

Resources for Pharmacies



TIRF REMS Access Web Prototype

Resources for Distributors



TIRF REMS Access Web Prototype

ABOUT

Log In

About the TIRF REMS Access Program

The Transmucosal Immediate Release Fentanyl (TIRF) products are available only through a Food and Drug Administration (FDA) mandated Risk Evaluation and Mitigation Strategy (REMS) program called the Transmucosal Immediate Release Fentanyl (TIRF) program. The TIRF REMS Access program is designed to ensure informed risk-benefit decisions before initiating treatment, and while patients are on treatment, to ensure appropriate use of TIRF medicines. The purpose of the TIRF REMS Access program is to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

Prescribers are not eligible to prescribe TIRF medicines for outpatient use unless they are enrolled in the TIRF REMS Access program after reviewing the prescriber educational materials, including the Full Prescribing Information and have successfully completed the Knowledge Assessment and enrollment form.

Patients must complete a Patient-Prescriber Agreement Form before they can be prescribed a TIRF medicine (not required for inpatients).

Outpatient Pharmacies will not be eligible to purchase or dispense TIRF medicines unless an authorized pharmacist has reviewed the TIRF REMS Access Education Program and successfully completed the Knowledge Assessment and enrollment form. Enrolled pharmacies can only dispense prescriptions for TIRF medicines if the prescriber and pharmacy are enrolled and active and the patient has not been inactivated in the program.

Inpatient Pharmacies will not be eligible to purchase or dispense TIRF medicines unless an authorized pharmacist has reviewed the TIRF REMS Access Education program and successfully completed the Knowledge Assessment and enrollment form. For inpatient use of Fentanyl , patient and prescriber enrollment in the TIRF REMS Access program is not required. Inpatient pharmacies may not dispense Fentanyl for outpatient use.

Distributors enrolled in the program must verify current enrollment of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines.

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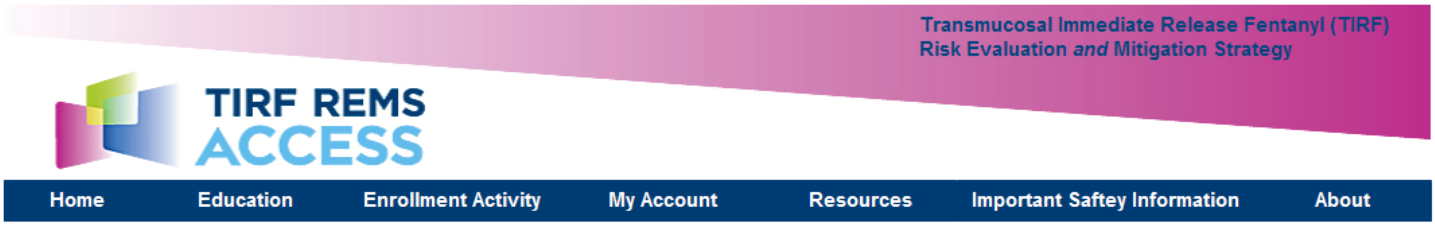
TIRF REMS Access Web Prototype

CONTACT US



Contact Us

If you have any questions, or require additional information, please call the TIRF REMS Access program at **1-866-822-1483.**

TIRF REMS Access program fax number: **1-866-822-1487.**

In the United States, please contact

TIRF REMS Access
PO BOX 29036
PHOENIX AZ 85038

www.TIRFREMSaccess.com

TIRF REMS Access Web Prototype

PRESCRIBER RE-ENROLLMENT

Home | Education | Enrollment Activity | My Account | Resources | Important Saftey Information | About

Login | Change Password | My Activity | Re-Enroll

Prescriber Re-Enrollment

<logged in as username> Logout

Re-Enrollment requires the following steps to be completed:

1. Confirm your current identifiers on file. You will be provided the opportunity to add, update or delete identifiers.
2. Re-review the TIRF REMS Access Education Program.
3. Re-take the TIRF REMS Access Knowledge Assessment.
4. Resubmit your enrollment form by providing your attestation and electronic signature.

Re-Enroll

INPATIENT PHARMACY RE-ENROLLMENT

Home | Education | Enrollment Activity | My Account | Resources | Important Saftey Information | About

Login | Change Password | My Activity | Re-Enroll

Inpatient Pharmacy Re-Enrollment

<logged in as username> Logout

Re-Enrollment requires the following steps to be completed:

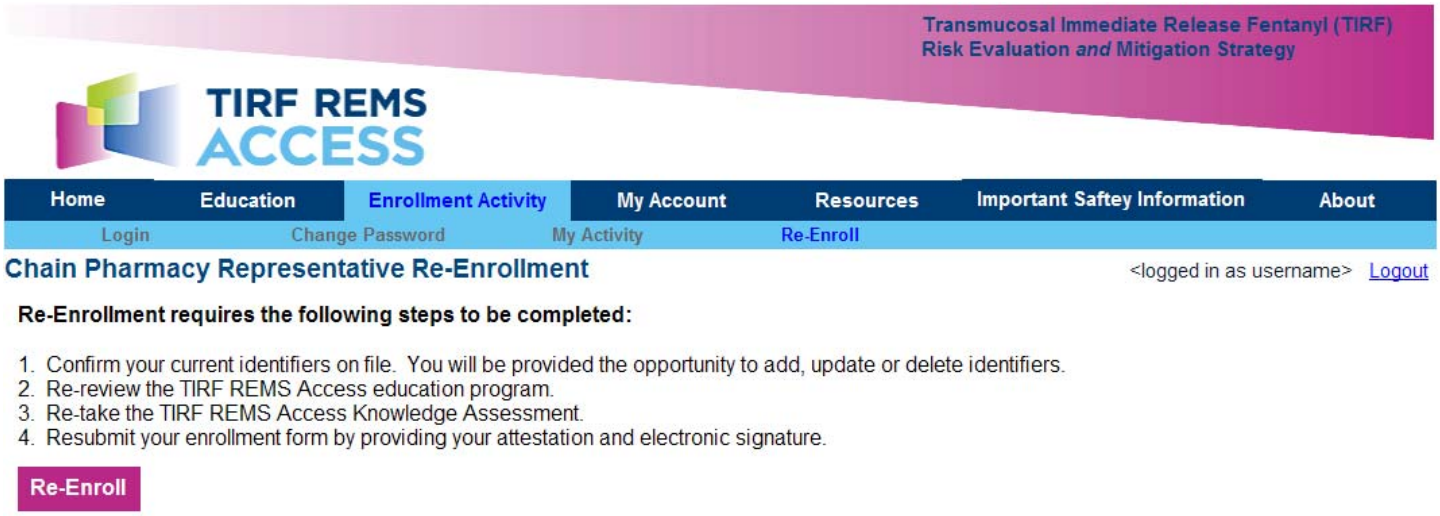
1. Confirm your current identifiers on file. You will be provided the opportunity to add, update or delete identifiers.
2. Re-review the TIRF REMS Access Education Program.
3. Re-take the TIRF REMS Access Knowledge Assessment.
4. Resubmit your enrollment form by providing your attestation and electronic signature.

Re-Enroll

TIRF REMS Access Web Prototype

OUTPATIENT PHARMACY RE-ENROLLMENT

CHAIN PHARMACY RE-ENROLLMENT



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ATTACHMENT 1

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Continued on next page

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

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PROPOSED TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for <u>outpatient</u> use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.

2) My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

4) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

5) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

6) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain pharmacy) or authorized pharmacist (outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. There is a different set of enrollment requirements for **outpatient pharmacies,** (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use), **including chain pharmacies,** and **inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Outpatient Pharmacy Enrollment Form* or the *Chain Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Outpatient Pharmacy Enrollment Form or Chain Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

e. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

g. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Outpatient Pharmacy, Chain Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Outpatient, Chain, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program. For outpatient pharmacies (including chain pharmacies) only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the TIRF REMS Access program. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2, respectively.

c. Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

   ii. The patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are

available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

2. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

3. TIRF Sponsors will develop a TIRF REMS Access system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

4. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF

medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

5. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. This will be accomplished by reconciling the *Patient-Prescriber Agreements* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.
6. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
7. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
8. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
9. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
10. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
11. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Product Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Product Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Prescribers

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.)). Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To prescribe TIRF medicines, you will need to enroll in the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, or receive TIRF medicines in an outpatient setting.

TIRF medicines which have previously been available under individual REMS programs have been transitioned to the shared TIRF REMS Access program.

For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

TIRF REMS Access Program Enrollment:

To reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines, you will need to be enrolled in the TIRF REMS Access program. Enrollment requires you to complete the TIRF REMS Access Education Program and Knowledge Assessment. The TIRF REMS Access Education Program and Knowledge Assessment are available online at the TIRF REMS Access program website (www.TIRFREMSaccess.com) or by contacting the TIRF REMS Access program call center at **1-866-822-1483** to request materials. When you enroll, you will be required to acknowledge your understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements. Without this enrollment, you will not be eligible to prescribe TIRF medicines for outpatient use. Outpatient prescriptions written by prescribers who are not enrolled, or for patients who are not enrolled, will not be authorized by the TIRF REMS Access program and will not be dispensed to the patient.

If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. You can use your existing secure username and password to access the TIRF REMS website at www.TIRFREMSaccess.com and prescribe all TIRF medicines. The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website (www.TIRFREMSaccess.com). Alternatively, you can request this information by calling **1-866-822-1483**.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS Program

- **Beginning mm/dd/yyyy,** your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2*: *If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

Patient Program Requirements:

Patient Education - *All Prescribers Who Prescribe to Outpatients*

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education program and the product-specific Full Prescribing Information.

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available on the TIRF REMS Access program website.
- Encourage the patient to ask questions.
- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).
- Submit the signed Patient-Prescriber Agreement Form to the TIRF REMS Access program through the TIRF REMS Access program website at www.TIRFREMSaccess.com. Submissions can also be made via fax at 1-866-822-1487.
- The signed Patient-Prescriber Agreement Form must be submitted within 10 working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

Prescribing

- Write a prescription for the appropriate TIRF medicine.
- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS program.

If you have any questions or require additional information or further copies of any TIRF REMS documents, please either visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

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		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
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		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
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		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl) buccal soluble film
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and Enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This education program contains key safety information critical for minimizing the risks associated with TIRF medicines.

- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program Overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.

- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.

- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guides for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.

- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid

- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.

- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.

- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

  Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.

- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.

- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse

- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines

- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically .mportant differences in the amount of fentanyl absorbed.
- TIRF medicines are not equivalent to any other fentanyl product, including another TIRF medicine¸ on a micro¸ram-per-micro¸ram basis. The onl¸ exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
  - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the cancer breakthrough pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl citrate) buccal tablet	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per breakthrough pain cancer episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl) buccal soluble film	Always 200 mcg.	**ONSOLIS should be used only once per cancer breakthrough pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.

- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You must take TIRF medicines exactly as prescribed.

Patient Counseling

Tell the patient (cont.):

- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
  - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
  - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy andreconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between ONLY two TIRF medicines has been established and is described in the Prescribing Information for which two products?
Select one option.

A. Lazanda to Actiq
B. Actiq to Fentora
C. Abstral to Fentora
D. Fentora to Actiq

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

Prescriber Name* (please print):_____

11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____	**State License Number*** _____
Address* _____	**State Issued*** _____
City* _____	**DEA Number*** _____
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

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To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.
2. My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
3. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
4. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
5. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
6. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number*** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program – I allow each of my doctors, pharmacists, and other healthcare providers to share personal information, that can be used to identify myself. This includes information about my medical problems, diseases, treatment, lab and prescription information, name, address and telephone number. This information is my "Health Information"

This information may be given to the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Evaluate the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.

III. Provide me with educational information about the TIRF REMS Access program.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

IV. Contact my health care providers to collect, enter and keep my Health Information in a secure TIRF REMS Access database.

V. Report to the FDA, about side effects from TIRF medicines and the TIRF REMS Access program effectiveness.

I understand that I am not required to sign this written approval.. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. The TIRF REMS Access program shall contact my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

How does a pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transaction(s) to validate the system enhancements.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on pharmacy chain enrollment below.)

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS?

Outpatient Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not to agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Chain Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF

REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
    - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

How does a pharmacy chain enroll in the TIRF REMS Access program?
An authorized chain pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?

If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website homepage under the link “Pharmacy Lookup”. You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?

Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy

needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing this class of products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you have previously enrolled in an individual TIRF REMS program, your enrollment information will be automatically entered into the new shared TIRF REMS program.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.

By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

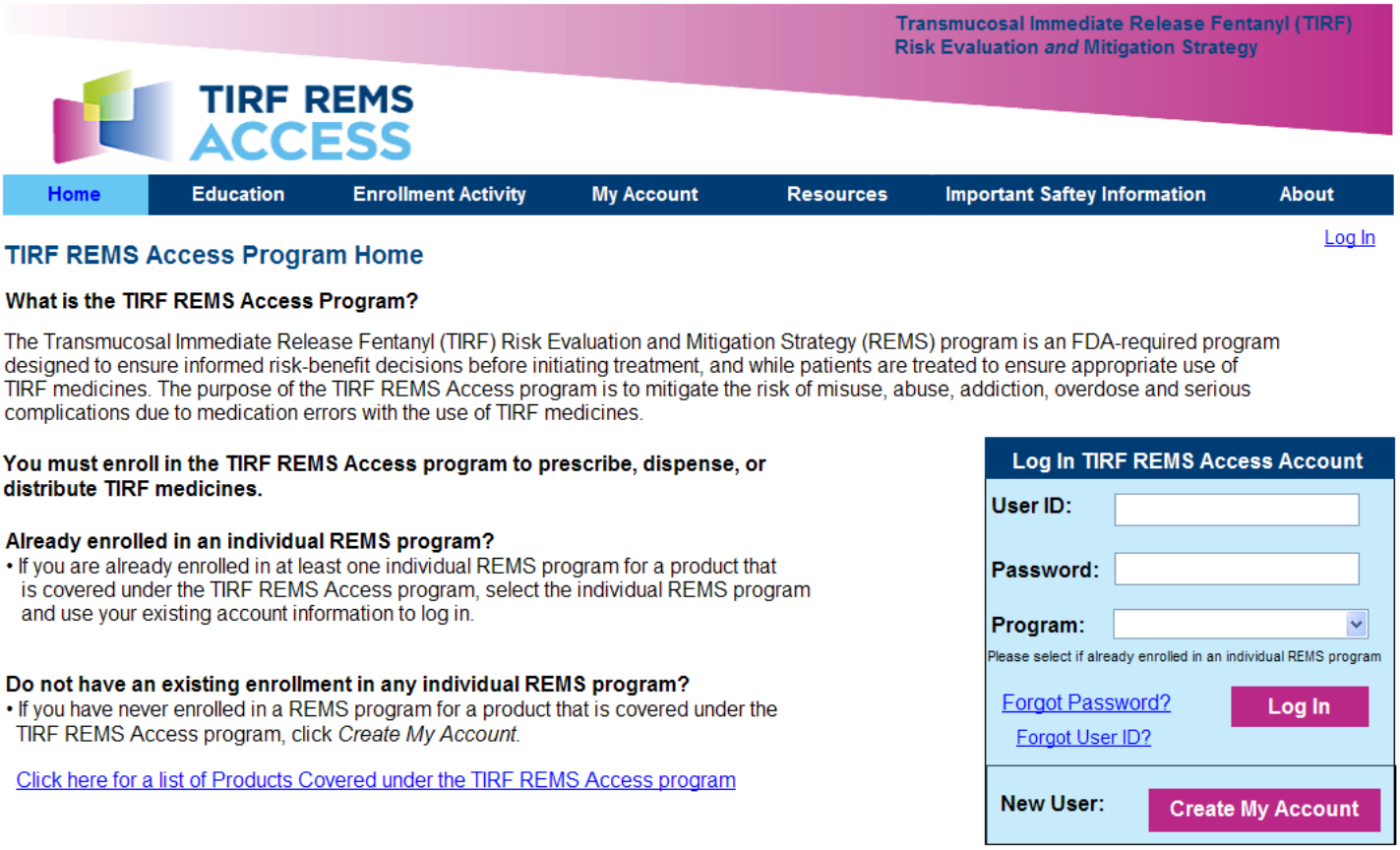
What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

TIRF REMS Access Web Prototype

HOME PAGE



Click here for a list of Products Covered under the TIRF REMS Access program hyper link will open the document in a pdf window

TIRF REMS Access Program

Products covered Under the TIRF REMS Access Program:

- Abstral ® (fentanyl) sublingual tablets
- Actiq ® (fentanyl citrate) oral transmucosal lozenge
- Fentora ® (fentanyl citrate) buccal tablet
- Lazanda ® (fentanyl) nasal spray
- Onsolis ® (fentanyl) sublingual spray
- Approved generic equivalents of these products are also covered under this program

Comprehensive table is also available at the Education section of the website

www.TIRFREMSaccess.com

Important Safety Information is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1
List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Outpatient Pharmacies

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1). Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To dispense TIRF medicines, your pharmacy will need to be enrolled in the TIRF REMS Access program.

Outpatient Pharmacy Enrollment

To reduce the risk of inappropriate patient selection and to ensure appropriate dosing and administration of TIRF medicines, your pharmacy will need to be enrolled in the TIRF REMS Access program. Enrollment requires the authorized pharmacist at the pharmacy to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the pharmacy.

Pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will be automatically transitioned to the shared TIRF REMS Access program but will need to agree to new terms and conditions before they can order and dispense all TIRF medicines.

The authorized pharmacist, who is enrolling on behalf of the pharmacy, must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines. Pharmacies will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Only enrolled pharmacies will be eligible to purchase or dispense TIRF medicines. In addition, pharmacies will only be able to dispense prescriptions if the patient and the prescriber are enrolled in the TIRF REMS Access program. Patients will be automatically enrolled in the TIRF REMS Access program upon processing of their first TIRF prescription. If the patient and/or the prescriber are not enrolled in the TIRF REMS Access program, the TIRF prescription will not be authorized by the TIRF REMS Access program, the pharmacy will receive a rejection message and the prescription will not be dispensed to the patient.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Options and Requirements for the TIRF REMS Access Program for Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in an individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.

Pharmacy Program Requirements:

Training Other Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Enrollment Confirmation

- Confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim from your pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment you must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800- FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Chain Pharmacies

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.) Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To dispense TIRF medicines, your pharmacy chain will need to be enrolled in the TIRF REMS Access program.

TIRF medicines, which may have previously been available under individual product REMS programs, will be transitioned to the shared TIRF REMS Access program.

Chain Pharmacy Enrollment
To reduce the risks of inappropriate patient selection and to ensure appropriate dosing and administration of TIRF medicines, chain pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized chain pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the chain.

Chain pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program but will need to execute a TIRF REMS Access contract with their switch provider before they can order and dispense all TIRF medicines.

The authorized chain pharmacy representative who is enrolling on behalf of the chain pharmacy must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy within the chain in the TIRF REMS Access program before shipping TIRF medicines. The chain pharmacy will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Only chain pharmacies that are enrolled in the TIRF REMS Access program will be eligible to purchase or dispense TIRF medicines. In addition, pharmacies within the chain will only be able to dispense prescriptions if the patient and the prescriber are enrolled in the TIRF REMS Access program. Patients will be automatically enrolled in the TIRF REMS Access program upon processing of their first TIRF prescription. If the patient and/or the prescriber are not

enrolled in the TIRF REMS Access program, the TIRF prescription will not be authorized by the TIRF REMS Access program, the chain pharmacy will receive a rejection message and the prescription will not be dispensed to the patient.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Overview of the TIRF REMS Access Program for Chain Pharmacies: Steps for Enrollment and Program Requirements

Chain Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS program:

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
  - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: ***If you do not have an existing enrollment in an individual REMS program:***

- Select an authorized chain pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Execute a TIRF REMS Access contract with your switch provider.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account and complete registration at the corporate level on behalf of your individual pharmacies.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Chain Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.
- Ensure the chain pharmacy enables the pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and ensure that the chain pharmacy runs the standardized validation test transactions to validate the system enhancements once on behalf of all their stores.

Chain Pharmacy Program Requirements:

Training Chain Pharmacy Staff

- Ensure that all chain pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the chain Authorized Representative on the Chain Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Enrollment Confirmation

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment the chain pharmacy practice management system must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.) Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

In order for inpatient pharmacies to dispense TIRF medicines for inpatient use only, the inpatient pharmacy must be enrolled in the TIRF REMS Access program. For inpatient administration of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Inpatient pharmacies must not dispense TIRF medicines for outpatient use.

Inpatient Pharmacy Enrollment
In order to reduce the risk of inappropriate patient selection, and to ensure appropriate dosing and administration of TIRF medicines, inpatient pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the pharmacy.

Inpatient pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program. You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

The authorized pharmacist must ensure that inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines. Pharmacies will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy** your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in an individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

Inpatient Pharmacy Program Requirements:

Implementation

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- The authorized inpatient pharmacist must ensure that the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch .
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Outpatient Pharmacy Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 - 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Pharmacist Name* (please print):_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Please note: If you are a Chain pharmacy, please complete the Chain Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65,
0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacist Name* (please print):_____

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

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		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
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		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
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		400 mcg	63459-544-28
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		800 mcg	63459-548-28
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		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
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Chain Pharmacy Enrollment Form

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To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of the TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Authorized Chain Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

Chain ID*:_____

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment

- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1

List of TIRF medicines Available only through the TIRF REMS Access program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

• Patient First Name..... TIRFREMSTEST
• Patient Last Name..... Smithers
• Date of Birth..... 19841105
• Patient ZIP/Postal Zone..... 07921
• Drug Name..... TIRFPRODUCT 100 mcg – NDC # 42747-0221-32
• Quantity Dispensed..... 12
• Days Supply..... 4
• Prescriber ID..... BA1111119
• Prescriber Last Name..... REMSTEST

• Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNN]***

° Next Step – Proceed to Test #2

° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1
List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
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		1600 mcg	63459-516-30
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		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

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		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
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- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1**: **If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

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LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
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		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
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		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date**_____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

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Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

Submitted to FDA via ESG

December 22, 2011

Keith Webber, Ph.D., Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

AMENDMENT TO SUPPLEMENT – PROPOSED REMS

RE: ANDA 077312
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Webber:

Reference is made to the above referenced application and Par's Supplement – Proposed REMS dated December 5, 2011, in which Par submitted a proposed REMS program as a sponsor participating in the TIRF REMS Program.

Subsequent to the submission of the referenced Supplement, the Agency, in working with the NDA holders of fentanyl products, has requested various changes to the originally submitted labeling, i.e, Package Insert and Medication Guide (PI/MG). Cephalon, the NDA holder for Actiq®, has informed Par of the additional revisions requested by the Agency.

As a sponsor participating in the TIRF REMS program, Par hereby submits this Amendment to our original Supplement to incorporate the changes requested by the Agency.

Per the telephone conversation today between Adolf Vezza, FDA, OGD, and Krista Richardson, Par Pharmaceuticals, Inc., it was agreed that clean versions of the PI and Medication Guide were preferred due to the amount of revisions that have since occurred. The requested labeling is provided in Module 1.14. Par has provided clean versions of the PI and Medication Guide in both Microsoft Word and PDF formats.

As stated in the original supplement, please note that the revised labelling provided does not represent the currently approved PI and Medication Guide for the application. The RLD (Actiq) was updated by Cephalon in July 2011 to implement REMS/safety information. Teva/Barr (former ANDA holder) did not implement the updates, as they were not part of an approved REMS program at that time. With the current initiative underway (TIRF REMS ACCESS program), Par has revised the subject labelling to be in compliance with the current RLD labelling, and is representative of what will be implemented upon approval of the REMS program.

This is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Krista Richardson

Digitally signed by Krista Richardson
DN: o=VeriSign Inc ou=VeriSign Trust Network ou=www verisign com/repository/RPA Incorp by Ref LIAB LTD(c)98 ou=Persona Not Validated ou=Digital ID Class 1 Microsoft Full Service cn=Krista Richardson email=krista richardson@parpharm com
Date: 2011 12 22 13:20:03 05'00'

Krista Richardson
Senior Manager, Regulatory Affairs

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Oral Transmucosal Fentanyl Citrate (OTFC) safely and effectively. See full prescribing information for OTFC.

Oral Transmucosal Fentanyl Citrate (OTFC) Lozenge, CII

Initial U.S. Approval: 1998

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depressions, OTFC is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)**
- **Keep out of reach of children. (5.3)**
- **Use with CYP450 3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucoal fentanyl product to OTFC. (2.1, 5.1)**
- **When dispensing, do not substitute with any other fentanyl products. (5.1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Oral Transmucosal Fentanyl Citrate (OTFC) is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.10)**

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	12/2011
Warnings and Precautions –TIRF REMS Access Program (5.10)	12/2011

----------INDICATIONS AND USAGE----------

Oral Transmucosal Fentanyl Citrate (OTFC) is an opioid agonist indicated for the management of breakthrough cancer pain in patients 16 and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

Limitations of Use:

OTFC may be dispensed only to patients enrolled in the TIRF REMS Access program. (1)

----------DOSAGE AND ADMINISTRATION----------

- Patients must require and use around-the-clock opioids when taking OTFC. (1)
- Initial dose of Oral Transmucosal Fentanyl Citrate (OTFC): 200 mcg. Prescribe an initial supply of six 200 mcg OTFC units. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single OTFC dosage unit per breakthrough cancer pain episode. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with OTFC. (2.3)
- Limit consumption to four or fewer units per day once successful dose is found. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Solid oral transmucosal lozenge in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraines and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl, OTFC, or its components. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Full and partially consumed Oral Transmucosal Fentanyl Citrate (OTFC) units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("OTFC Child Safety Kit"). (5.3)
- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate OTFC cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO_2 retention. (5.6, 5.7)

----------ADVERSE REACTIONS----------

Most common (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache, dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 option 2 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- See Boxed Warning and Warnings and Precautions (5.4, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Administer Oral Transmucosal Fentanyl Citrate (OTFC) with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with Oral Transmucosal Fentanyl Citrate (OTFC), including following use in opioid non-tolerant patients and improper dosing. The substitution of OTFC for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, OTFC is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Death has been reported in children who have accidentally ingested Oral Transmucosal Fentanyl Citrate (OTFC). OTFC must be kept out of reach of children. *[see Patient Counseling Information (17.3) and How Supplied/Storage and Handling(16.1)]*

The concomitant use of OTFC with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially cause fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to Oral Transmucosal Fentanyl Citrate (OTFC). *[see Dosage and Administration(2.1)]***
- **When dispensing, do not substitute an OTFC prescription for other fentanyl product.**

ABUSE POTENTIAL

Oral Transmucosal Fentanyl Citrate (OTFC) contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. OTFC can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OTFC in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, OTFC is available only through a restricted program required by the Food and Drug Administration, called the Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. *[see Warning and Precautions (5.10)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Oral Transmucosal Fentanyl Citrate (OTFC) is indicated for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain**.** Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking OTFC.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, OTFC is contraindicated in the management of acute or postoperative pain.

OTFC is intended to be used only in the care of opioid-tolerant cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Limitations of Use:

As a part of the TIRF REMS Access Program, OTFC may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.10)]*. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of OTFC, patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe OTFC on an outpatient basis must enroll in the TIRF REMS ACCESS program and comply with the requirements of the REMS to ensure safe use of OTFC *[see Warnings and Precautions (5.10)]*.

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

2.1 Initial Dose

Individually titrate Oral Transmucosal Fentanyl Citrate (OTFC) to a dose that provides adequate analgesia and minimizes side effects. The initial dose of OTFC to treat episodes of breakthrough cancer pain is **always** 200 mcg**.** The OTFC unit should be consumed over 15 minutes. Patients should be prescribed an initial titration supply of six 200 mcg OTFC units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose to prevent confusion and possible overdose.

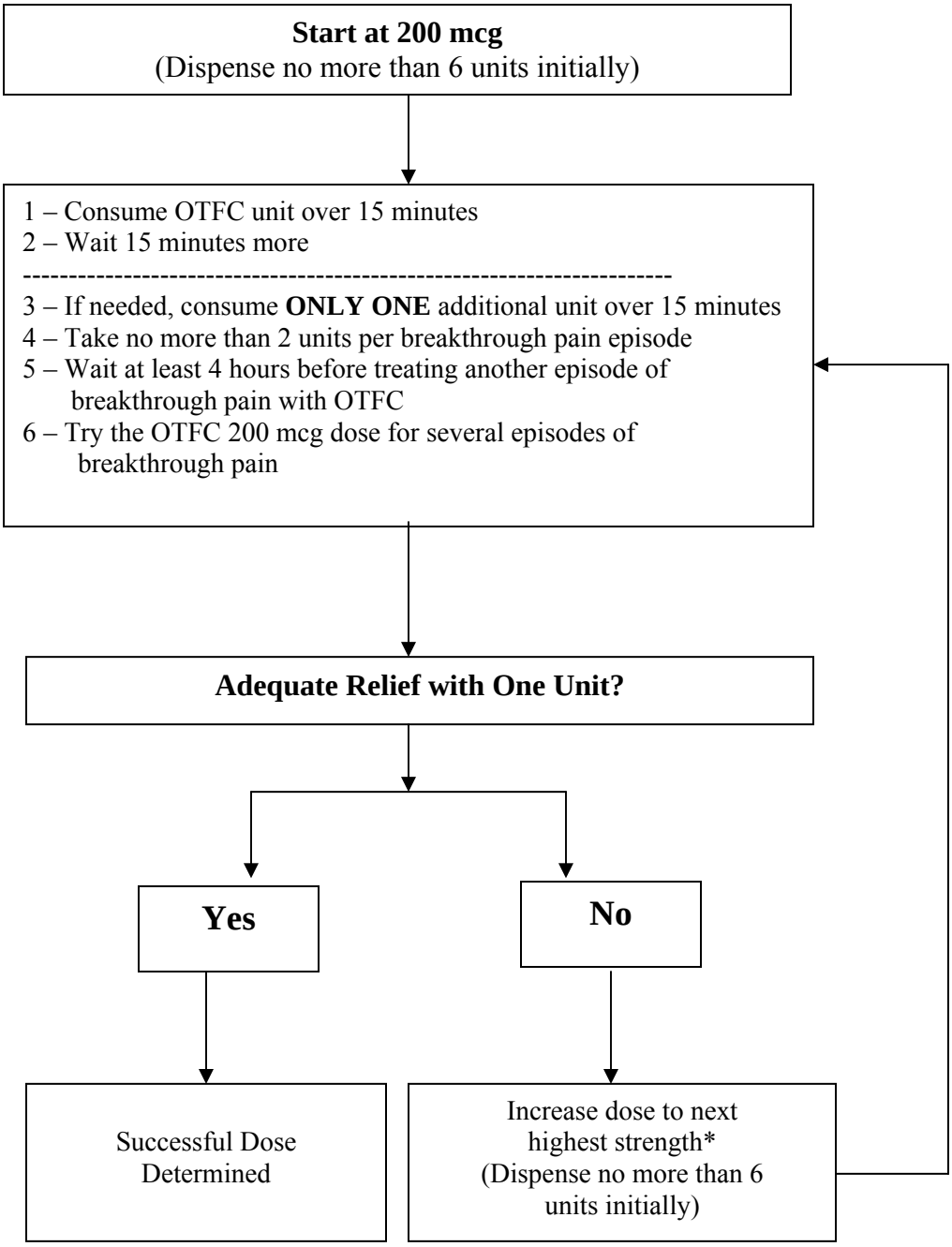
2.2 Dose Titration

From this initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single OTFC dosage unit per breakthrough cancer pain episode. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased. Patients should record their use of OTFC over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

In cases where the breakthrough pain episode is not relieved 15 minutes after completion of the OTFC unit (30 minutes after the start of the unit), patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus, patients should take a maximum of two doses of OTFC for any breakthrough pain episode.

Patients must wait **at least 4 hours** before treating another episode of breakthrough pain with OTFC. To reduce the risk of overdosing during titration, patients should have only one strength of OTFC available at any one time.

OTFC Titration Process
See Boxed Warning



* Available dosage strengths include: 200, 400, 600, 800, 1200, and 1600 mcg.

2.3 Maintenance Dosing

Once titrated to an effective dose, patients should generally use **ONLY ONE** Oral Transmucosal Fentanyl Citrate (OTFC) unit of the appropriate strength per breakthrough pain episode.

On those occasions when the breakthrough pain episode is not relieved 15 minutes after completion of the OTFC unit, patient may take **ONLY ONE** additional dose using the same strength for that episode.

Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with OTFC. Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day.

Dosage adjustment of OTFC may be required in some patients in order to continue to provide adequate relief of breakthrough pain.

Generally, the OTFC dose should be increased only when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

If the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated.

2.4 Administration of OTFC

Open the blister package with scissors immediately prior to product use. The patient should place the Oral Transmucosal Fentanyl Citrate (OTFC) unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The OTFC unit should be sucked, not chewed. A unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed [*see Clinical Pharmacology (12.3)*].

The OTFC unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in OTFC clinical trials. If signs of excessive opioid effects appear before the unit is consumed, remove the drug matrix from the patient's mouth immediately and decrease future doses.

2.5 Discontinuation of OTFC

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

3 DOSAGE FORMS AND STRENGTHS

Each dosage unit has white to off-white color and is a solid drug matrix on a handle. Each strength is marked on the individual solid drug matrix and the handle tag. Oral Transmucosal Fentanyl Citrate (OTFC) is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths [*see How Supplied/Storage and Handling (16.3)*].

4 CONTRAINDICATIONS

OTFC is contraindicated in opioid non-tolerant patients. OTFC is contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

OTFC is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of OTFC.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning - WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in ACTIQ. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 Important Information Regarding Prescribing and Dispensing

When prescribing, DO NOT convert a patient to OTFC from any other fentanyl product on a mcg per mcg basis as OTFC and other fentanyl products are not equivalent on a microgram per microgram basis.

OTFC is NOT a generic version of fentanyl buccal tablets (Fentora®). **When dispensing, DO NOT substitute an OTFC prescription for fentanyl buccal tablets (Fentora®) prescription under any circumstances. Fentanyl buccal tablets (Fentora®) and OTFC are not equivalent.** Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products including fentanyl buccal tablets (Fentora®) that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of OTFC for any other fentanyl product may result in a fatal overdose.**

There are no safe conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of OTFC should **always** be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [*see Dosage and Administration (2.2)*].

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that Oral Transmucosal Fentanyl Citrate (OTFC) contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested OTFC. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [s*ee How Supplied/Storage and Handling, (16.1, 16.2), Patient Counseling Information (17.3), and Medication Guide*].

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

OTFC could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

5.4 Additive CNS Depressant Effects

The concomitant use of OTFC with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., respiratory depression, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [*see Drug Interactions (7)*].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of OTFC if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate OTFC with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of OTFC may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer OTFC with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.8 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use OTFC with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors

OTFC is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose [*see Drug Abuse and Dependence(9)]*, OTFC is available only through a restricted program called the TIRF REMS Access Program. Under the TIRF REMS ACCESS program, outpatients, healthcare professionals who prescribe for outpatient use, pharmacies and distributors must enroll in the program. For inpatient administration, (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of OTFC, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access Program are:

- Healthcare professionals, who prescribe OTFC for outpatient use, must review the prescriber educational materials for the TIRF REMS Access Program, enroll in the program, and comply with the REMS requirements.
- To receive OTFC, patients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies, that dispense OTFC , must enroll in the program, and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute OTFC must enroll in the program, and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFREMSAccess.com or by calling 1-866-822 1483.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety of Oral Transmucosal Fentanyl Citrate (OTFC) has been evaluated in 257 opioid-tolerant chronic cancer pain patients. The duration of OTFC use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

The adverse reactions seen with OTFC are typical opioid side effects. Frequently, these adverse reactions will cease or decrease in intensity with continued use of OTFC, as the patient is titrated to the proper dose. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including OTFC are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

Because the clinical trials of OTFC were designed to evaluate safety and efficacy in treating breakthrough cancer pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received OTFC for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of OTFC therapy, or cancer-related symptoms. Adverse reactions are included regardless of causality or severity.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of OTFC that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. **Table 1** lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schemes used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1.

Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Titration

(Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=230)	800-1400 mcg (n=138)	1600 mcg (n=54)	>1600 mcg (n=41)	Any Dose* (n=254)
Body As A Whole					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2

Digestive					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	9	9	11	20	17
Confusion	1	6	2	0	4
Anxiety	3	0	2	0	3
Abnormal Gait	0	1	4	0	2
Dry Mouth	1	1	2	0	2
Nervousness	1	1	0	0	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following adverse reactions not reflected in **Table 1** occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, abdominal pain, chills, back pain, chest pain, infection

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

The following reactions occurred during titration with an overall frequency of less than 1% and are listed in descending order of frequency within each body system.

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

Nervous: Abnormal dreams, urinary retention, agitation, amnesia, emotional lability, euphoria, incoordination, libido decreased, neuropathy, paresthesia, speech disorder

Respiratory: Hemoptysis, pleural effusion, rhinitis, asthma, hiccup, pneumonia, respiratory insufficiency, sputum increased

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

Urogenital: Vaginal hemorrhage, dysuria, hematuria, urinary incontinence, urinary tract infection

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. **Table 2** lists by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse reactions are listed in descending order of frequency within each body system.

Table 2.

Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment
(Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=98)	800-1400 mcg (n=83)	1600 mcg (n=53)	>1600 mcg (n=27)	Any Dose* (n=152)

Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	9
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	36	25	26	45
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anxiety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confusion	2	5	13	7	10
Depression	9	4	2	7	9
Insomnia	5	1	8	4	7
Abnormal Gait	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	0	4	3
Stupor	4	1	0	0	3
Vasodilatation	1	1	4	0	3
Thinking Abnormal	2	1	0	0	2
Abnormal Dreams	1	1	0	0	1
Convulsion	0	1	2	0	1
Myoclonus	0	0	4	0	1
Tremor	0	1	2	0	1
Vertigo	0	0	4	0	1

Respiratory					
Dyspnea	15	16	8	7	22
Skin					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following reactions not reflected in **Table 2** occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

The following reactions occurred with a frequency of less than 1% in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness

Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

6.2 Postmarketing Experience

Adverse reactions are reported voluntarily from a population of uncertain size, and, therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to OTFC.

The following adverse reactions have been identified during post-approval use of OTFC (which contains approximately 2 grams of sugar per unit):

Digestive: Dental decay of varying severity including dental caries, tooth loss, and gum line erosion.

General Disorders and Administration Site Conditions: Application site reactions including irritation, pain, and ulcer.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when OTFC is given concurrently with agents that affect CYP3A4 activity. The concomitant use of OTFC with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole,

troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving OTFC concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, thus should be avoided.

Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.

Concomitant use of OTFC with an MAO inhibitor, or within 14 days of discontinuation, is not recommended [*see Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Oral Transmucosal Fentanyl Citrate (OTFC) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for OTFC.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m^2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore do not use OTFC during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use OTFC in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using OTFC.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below 16 years of age have not been established.

In a clinical study, 15 opioid-tolerant pediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with OTFC. The study was too small to allow conclusions on safety and efficacy in this patient population. Twelve of the fifteen opioid-tolerant children and adolescents aged 5 to 15 years in this study received OTFC at doses ranging from 200 mcg to 600 mcg. The mean (CV%; range) dose-normalized (to 200 mcg) C_{max} and AUC_{0-8} values were 0.87 ng/mL (51%; 0.42 to 1.30) and 4.54 ng·h/mL (42%; 2.37 to 6), respectively, for children ages 5 to <11 years old (N = 3) and 0.68 ng/mL (72%; 0.15 to 1.44) and 8.38 (192%; 0.84 to 50.78), respectively, for children ages ≥11 to <16 y (N = 9).

8.5 Geriatric Use

Of the 257 patients in clinical studies of OTFC in breakthrough cancer pain, 61 (24%) were 65 years of age and older, while 15 (6%) were 75 years of age and older. Those patients over the age of 65 years were titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in OTFC clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, exercise caution when individually titrating OTFC in elderly patients to provide adequate efficacy while minimizing risk.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of OTFC in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

8.7 Gender

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. Oral Transmucosal Fentanyl Citrate (OTFC) may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of OTFC to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [s*ee How Supplied/Storage and Handling (16.1, 16.2)*].

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since OTFC may be diverted for nonmedical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Guide the administration of OTFC by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of Oral Transmucosal Fentanyl Citrate (OTFC) overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being respiratory depression [*see Clinical Pharmacology (12.2)*].

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the OTFC unit, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of severe OTFC overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of respiratory depression or apnea, assist or control ventilation, and administer oxygen as indicated.

Although muscle rigidity interfering with respiration has not been seen following the use of OTFC, this is possible with fentanyl and other opioids. If it occurs, manage it by

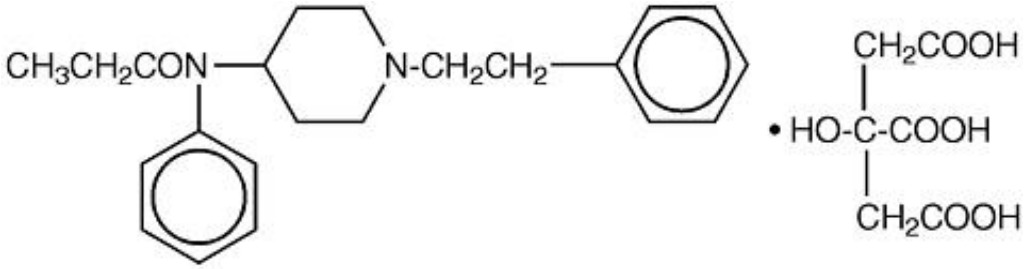
using assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

11 DESCRIPTION

Oral Transmucosal Fentanyl Citrate (OTFC) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. OTFC is formulated as a white to off-white solid drug matrix on a handle that is fracture resistant (ABS plastic) under normal conditions when used as directed.

OTFC is designed to be dissolved slowly in the mouth to facilitate transmucosal absorption. The handle allows the OTFC unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol, and purified shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of Oral Transmucosal Fentanyl Citrate (OTFC) should be individually titrated to achieve the desired effect [*see Dosage and Administration (2.2)*].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid

stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System

All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of OTFC. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Contraindications (4), Warnings and Precautions (5.2), Adverse Reactions (6), and Overdosage (10)*].

12.3 Pharmacokinetics

Absorption

The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

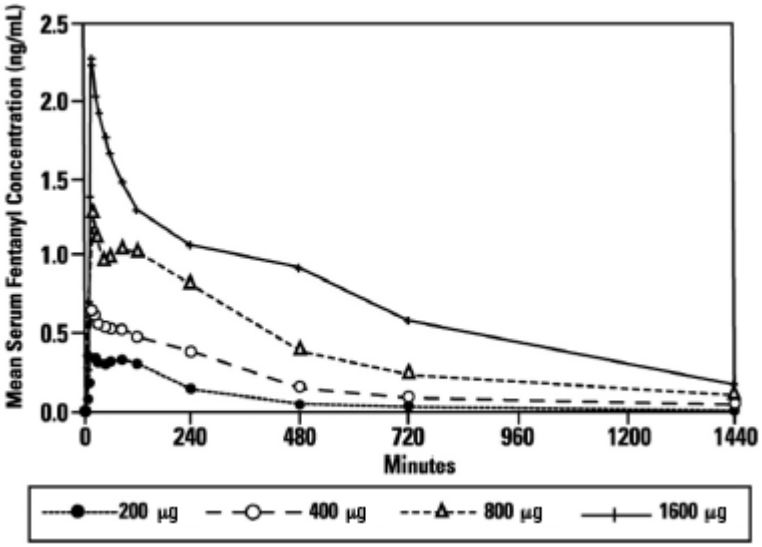
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

Normally, approximately 25% of the total dose of Oral Transmucosal Fentanyl Citrate (OTFC) is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of OTFC is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

Dose proportionality among four of the available strengths of OTFC (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects (n=11). Mean serum fentanyl levels following these four doses of OTFC are shown in **Figure 1**. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0\rightarrow\infty}$ increased in a dose-dependent manner that is approximately proportional to the OTFC administered.

Figure 1.

Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of OTFC



The pharmacokinetic parameters of the four strengths of OTFC tested in the dose-proportionality study are shown in Table 3. The mean C_{max} ranged from 0.39 to 2.51 ng/mL. The median time of maximum plasma concentration (T_{max}) across these four doses of OTFC varied from 20 to 40 minutes (range of 20 to 480 minutes) as measured after the start of administration.

Table 3.

Pharmacokinetic Parameters* in Adult Subjects
Receiving 200, 400, 800, and 1600 mcg Units of OTFC

Pharmacokinetic Parameter	**200 mcg**	**400 mcg**	**800 mcg**	**1600 mcg**
T_{max}, minute median (range)	40 (20 to 120)	25 (20 to 240)	25 (20 to 120)	20 (20 to 480)
C_{max}, ng/mL mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)
$t_{½}$, minute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

* Based on arterial blood samples.

Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80 to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady-state (Vss) was 4 L/kg.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies [*see Drug Interactions (7)*].

Elimination

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for OTFC.

14 CLINICAL STUDIES

Oral Transmucosal Fentanyl Citrate (OTFC) was investigated in clinical trials involving 257 opioid tolerant adult cancer patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in cancer patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of OTFC to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200 and 1600 mcg). A “successful” dose was defined as a dose where one unit of OTFC could be used consistently for at least two

consecutive days to treat breakthrough cancer pain without unacceptable side effects. In these studies 11% of patients withdrew due to adverse reactions and 14% withdrew due to other reasons.

The successful dose of OTFC for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and is thus best determined by dose titration.

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of OTFC for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in **Table 4**.

Table 4.

Successful Dose of OTFC Following Initial Titration

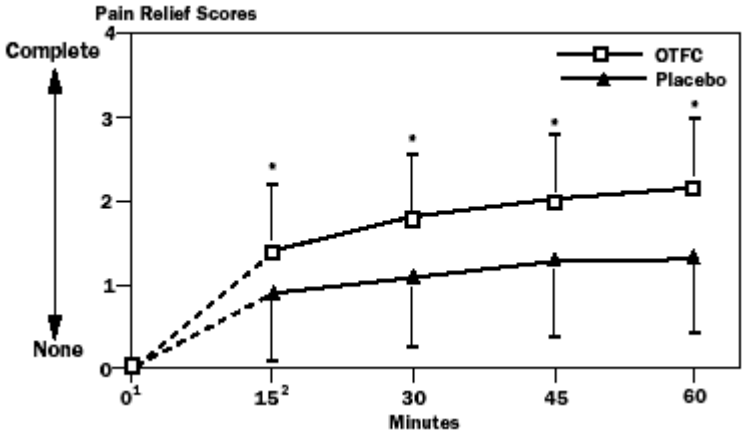
OTFC Dose	**Total No. (%) (N=92)**
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean +/- SD	789 +/- 468 mcg

On average, patients over 65 years of age titrated to a mean dose that was about 200 mcg less than the mean dose to which younger adult patients were titrated.

OTFC was administered beginning at Time 0 minutes and produced more pain relief compared with placebo at 15, 30, 45, and 60 minutes as measured after the start of administration (see **Figure 2**). The differences were statistically significant.

Figure 2.

Pain Relief (PR) Scores (Mean ± SD) During the Double-Blind Phase - All Patients with Evaluable Episodes on Both OTFC and Placebo (N=86)



[1] 0 minutes = Start of administration of OTFC
[2] 15 minutes = First time to measure pain relief

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in OTFC can be fatal to a child. Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)*].

Store at 20° to 25ºC (68° to 77ºF) [See USP Controlled Room Temperature] until ready to use. Protect OTFC from freezing and moisture. Do not use if the blister package has been opened.

16.2 Disposal of OTFC

Patients must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child-resistant blister package, yet may contain enough medicine to be fatal to a child [*see Patient Counseling Information (17.5)*].

A temporary storage bottle is provided as part of the Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit [*see Patient Counseling Information (17.4)*]. This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the *Medication Guide*.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in *Patient Counseling Information (17.6)* and in the *Medication Guide*. If additional assistance is required, call PAR PHARMACEUTICAL at 1-800-828-9393.

16.3 How Supplied

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

Each dosage unit has a white to off-white color. Each individual solid drug matrix is marked with "Fentanyl" and the strength of the unit ("200 mcg", "400 mcg", "600 mcg", "800 mcg" ,"1200 mcg", or "1600 mcg"). The dosage strength is also marked on the handle tag, the blister package and the carton. See blister package and carton for product information.

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied as white to off-white, round cylindrical shaped lozenges attached to a fracture resistant plastic handle, as:

200 mcg: Imprinted Fentanyl over 200 mcg in blue ink, debossed with 1 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

400 mcg: Imprinted Fentanyl over 400 mcg in blue ink, debossed with 2 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

600 mcg: Imprinted Fentanyl over 600 mcg in blue ink, debossed with 3 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

800 mcg: Imprinted Fentanyl over 800 mcg in blue ink, debossed with 4 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

1200 mcg: Imprinted Fentanyl over 1200 mcg in blue ink, debossed with 5 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

1600 mcg: Imprinted Fentanyl over 1600 mcg in blue ink, debossed with 6 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide)*.

17.1 Patient/Caregiver Instructions

- Before initiating treatment with Oral Transmucosal Fentanyl Citrate (OTFC), explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time OTFC is dispensed because new information may be available.
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive OTFC.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding OTFC or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access Program, prescribers must review the contents of the OTFC Medication Guide with every patient before initiating treatment with OTFC.
  - Advise the patient that OTFC is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug
  - Advise the patient that only enrolled healthcare providers may prescribe OTFC.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of OTFC.
  - Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program.

- **Patients and their caregivers must be instructed that children exposed to OTFC are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*See How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.2 and 5.3) and Medication Guide for specific patient instructions.*]
- Provide patients and their caregivers with a *Medication Guide* and review it with them each time OTFC is dispensed because new information may be available.
- Instruct patients and their caregivers to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [*see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3), and Patient Counseling Information (17.5)*].
- Instruct patients not to take OTFC for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and that OTFC is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.

- Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take OTFC.
- Instruct patients that, if the breakthrough pain episode is not relieved 15 minutes after finishing the OTFC unit, they may take **ONLY ONE ADDITIONAL UNIT OF OTFC USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take no more than two units of OTFC for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with OTFC.
- Instruct patients NOT to share OTFC and that sharing OTFC with anyone else could result in the other individual's death due to overdose.
- Make patients aware that OTFC contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in OTFC, fentanyl, is a drug that some people abuse. OTFC should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking OTFC.
- Instruct patients to use OTFC exactly as prescribed by their doctor and not to take OTFC more often than prescribed.
- Caution patients that OTFC can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.
- Warn patients to not combine OTFC with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Inform female patients that if they become pregnant or plan to become pregnant during treatment with OTFC, they should ask their doctor about the effects that OTFC (or any medicine) may have on them and their unborn children.
- Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

17.2 Dental Care

Because each OTFC unit contains approximately 2 grams of sugar, frequent consumption may increase the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Postmarketing reports of dental decay have been received in patients taking OTFC [*see Adverse Reactions (6.2)*]. In some of these patients, dental decay occurred despite reported routine oral hygiene. As dental decay in cancer patients may be multi-factorial, patients using OTFC should consult their dentist to ensure appropriate oral hygiene.

17.3 Diabetic Patients

Advise diabetic patients that OTFC contains approximately 2 grams of sugar per unit.

17.4 OTFC Child Safety Kit

Provide patients and their caregivers who have children in the home or visiting with an Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit, which contains educational materials and safe interim storage containers to help patients store OTFC and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, healthcare professionals can call PAR PHARMACEUTICAL at 1-800-391-5974.

17.5 Disposal of Used OTFC Units

Patients must be instructed to dispose of completely used and partially used OTFC units.

1. After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2. If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3. Dispose of handles in the child-resistant container (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the OTFC unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

17.6 Disposal of Unopened OTFC Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused OTFC units:

1. Remove the OTFC unit from its blister package using scissors, and hold the OTFC by its handle over the toilet bowl.
2. Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3. Dispose of the handle in a place that is out of the reach of children.
4. Repeat steps 1, 2, and 3 for each OTFC unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire OTFC units, OTFC handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it [*see How Supplied/Storage and Handling (16.1)*].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of OTFC are provided in the OTFC *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for PAR PHARMACEUTICAL (1-800-828-9393) or seek assistance from their local DEA office.

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt) Lozenge CII
(OTFC)

200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**

- You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
- You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**

4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

   OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.
   - **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
7. OTFC is available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of OTFC
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.

- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS ACCESS program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions

- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

- Your healthcare provider will explain the TIRF REMS ACCESS program to you.
- You will sign the TIRM REMS ACCESS program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS ACCESS program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC during each episode of breakthrough cancer pain:

- Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
- If your breakthrough cancer pain is not relieved 15 minutes after you finished the OTFC unit, use **only 1** more unit of OTFC at this time.
- If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**

- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:

   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**

2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088**.**

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
    - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
    - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-391-5974 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

- **A child-resistant lock that** you use to secure the storage space where you keep OTFC (See **Figure 1**).

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
    - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See **Figure 2**).

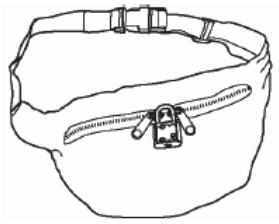


Figure 2

- **A child-resistant temporary storage bottle** (See **Figure 3**).

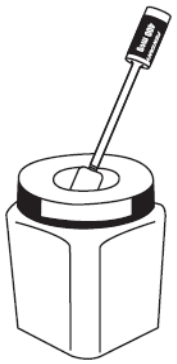


Figure 3

- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.
- **Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.**
- Keep OTFC dry.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.**

After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If **any** medicine remains on the used OTFC unit after you have finished:

- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See **Figure 4**).

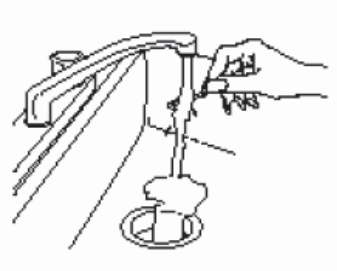


Figure 4

<u>Temporary Storage of Used OTFC Units</u>:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

<u>Disposing of Used OTFC Units from the Temporary Storage Bottle</u>:

You must dispose of all used OTFC units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See **Figure 6**).

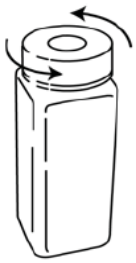


Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

Disposing of unopened OTFC units: Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all OTFC from the locked storage space (See **Figure 7**).

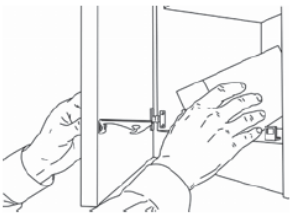


Figure 7

2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See **Figures 8A** and **8B**).

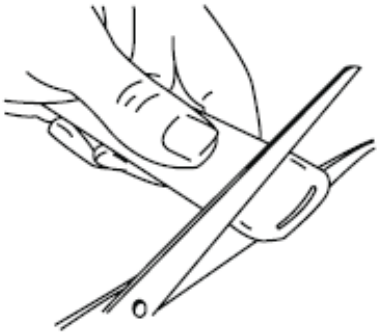


Figure 8A

Figure 8B

3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See **Figures 9A** and **9B**).

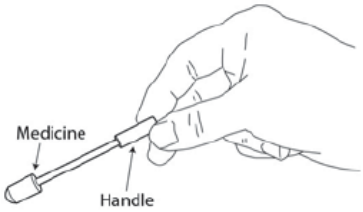


Figure 9A

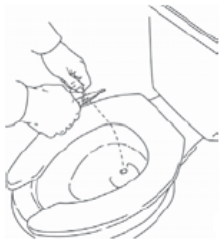


Figure 9B

4. Throw the handle away in a place that is out of the reach of children (See **Figure 10**).

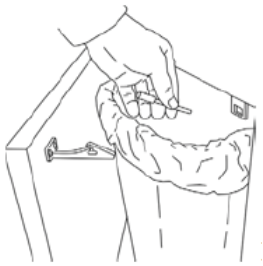


Figure 10

5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See **Figure 11**). Do not flush more than 5 OTFC units at a time.

Figure 11

• Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have**. OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.

For more information about the TIRF REMS ACCESS program, go to www.TIRFREMSaccess.com or call 1-866-822-1483.

What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

Active Ingredient: fentanyl citrate
Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See **Figure12**). **Do not open the blister package until you are ready to use OTFC.**

Figure 12

- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See **Figures 13A** and **13B**). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See **Figure 14**).

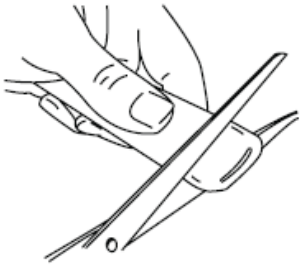


Figure 13A

Figure 13B

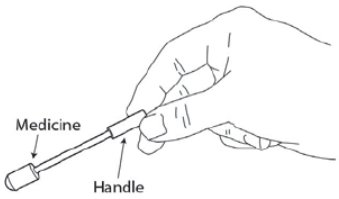


Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See **Figure 15**).

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured For:
PAR PHARMACEUTICAL
Spring Valley, NY 10977

U.S. Patent No. 7,908,729 Rev. 12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312/S-002

SUPPLEMENTAL APPROVAL

Par Pharmaceutical, Inc
Attention: Krista Richardson
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Richardson:

Please refer to your Supplemental Abbreviated New Drug Application (sANDA) dated December 5, 2011, received December 5, 2011 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg .

We also acknowledge receipt of your amendment dated December 22, 2011.

This "Prior Approval" supplemental new drug application provides for labeling updates and a proposed risk evaluation and mitigation strategy (REMS).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this ANDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for the class of transmucosal immediate-release fentanyl (TIRF) products, including OTCF, to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors. The details for the REMS requirements and the need for a single, shared system to implement the REMS for all members of the TIRF products were outlined in our REMS notification letters dated November 12, 2010 and August 19, 2011.

Your proposed REMS, submitted on December 5, 2011, with the agreed revisions and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and implementation system.

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. The individual sponsors who are part of the single shared system are collectively referred to as TIRF sponsors. This single shared system, TIRF REMS Access program, includes the following products:

NDA 021947	Fentora (fentanyl buccal tablets)
NDA 022266	Onsolis (fentanyl buccal soluble film)
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanyl) nasal spray
NDA 020747	Actiq (fentanyl citrate) oral transmucosal lozenge
ANDA 077312	Oral Transmucosal Fentanyl Citrate

Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy.

Prominently identify any submission containing a REMS proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR ANDA 077312
PROPOSED REMS MODIFICATION

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.80 and 314.81).

If you have any questions, call Adolph Vezza, Labeling Reviewer, at 240-276-8987

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosures:
REMS
Medication Guide
Final product Labeling

Initial REMS Approval: 12/2011

PROPOSED TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.

2) My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

4) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

5) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

6) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain pharmacy) or authorized pharmacist (outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. There is a different set of enrollment requirements for **outpatient pharmacies,** (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use), **including chain pharmacies,** and **inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment.*

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Outpatient Pharmacy Enrollment Form* or the *Chain Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Outpatient Pharmacy Enrollment Form or Chain Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

e. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

g. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Outpatient Pharmacy, Chain Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Outpatient, Chain, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program. For outpatient pharmacies (including chain pharmacies) only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. **TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.**

   a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

   b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the TIRF REMS Access program. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2, respectively.

   c. Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

      i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

      ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

   d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

      i. The patient has not filled a prescription for more than six (6) months.

      ii. The patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

   e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

   f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

   g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are

available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

2. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

3. TIRF Sponsors will develop a TIRF REMS Access system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

4. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF

medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

5. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. This will be accomplished by reconciling the *Patient-Prescriber Agreements* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.
6. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
7. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
8. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
9. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
10. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
11. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Prescribers

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.). Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To prescribe TIRF medicines, you will need to enroll in the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, distributors and patients enrolled in the program are able to prescribe, dispense, distribute, or receive TIRF medicines in an outpatient setting.

TIRF medicines which have previously been available under individual REMS programs have been transitioned to the shared TIRF REMS Access program.

For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

TIRF REMS Access Program Enrollment:

To reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines, you will need to be enrolled in the TIRF REMS Access program. Enrollment requires you to complete the TIRF REMS Access Education Program and Knowledge Assessment. The TIRF REMS Access Education Program and Knowledge Assessment are available online at the TIRF REMS Access program website (www.TIRFREMSaccess.com) or by contacting the TIRF REMS Access program call center at **1-866-822-1483** to request materials. When you enroll, you will be required to acknowledge your understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements. Without this enrollment, you will not be eligible to prescribe TIRF medicines for outpatient use. Outpatient prescriptions written by prescribers who are not enrolled, or for patients who are not enrolled, will not be authorized by the TIRF REMS Access program and will not be dispensed to the patient.

If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. You can use your existing secure username and password to access the TIRF REMS website at www.TIRFREMSaccess.com and prescribe all TIRF medicines. The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website (www.TIRFREMSaccess.com). Alternatively, you can request this information by calling **1-866-822-1483**.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS Program

- **Beginning mm/dd/yyyy,** your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2*: *If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

Patient Program Requirements:

Patient Education - *All Prescribers Who Prescribe to Outpatients*

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education program and the product-specific Full Prescribing Information.

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available on the TIRF REMS Access program website.
- Encourage the patient to ask questions.
- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).
- Submit the signed Patient-Prescriber Agreement Form to the TIRF REMS Access program through the TIRF REMS Access program website at www.TIRFREMSaccess.com. Submissions can also be made via fax at 1-866-822-1487.
- The signed Patient-Prescriber Agreement Form must be submitted within 10 working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

Prescribing

- Write a prescription for the appropriate TIRF medicine.
- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS program.

If you have any questions or require additional information or further copies of any TIRF REMS documents, please either visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl) buccal soluble film
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and Enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1.Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2.Preventing inappropriate conversion between fentanyl products.

3.Preventing accidental exposure to children and others for whom it was not prescribed.

4.Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This education program contains key safety information critical for minimizing the risks associated with TIRF medicines.

- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program Overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.

- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.

- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guides for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patient with cancer ~~18 years of a~~ge and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.

- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid

- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.

- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.

- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

  Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.

- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.

- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse

- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines

- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are not equivalent to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
  - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the cancer breakthrough pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl citrate) buccal tablet	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per breakthrough pain cancer episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl) buccal soluble film	Always 200 mcg.	**ONSOLIS should be used only once per cancer breakthrough pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.

- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You must take TIRF medicines exactly as prescribed.

Patient Counseling

Tell the patient (cont.):

- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
  - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
  - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between ONLY two TIRF medicines has been established and is described in the Prescribing Information for which two products?
Select one option.

A. Lazanda to Actiq
B. Actiq to Fentora
C. Abstral to Fentora
D. Fentora to Actiq

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Additional Prescriber Information (All Fields Required)

Site Name* _____	**State License Number*** _____
Address* _____	**State Issued*** _____
City* _____	**DEA Number*** _____
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.
2. My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
3. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
4. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
5. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
6. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Reference ID: 3064426

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number*** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program – I allow each of my doctors, pharmacists, and other healthcare providers to share personal information, that can be used to identify myself. This includes information about my medical problems, diseases, treatment, lab and prescription information, name, address and telephone number. This information is my "Health Information"

This information may be given to the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Evaluate the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.

III. Provide me with educational information about the TIRF REMS Access program.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

IV. Contact my health care providers to collect, enter and keep my Health Information in a secure TIRF REMS Access database.

V. Report to the FDA, about side effects from TIRF medicines and the TIRF REMS Access program effectiveness.

I understand that I am not required to sign this written approval.. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. The TIRF REMS Access program shall contact my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs
II. PATIENT FAQs
III. OUTPATIENT PHARMACY FAQs
IV. PRESCRIBER FAQs
V. INPATIENT PHARMACY FAQs
VI. DISTRIBUTOR (WHOLESALER) FAQs

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

How does a pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transaction(s) to validate the system enhancements.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on pharmacy chain enrollment below.)

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS?

Outpatient Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not to agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Chain Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF

REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
    - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

How does a pharmacy chain enroll in the TIRF REMS Access program?
An authorized chain pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?

If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website homepage under the link “Pharmacy Lookup”. You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?

Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy

needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing this class of products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you have previously enrolled in an individual TIRF REMS program, your enrollment information will be automatically entered into the new shared TIRF REMS program.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.

By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

TIRF REMS Access Web Prototype

IMPORTANT SAFETY INFORMATION

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
Patients considered opioid-tolerant are those who are taking:
- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions
The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting
Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at 1-866-822-1483. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide
It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

You must provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:
- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at 1-866-822-1483.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For <u>inpatient</u> administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Outpatient Pharmacies

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1). Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To dispense TIRF medicines, your pharmacy will need to be enrolled in the TIRF REMS Access program.

Outpatient Pharmacy Enrollment

To reduce the risk of inappropriate patient selection and to ensure appropriate dosing and administration of TIRF medicines, your pharmacy will need to be enrolled in the TIRF REMS Access program. Enrollment requires the authorized pharmacist at the pharmacy to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the pharmacy.

Pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will be automatically transitioned to the shared TIRF REMS Access program but will need to agree to new terms and conditions before they can order and dispense all TIRF medicines.

The authorized pharmacist, who is enrolling on behalf of the pharmacy, must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines. Pharmacies will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Only enrolled pharmacies will be eligible to purchase or dispense TIRF medicines. In addition, pharmacies will only be able to dispense prescriptions if the patient and the prescriber are enrolled in the TIRF REMS Access program. Patients will be automatically enrolled in the TIRF REMS Access program upon processing of their first TIRF prescription. If the patient and/or the prescriber are not enrolled in the TIRF REMS Access program, the TIRF prescription will not be authorized by the TIRF REMS Access program, the pharmacy will receive a rejection message and the prescription will not be dispensed to the patient.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Options and Requirements for the TIRF REMS Access Program for Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in an individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.

Pharmacy Program Requirements:

Training Other Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Enrollment Confirmation

- Confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim from your pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment you must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800- FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Chain Pharmacies

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.) Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

To dispense TIRF medicines, your pharmacy chain will need to be enrolled in the TIRF REMS Access program.

TIRF medicines, which may have previously been available under individual product REMS programs, will be transitioned to the shared TIRF REMS Access program.

Chain Pharmacy Enrollment
To reduce the risks of inappropriate patient selection and to ensure appropriate dosing and administration of TIRF medicines, chain pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized chain pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the chain.

Chain pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program but will need to execute a TIRF REMS Access contract with their switch provider before they can order and dispense all TIRF medicines.

The authorized chain pharmacy representative who is enrolling on behalf of the chain pharmacy must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy within the chain in the TIRF REMS Access program before shipping TIRF medicines. The chain pharmacy will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Only chain pharmacies that are enrolled in the TIRF REMS Access program will be eligible to purchase or dispense TIRF medicines. In addition, pharmacies within the chain will only be able to dispense prescriptions if the patient and the prescriber are enrolled in the TIRF REMS Access program. Patients will be automatically enrolled in the TIRF REMS Access program upon processing of their first TIRF prescription. If the patient and/or the prescriber are not

enrolled in the TIRF REMS Access program, the TIRF prescription will not be authorized by the TIRF REMS Access program, the chain pharmacy will receive a rejection message and the prescription will not be dispensed to the patient.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Overview of the TIRF REMS Access Program for Chain Pharmacies: Steps for Enrollment and Program Requirements

Chain Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:

Option 1: If you are already enrolled in at least one individual REMS program:

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
  - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: ***If you do not have an existing enrollment in an individual REMS program:***

- Select an authorized chain pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Execute a TIRF REMS Access contract with your switch provider.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account and complete registration at the corporate level on behalf of your individual pharmacies.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Chain Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.
- Ensure the chain pharmacy enables the pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and ensure that the chain pharmacy runs the standardized validation test transactions to validate the system enhancements once on behalf of all their stores.

Chain Pharmacy Program Requirements:

Training Chain Pharmacy Staff

- Ensure that all chain pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the chain Authorized Representative on the Chain Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Enrollment Confirmation

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment the chain pharmacy practice management system must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines (refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.) Because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors, TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA).

In order for inpatient pharmacies to dispense TIRF medicines for inpatient use only, the inpatient pharmacy must be enrolled in the TIRF REMS Access program. For inpatient administration of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Inpatient pharmacies must not dispense TIRF medicines for outpatient use.

Inpatient Pharmacy Enrollment
In order to reduce the risk of inappropriate patient selection, and to ensure appropriate dosing and administration of TIRF medicines, inpatient pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the pharmacy.

Inpatient pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program. You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

The authorized pharmacist must ensure that inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines. Pharmacies will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Important Information about Outpatient Pharmacies within the Facility
Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

Enrollment Options:
Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy** your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in an individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

Inpatient Pharmacy Program Requirements:

Implementation

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- The authorized inpatient pharmacist must ensure that the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Monitoring

- Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch .
- Respond to requests for additional information from the TIRF REMS Access program.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Outpatient Pharmacy Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 - 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Pharmacist Name* (please print):_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Please note: If you are a Chain pharmacy, please complete the Chain Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65,
0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacist Name* (please print):_____

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Pharmacy Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of the TIRF medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Authorized Chain Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, ""the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55523-0072-30, 55523-0073-30, 55253-0074-30, 55253-0075-30,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

Chain ID*:_____

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserves the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment

- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

• Patient First Name..... TIRFREMSTEST
• Patient Last Name..... Smithers
• Date of Birth..... 19841105
• Patient ZIP/Postal Zone..... 07921
• Drug Name..... TIRFPRODUCT 100 mcg – NDC # 42747-0221-32
• Quantity Dispensed..... 12
• Days Supply..... 4
• Prescriber ID..... BA1111119
• Prescriber Last Name..... REMSTEST

• Test #1 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicines.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1*: *If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Oral Transmucosal Fentanyl Citrate (OTFC) safely and effectively. See full prescribing information for OTFC.

Oral Transmucosal Fentanyl Citrate (OTFC) Lozenge, CII

Initial U.S. Approval: 1998

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depressions, OTFC is contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (4)**
- **Keep out of reach of children. (5.3)**
- **Use with CYP450 3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucoal fentanyl product to OTFC. (2.1, 5.1)**
- **When dispensing, do not substitute with any other fentanyl products. (5.1)**
- **Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. (9.1)**
- **Oral Transmucosal Fentanyl Citrate (OTFC) is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.10)**

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	12/2011
Warnings and Precautions –TIRF REMS Access Program (5.10)	12/2011

----------INDICATIONS AND USAGE----------

Oral Transmucosal Fentanyl Citrate (OTFC) is an opioid agonist indicated for the management of breakthrough cancer pain in patients 16 and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

Limitations of Use:

OTFC may be dispensed only to patients enrolled in the TIRF REMS Access program. (1)

----------DOSAGE AND ADMINISTRATION----------

- Patients must require and use around-the-clock opioids when taking OTFC. (1)
- Initial dose of Oral Transmucosal Fentanyl Citrate (OTFC): 200 mcg. Prescribe an initial supply of six 200 mcg OTFC units. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single OTFC dosage unit per breakthrough cancer pain episode. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with OTFC. (2.3)
- Limit consumption to four or fewer units per day once successful dose is found. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- Solid oral transmucosal lozenge in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain including headache/migraines and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl, OTFC, or its components. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Full and partially consumed Oral Transmucosal Fentanyl Citrate (OTFC) units contain medicine that can be fatal to a child. Ensure proper storage and disposal. Interim safe storage container available ("OTFC Child Safety Kit"). (5.3)
- Use with other CNS depressants and potent cytochrome P450 3A4 inhibitors may increase depressant effects including respiratory depression, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate OTFC cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression and in patients susceptible to intracranial effects of CO_2 retention. (5.6, 5.7)

----------ADVERSE REACTIONS----------

Most common (frequency ≥5%): nausea, dizziness, somnolence, vomiting, asthenia, and headache, dyspnea, constipation, anxiety, confusion, depression, rash, and insomnia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 option 2 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

- See Boxed Warning and Warnings and Precautions (5.4, 7)

----------USE IN SPECIFIC POPULATIONS----------

- Administer Oral Transmucosal Fentanyl Citrate (OTFC) with caution to patients with liver or kidney dysfunction. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with Oral Transmucosal Fentanyl Citrate (OTFC), including following use in opioid non-tolerant patients and improper dosing. The substitution of OTFC for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, OTFC is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Death has been reported in children who have accidentally ingested Oral Transmucosal Fentanyl Citrate (OTFC). OTFC must be kept out of reach of children. *[see Patient Counseling Information (17.3) and How Supplied/Storage and Handling(16.1)]*

The concomitant use of OTFC with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially cause fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in fatal overdose.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to Oral Transmucosal Fentanyl Citrate (OTFC). *[see Dosage and Administration(2.1)]***
- **When dispensing, do not substitute an OTFC prescription for other fentanyl product.**

ABUSE POTENTIAL

Oral Transmucosal Fentanyl Citrate (OTFC) contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. OTFC can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OTFC in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

Because of the risk for misuse, abuse, addiction, and overdose, OTFC is available only through a restricted program required by the Food and Drug Administration, called the Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program. *[see Warning and Precautions (5.10)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Oral Transmucosal Fentanyl Citrate (OTFC) is indicated for the management of breakthrough cancer pain in patients 16 and older with malignancies who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain**.** Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids when taking OTFC.

This product **must not** be used in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, OTFC is contraindicated in the management of acute or postoperative pain.

OTFC is intended to be used only in the care of opioid-tolerant cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain.

Limitations of Use:

As a part of the TIRF REMS Access Program, OTFC may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.10)]*. For inpatient administration (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of OTFC, patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe OTFC on an outpatient basis must enroll in the TIRF REMS ACCESS program and comply with the requirements of the REMS to ensure safe use of OTFC *[see Warnings and Precautions (5.10)]*.

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

2.1 Initial Dose

Individually titrate Oral Transmucosal Fentanyl Citrate (OTFC) to a dose that provides adequate analgesia and minimizes side effects. The initial dose of OTFC to treat episodes of breakthrough cancer pain is **always** 200 mcg**.** The OTFC unit should be consumed over 15 minutes. Patients should be prescribed an initial titration supply of six 200 mcg OTFC units, thus limiting the number of units in the home during titration. Patients should use up all units before increasing to a higher dose to prevent confusion and possible overdose.

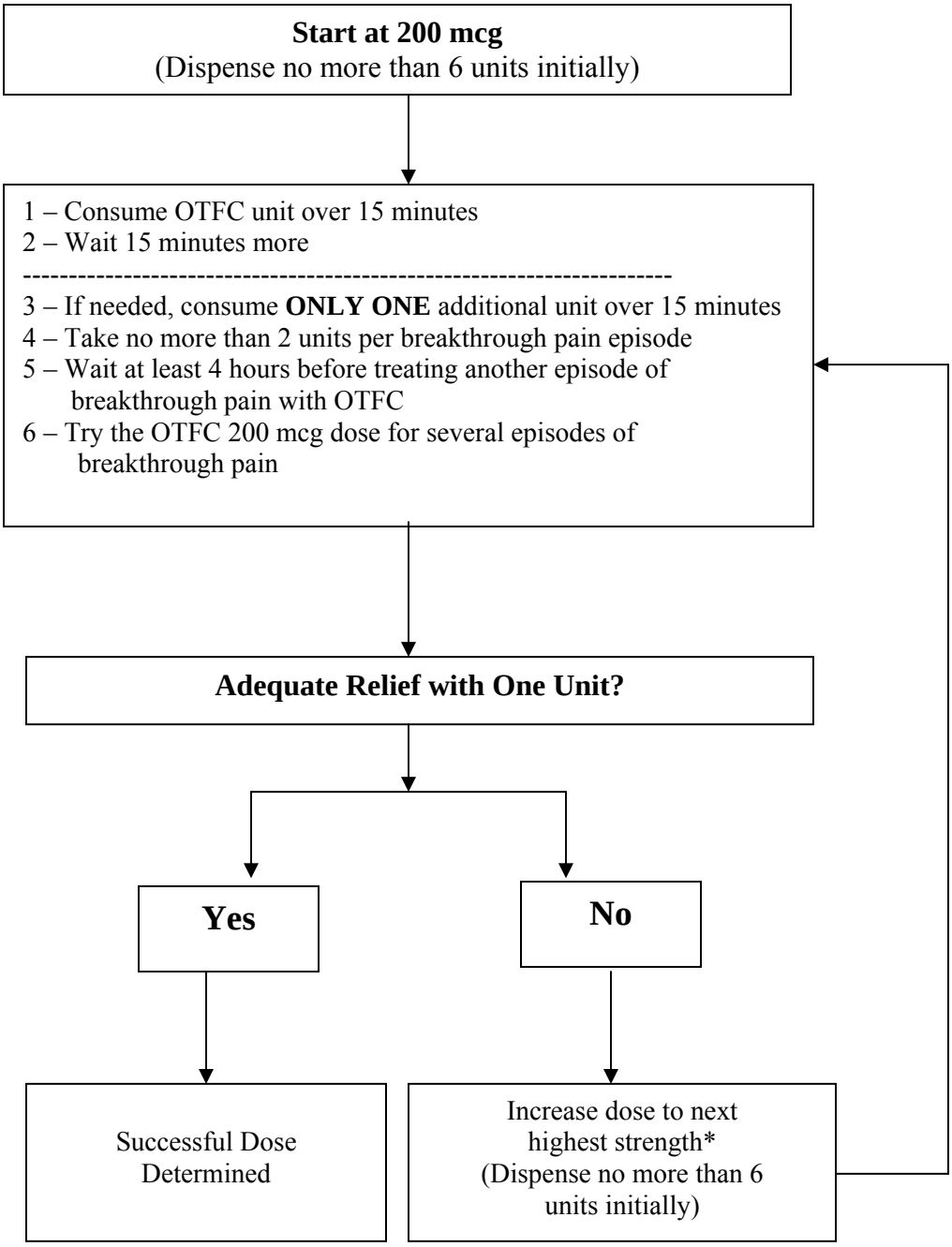
2.2 Dose Titration

From this initial dose, closely follow patients and change the dosage level until the patient reaches a dose that provides adequate analgesia using a single OTFC dosage unit per breakthrough cancer pain episode. If signs of excessive opioid effects appear before the unit is consumed, the dosage unit should be removed from the patient's mouth immediately, disposed of properly, and subsequent doses should be decreased. Patients should record their use of OTFC over several episodes of breakthrough cancer pain and review their experience with their physicians to determine if a dosage adjustment is warranted.

In cases where the breakthrough pain episode is not relieved 15 minutes after completion of the OTFC unit (30 minutes after the start of the unit), patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus, patients should take a maximum of two doses of OTFC for any breakthrough pain episode.

Patients must wait **at least 4 hours** before treating another episode of breakthrough pain with OTFC. To reduce the risk of overdosing during titration, patients should have only one strength of OTFC available at any one time.

OTFC Titration Process
See Boxed Warning



* Available dosage strengths include: 200, 400, 600, 800, 1200, and 1600 mcg.

2.3 Maintenance Dosing

Once titrated to an effective dose, patients should generally use **ONLY ONE** Oral Transmucosal Fentanyl Citrate (OTFC) unit of the appropriate strength per breakthrough pain episode.

On those occasions when the breakthrough pain episode is not relieved 15 minutes after completion of the OTFC unit, patient may take **ONLY ONE** additional dose using the same strength for that episode.

Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with OTFC. Once a successful dose has been found (i.e., an average episode is treated with a single unit), patients should limit consumption to four or fewer units per day.

Dosage adjustment of OTFC may be required in some patients in order to continue to provide adequate relief of breakthrough pain.

Generally, the OTFC dose should be increased only when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

If the patient experiences greater than four breakthrough pain episodes per day, the dose of the maintenance (around-the-clock) opioid used for persistent pain should be re-evaluated.

2.4 Administration of OTFC

Open the blister package with scissors immediately prior to product use. The patient should place the Oral Transmucosal Fentanyl Citrate (OTFC) unit in his or her mouth between the cheek and lower gum, occasionally moving the drug matrix from one side to the other using the handle. The OTFC unit should be sucked, not chewed. A unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed [*see Clinical Pharmacology (12.3)*].

The OTFC unit should be consumed over a 15-minute period. Longer or shorter consumption times may produce less efficacy than reported in OTFC clinical trials. If signs of excessive opioid effects appear before the unit is consumed, remove the drug matrix from the patient's mouth immediately and decrease future doses.

2.5 Discontinuation of OTFC

For patients requiring discontinuation of opioids, a gradual downward titration is recommended because it is not known at what dose level the opioid may be discontinued without producing the signs and symptoms of abrupt withdrawal.

3 DOSAGE FORMS AND STRENGTHS

Each dosage unit has white to off-white color and is a solid drug matrix on a handle. Each strength is marked on the individual solid drug matrix and the handle tag. Oral Transmucosal Fentanyl Citrate (OTFC) is available in 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg strengths [*see How Supplied/Storage and Handling (16.3)*].

4 CONTRAINDICATIONS

OTFC is contraindicated in opioid non-tolerant patients. OTFC is contraindicated in the management of acute or postoperative pain including headache/migraine and dental pain. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine daily, at least 25 mcg of transdermal fentanyl/hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, at least 25 mg oral oxymorphone daily, or an equianalgesic dose of another opioid daily for a week or longer.

OTFC is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of OTFC.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning - WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in ACTIQ. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, usually following large initial doses in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.2 Important Information Regarding Prescribing and Dispensing

When prescribing, DO NOT convert a patient to OTFC from any other fentanyl product on a mcg per mcg basis as OTFC and other fentanyl products are not equivalent on a microgram per microgram basis.

OTFC is NOT a generic version of fentanyl buccal tablets (Fentora®). **When dispensing, DO NOT substitute an OTFC prescription for fentanyl buccal tablets (Fentora®) prescription under any circumstances. Fentanyl buccal tablets (Fentora®) and OTFC are not equivalent.** Substantial differences exist in the pharmacokinetic profile of OTFC compared to other fentanyl products including fentanyl buccal tablets (Fentora®) that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of OTFC for any other fentanyl product may result in a fatal overdose.**

There are no safe conversion directions available for patients on any other fentanyl products. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) Therefore, for opioid tolerant patients, the initial dose of OTFC should **always** be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects [*see Dosage and Administration (2.2)*].

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that Oral Transmucosal Fentanyl Citrate (OTFC) contains a medicine in an amount which can be fatal to a child. Death has been reported in children who have accidentally ingested OTFC. Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [s*ee How Supplied/Storage and Handling, (16.1, 16.2), Patient Counseling Information (17.3), and Medication Guide*].

Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

OTFC could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

5.4 Additive CNS Depressant Effects

The concomitant use of OTFC with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., respiratory depression, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [*see Drug Interactions (7)*].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects. Consideration should be given to adjusting the dose of OTFC if warranted.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate OTFC with caution in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of OTFC may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer OTFC with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury and should be used only if clinically warranted.

5.8 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use OTFC with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors

OTFC is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

5.10 Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose [*see Drug Abuse and Dependence(9)]*, OTFC is available only through a restricted program called the TIRF REMS Access Program. Under the TIRF REMS ACCESS program, outpatients, healthcare professionals who prescribe for outpatient use, pharmacies and distributors must enroll in the program. For inpatient administration, (e.g. hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of OTFC, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access Program are:

- Healthcare professionals, who prescribe OTFC for outpatient use, must review the prescriber educational materials for the TIRF REMS Access Program, enroll in the program, and comply with the REMS requirements.
- To receive OTFC, patients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies, that dispense OTFC , must enroll in the program, and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute OTFC must enroll in the program, and distribute only to authorized pharmacies.

Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFREMSAccess.com or by calling 1-866-822 1483.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The safety of Oral Transmucosal Fentanyl Citrate (OTFC) has been evaluated in 257 opioid-tolerant chronic cancer pain patients. The duration of OTFC use varied during the open-label study. Some patients were followed for over 21 months. The average duration of therapy in the open-label study was 129 days.

The adverse reactions seen with OTFC are typical opioid side effects. Frequently, these adverse reactions will cease or decrease in intensity with continued use of OTFC, as the patient is titrated to the proper dose. Expect opioid side effects and manage them accordingly.

The most serious adverse reactions associated with all opioids including OTFC are respiratory depression (potentially leading to apnea or respiratory arrest), circulatory depression, hypotension, and shock. Follow all patients for symptoms of respiratory depression.

Because the clinical trials of OTFC were designed to evaluate safety and efficacy in treating breakthrough cancer pain, all patients were also taking concomitant opioids, such as sustained-release morphine or transdermal fentanyl, for their persistent cancer pain. The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received OTFC for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of OTFC therapy, or cancer-related symptoms. Adverse reactions are included regardless of causality or severity.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Three short-term clinical trials with similar titration schemes were conducted in 257 patients with malignancy and breakthrough cancer pain. Data are available for 254 of these patients. The goal of titration in these trials was to find the dose of OTFC that provided adequate analgesia with acceptable side effects (successful dose). Patients were titrated from a low dose to a successful dose in a manner similar to current titration dosing guidelines. **Table 1** lists, by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during titration and are commonly associated with opioid administration or are of particular clinical interest. The ability to assign a dose-response relationship to these adverse reactions is limited by the titration schemes used in these studies. Adverse reactions are listed in descending order of frequency within each body system.

Table 1.

Percent of Patients with Specific Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Titration

(Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=230)	800-1400 mcg (n=138)	1600 mcg (n=54)	>1600 mcg (n=41)	Any Dose* (n=254)
Body As A Whole					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2

Digestive					
Nausea	14	15	11	22	23
Vomiting	7	6	6	15	12
Constipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	9	9	11	20	17
Confusion	1	6	2	0	4
Anxiety	3	0	2	0	3
Abnormal Gait	0	1	4	0	2
Dry Mouth	1	1	2	0	2
Nervousness	1	1	0	0	2
Vasodilatation	2	0	2	0	2
Hallucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Skin					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following adverse reactions not reflected in **Table 1** occurred during titration with an overall frequency of 1% or greater and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, abdominal pain, chills, back pain, chest pain, infection

Cardiovascular: Migraine

Digestive: Diarrhea, dyspepsia, flatulence

Metabolic and Nutritional: Peripheral edema, dehydration

Nervous: Hypesthesia

Respiratory: Pharyngitis, cough increased

The following reactions occurred during titration with an overall frequency of less than 1% and are listed in descending order of frequency within each body system.

Body as a Whole: Flu syndrome, abscess, bone pain

Cardiovascular: Deep thrombophlebitis, hypertension, hypotension

Digestive: Anorexia, eructation, esophageal stenosis, fecal impaction, gum hemorrhage, mouth ulceration, oral moniliasis

Hemic and Lymphatic: Anemia, leukopenia

Metabolic and Nutritional: Edema, hypercalcemia, weight loss

Musculoskeletal: Myalgia, pathological fracture, myasthenia

Nervous: Abnormal dreams, urinary retention, agitation, amnesia, emotional lability, euphoria, incoordination, libido decreased, neuropathy, paresthesia, speech disorder

Respiratory: Hemoptysis, pleural effusion, rhinitis, asthma, hiccup, pneumonia, respiratory insufficiency, sputum increased

Skin and Appendages: Alopecia, exfoliative dermatitis

Special Senses: Taste perversion

Urogenital: Vaginal hemorrhage, dysuria, hematuria, urinary incontinence, urinary tract infection

A long-term extension study was conducted in 156 patients with malignancy and breakthrough cancer pain who were treated for an average of 129 days. Data are available for 152 of these patients. **Table 2** lists by dose groups, adverse reactions with an overall frequency of 1% or greater that occurred during the long-term extension study and are commonly associated with opioid administration or are of particular clinical interest. Adverse reactions are listed in descending order of frequency within each body system.

Table 2.

Percent of Patients with Adverse Events Commonly Associated with Opioid Administration or of Particular Clinical Interest Which Occurred During Long Term Treatment
(Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200-600 mcg (n=98)	800-1400 mcg (n=83)	1600 mcg (n=53)	>1600 mcg (n=27)	Any Dose* (n=152)

Body As A Whole					
Asthenia	25	30	17	15	38
Headache	12	17	13	4	20
Accidental Injury	4	6	4	7	9
Hypertonia	2	2	2	0	3
Digestive					
Nausea	31	36	25	26	45
Vomiting	21	28	15	7	31
Constipation	14	11	13	4	20
Intestinal Obstruction	0	2	4	0	3
Cardiovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anxiety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confusion	2	5	13	7	10
Depression	9	4	2	7	9
Insomnia	5	1	8	4	7
Abnormal Gait	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	0	4	3
Stupor	4	1	0	0	3
Vasodilatation	1	1	4	0	3
Thinking Abnormal	2	1	0	0	2
Abnormal Dreams	1	1	0	0	1
Convulsion	0	1	2	0	1
Myoclonus	0	0	4	0	1
Tremor	0	1	2	0	1
Vertigo	0	0	4	0	1

Respiratory					
Dyspnea	15	16	8	7	22
Skin					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Senses					
Abnormal Vision	2	2	0	0	3
Urogenital					
Urinary Retention	1	2	0	0	2

* Any Dose = A patient who experienced the same adverse event at multiple doses was only counted once.

The following reactions not reflected in **Table 2** occurred with an overall frequency of 1% or greater in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Pain, fever, back pain, abdominal pain, chest pain, flu syndrome, chills, infection, abdomen enlarged, bone pain, ascites, sepsis, neck pain, viral infection, fungal infection, cachexia, cellulitis, malaise, pelvic pain

Cardiovascular: Deep thrombophlebitis, migraine, palpitation, vascular disorder

Digestive: Diarrhea, anorexia, dyspepsia, dysphagia, oral moniliasis, mouth ulceration, rectal disorder, stomatitis, flatulence, gastrointestinal hemorrhage, gingivitis, jaundice, periodontal abscess, eructation, glossitis, rectal hemorrhage

Hemic and Lymphatic: Anemia, leukopenia, thrombocytopenia, ecchymosis, lymphadenopathy, lymphedema, pancytopenia

Metabolic and Nutritional: Peripheral edema, edema, dehydration, weight loss, hyperglycemia, hypokalemia, hypercalcemia, hypomagnesemia

Musculoskeletal: Myalgia, pathological fracture, joint disorder, leg cramps, arthralgia, bone disorder

Nervous: Hypesthesia, paresthesia, hypokinesia, neuropathy, speech disorder

Respiratory: Cough increased, pharyngitis, pneumonia, rhinitis, sinusitis, bronchitis, epistaxis, asthma, hemoptysis, sputum increased

Skin and Appendages: Skin ulcer, alopecia

Special Senses: Tinnitus, conjunctivitis, ear disorder, taste perversion

Urogenital: Urinary tract infection, urinary incontinence, breast pain, dysuria, hematuria, scrotal edema, hydronephrosis, kidney failure, urinary urgency, urination impaired, breast neoplasm, vaginal hemorrhage, vaginitis

The following reactions occurred with a frequency of less than 1% in the long-term extension study and are listed in descending order of frequency within each body system.

Body as a Whole: Allergic reaction, cyst, face edema, flank pain, granuloma, bacterial infection, injection site pain, mucous membrane disorder, neck rigidity

Cardiovascular: Angina pectoris, hemorrhage, hypotension, peripheral vascular disorder, postural hypotension, tachycardia

Digestive: Cheilitis, esophagitis, fecal incontinence, gastroenteritis, gastrointestinal disorder, gum hemorrhage, hemorrhage of colon, hepatorenal syndrome, liver tenderness, tooth caries, tooth disorder

Hemic and Lymphatic: Bleeding time increased

Metabolic and Nutritional: Acidosis, generalized edema, hypocalcemia, hypoglycemia, hyponatremia, hypoproteinemia, thirst

Musculoskeletal: Arthritis, muscle atrophy, myopathy, synovitis, tendon disorder

Nervous: Acute brain syndrome, agitation, cerebral ischemia, facial paralysis, foot drop, hallucinations, hemiplegia, miosis, subdural hematoma

Respiratory: Hiccup, hyperventilation, lung disorder, pneumothorax, respiratory failure, voice alteration

Skin and Appendages: Herpes zoster, maculopapular rash, skin discoloration, urticaria, vesiculobullous rash

Special Senses: Ear pain, eye hemorrhage, lacrimation disorder, partial permanent deafness, partial transitory deafness

Urogenital: Kidney pain, nocturia, oliguria, polyuria, pyelonephritis

6.2 Postmarketing Experience

Adverse reactions are reported voluntarily from a population of uncertain size, and, therefore, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of the reporting, or (3) strength of causal connection to OTFC.

The following adverse reactions have been identified during post-approval use of OTFC (which contains approximately 2 grams of sugar per unit):

Digestive: Dental decay of varying severity including dental caries, tooth loss, and gum line erosion.

General Disorders and Administration Site Conditions: Application site reactions including irritation, pain, and ulcer.

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when OTFC is given concurrently with agents that affect CYP3A4 activity. The concomitant use of OTFC with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole,

troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects including fatal respiratory depression. Patients receiving OTFC concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, thus should be avoided.

Drugs that induce cytochrome P450 3A4 activity may have the opposite effects.

Concomitant use of OTFC with an MAO inhibitor, or within 14 days of discontinuation, is not recommended [*see Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Oral Transmucosal Fentanyl Citrate (OTFC) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for OTFC.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21, of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic (the high dose was approximately 3-times the human dose of 1600 mcg per pain episode on a mg/m^2 basis). Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation day 6 to 18, was embryo or fetal toxic, and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore do not use OTFC during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use OTFC in nursing women because of the possibility of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants at the cessation of nursing by women using OTFC.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below 16 years of age have not been established.

In a clinical study, 15 opioid-tolerant pediatric patients with breakthrough pain, ranging in age from 5 to 15 years, were treated with OTFC. The study was too small to allow conclusions on safety and efficacy in this patient population. Twelve of the fifteen opioid-tolerant children and adolescents aged 5 to 15 years in this study received OTFC at doses ranging from 200 mcg to 600 mcg. The mean (CV%; range) dose-normalized (to 200 mcg) C_{max} and AUC_{0-8} values were 0.87 ng/mL (51%; 0.42 to 1.30) and 4.54 ng·h/mL (42%; 2.37 to 6), respectively, for children ages 5 to <11 years old (N = 3) and 0.68 ng/mL (72%; 0.15 to 1.44) and 8.38 (192%; 0.84 to 50.78), respectively, for children ages ≥11 to <16 y (N = 9).

8.5 Geriatric Use

Of the 257 patients in clinical studies of OTFC in breakthrough cancer pain, 61 (24%) were 65 years of age and older, while 15 (6%) were 75 years of age and older. Those patients over the age of 65 years were titrated to a mean dose that was about 200 mcg less than the mean dose titrated to by younger patients. No difference was noted in the safety profile of the group over 65 years of age as compared to younger patients in OTFC clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously, compared with the younger population. Therefore, exercise caution when individually titrating OTFC in elderly patients to provide adequate efficacy while minimizing risk.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of OTFC in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

8.7 Gender

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were noted either in dosage requirement or in observed adverse reactions.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl is a Schedule II controlled substance that can produce drug dependence of the morphine type. Oral Transmucosal Fentanyl Citrate (OTFC) may be subject to misuse, abuse and addiction.

9.2 Abuse and Addiction

Manage the handling of OTFC to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [s*ee How Supplied/Storage and Handling (16.1, 16.2)*].

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since OTFC may be diverted for nonmedical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Guide the administration of OTFC by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with chronic cancer pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and subsequently, by decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of Oral Transmucosal Fentanyl Citrate (OTFC) overdosage are expected to be similar in nature to intravenous fentanyl and other opioids, and are an extension of its pharmacological actions with the most serious significant effect being respiratory depression [*see Clinical Pharmacology (12.2)*].

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the OTFC unit, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in the Opioid NON-Tolerant Person

Provide ventilatory support, obtain intravenous access, and employ naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of severe OTFC overdose includes: securing a patent airway, assisting or controlling ventilation, establishing intravenous access, and GI decontamination by lavage and/or activated charcoal, once the patient's airway is secure. In the presence of respiratory depression or apnea, assist or control ventilation, and administer oxygen as indicated.

Although muscle rigidity interfering with respiration has not been seen following the use of OTFC, this is possible with fentanyl and other opioids. If it occurs, manage it by

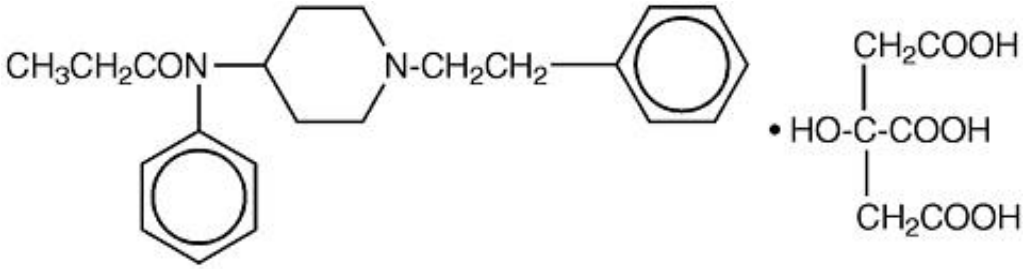
using assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

11 DESCRIPTION

Oral Transmucosal Fentanyl Citrate (OTFC) is a solid formulation of fentanyl citrate, a potent opioid analgesic, intended for oral transmucosal administration. OTFC is formulated as a white to off-white solid drug matrix on a handle that is fracture resistant (ABS plastic) under normal conditions when used as directed.

OTFC is designed to be dissolved slowly in the mouth to facilitate transmucosal absorption. The handle allows the OTFC unit to be removed from the mouth if signs of excessive opioid effects appear during administration.

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol, and purified shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Analgesia

The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals. As a result, the dose of Oral Transmucosal Fentanyl Citrate (OTFC) should be individually titrated to achieve the desired effect [*see Dosage and Administration (2.2)*].

Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid

stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System

All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. During the titration phase of the clinical trials, somnolence, which may be a precursor to respiratory depression, did increase in patients who were treated with higher doses of OTFC. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration. Therefore, physicians and other healthcare providers should be aware of this potential complication [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Contraindications (4), Warnings and Precautions (5.2), Adverse Reactions (6), and Overdosage (10)*].

12.3 Pharmacokinetics

Absorption

The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. Both the blood fentanyl profile and the bioavailability of fentanyl will vary depending on the fraction of the dose that is absorbed through the oral mucosa and the fraction swallowed.

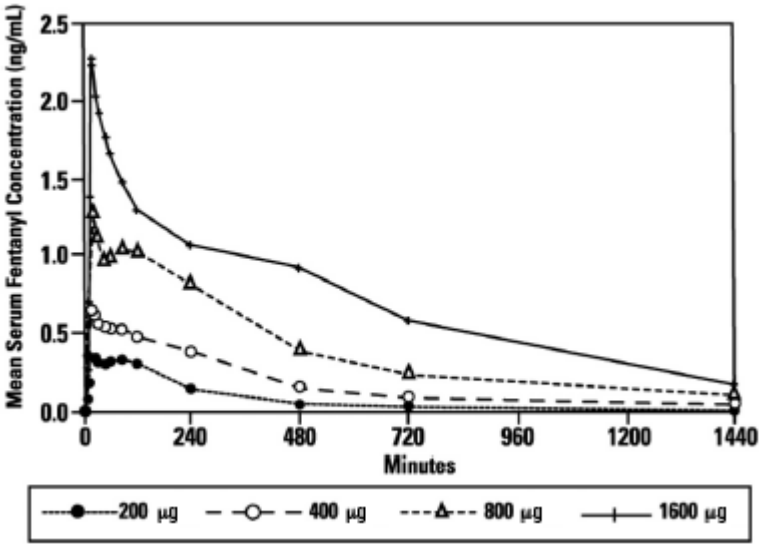
Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl.

Normally, approximately 25% of the total dose of Oral Transmucosal Fentanyl Citrate (OTFC) is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of OTFC is divided equally between rapid transmucosal and slower GI absorption. Therefore, a unit dose of OTFC, if chewed and swallowed, might result in lower peak concentrations and lower bioavailability than when consumed as directed.

Dose proportionality among four of the available strengths of OTFC (200, 400, 800, and 1600 mcg) has been demonstrated in a balanced crossover design in adult subjects (n=11). Mean serum fentanyl levels following these four doses of OTFC are shown in **Figure 1**. The curves for each dose level are similar in shape with increasing dose levels producing increasing serum fentanyl levels. C_{max} and $AUC_{0\rightarrow\infty}$ increased in a dose-dependent manner that is approximately proportional to the OTFC administered.

Figure 1.

Mean Serum Fentanyl Concentration (ng/mL) in Adult Subjects Comparing 4 Doses of OTFC



The pharmacokinetic parameters of the four strengths of OTFC tested in the dose-proportionality study are shown in Table 3. The mean C_{max} ranged from 0.39 to 2.51 ng/mL. The median time of maximum plasma concentration (T_{max}) across these four doses of OTFC varied from 20 to 40 minutes (range of 20 to 480 minutes) as measured after the start of administration.

Table 3.

Pharmacokinetic Parameters* in Adult Subjects
Receiving 200, 400, 800, and 1600 mcg Units of OTFC

Pharmacokinetic Parameter	**200 mcg**	**400 mcg**	**800 mcg**	**1600 mcg**
T_{max}, minute median (range)	40 (20 to 120)	25 (20 to 240)	25 (20 to 120)	20 (20 to 480)
C_{max}, ng/mL mean (%CV)	0.39 (23)	0.75 (33)	1.55 (30)	2.51 (23)
AUC_{0-1440}, ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 (67)
$t_{½}$, minute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

* Based on arterial blood samples.

Distribution

Fentanyl is highly lipophilic. Animal data showed that following absorption, fentanyl is rapidly distributed to the brain, heart, lungs, kidneys and spleen followed by a slower redistribution to muscles and fat. The plasma protein binding of fentanyl is 80 to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis. The mean volume of distribution at steady-state (Vss) was 4 L/kg.

Metabolism

Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. Norfentanyl was not found to be pharmacologically active in animal studies [*see Drug Interactions (7)*].

Elimination

Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important. The total plasma clearance of fentanyl was 0.5 L/hr/kg (range 0.3 to 0.7 L/hr/kg). The terminal elimination half-life after OTFC administration is about 7 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for OTFC.

14 CLINICAL STUDIES

Oral Transmucosal Fentanyl Citrate (OTFC) was investigated in clinical trials involving 257 opioid tolerant adult cancer patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in cancer patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg morphine/day, 50 mcg transdermal fentanyl/hour, or an equianalgesic dose of another opioid for a week or longer.

In two dose titration studies 95 of 127 patients (75%) who were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain titrated to a successful dose of OTFC to treat their breakthrough cancer pain within the dose range offered (200, 400, 600, 800, 1200 and 1600 mcg). A “successful” dose was defined as a dose where one unit of OTFC could be used consistently for at least two

consecutive days to treat breakthrough cancer pain without unacceptable side effects. In these studies 11% of patients withdrew due to adverse reactions and 14% withdrew due to other reasons.

The successful dose of OTFC for breakthrough cancer pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and is thus best determined by dose titration.

A double-blind placebo controlled crossover study was performed in cancer patients to evaluate the effectiveness of OTFC for the treatment of breakthrough cancer pain. Of 130 patients who entered the study 92 patients (71%) achieved a successful dose during the titration phase. The distribution of successful doses is shown in **Table 4**.

Table 4.

Successful Dose of OTFC Following Initial Titration

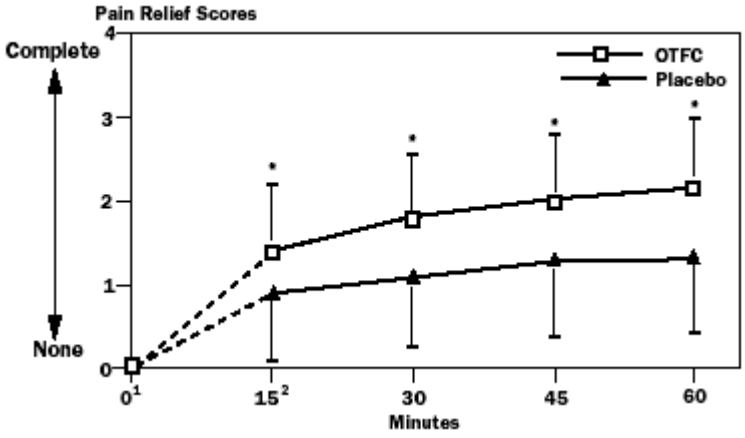
OTFC Dose	**Total No. (%) (N=92)**
200 mcg	13 (14)
400 mcg	19 (21)
600 mcg	14 (15)
800 mcg	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean +/- SD	789 +/- 468 mcg

On average, patients over 65 years of age titrated to a mean dose that was about 200 mcg less than the mean dose to which younger adult patients were titrated.

OTFC was administered beginning at Time 0 minutes and produced more pain relief compared with placebo at 15, 30, 45, and 60 minutes as measured after the start of administration (see **Figure 2**). The differences were statistically significant.

Figure 2.

Pain Relief (PR) Scores (Mean ± SD) During the Double-Blind Phase - All Patients with Evaluable Episodes on Both OTFC and Placebo (N=86)



[1] 0 minutes = Start of administration of OTFC
[2] 15 minutes = First time to measure pain relief

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in individually sealed child-resistant blister packages. The amount of fentanyl contained in OTFC can be fatal to a child. Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*see Boxed Warning - Warning: Risk of Respiratory Depression, Medication Errors, Abuse Potential, Warnings and Precautions (5.2), and Patient Counseling Information (17.1)*].

Store at 20° to 25ºC (68° to 77ºF) [See USP Controlled Room Temperature] until ready to use. Protect OTFC from freezing and moisture. Do not use if the blister package has been opened.

16.2 Disposal of OTFC

Patients must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. While all units should be disposed of immediately after use, partially consumed units represent a special risk because they are no longer protected by the child-resistant blister package, yet may contain enough medicine to be fatal to a child [*see Patient Counseling Information (17.5)*].

A temporary storage bottle is provided as part of the Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit [*see Patient Counseling Information (17.4)*]. This container is to be used by patients or their caregivers in the event that a partially consumed unit cannot be disposed of promptly. Instructions for usage of this container are included in the *Medication Guide*.

Patients and members of their household must be advised to dispose of any units remaining from a prescription as soon as they are no longer needed. Instructions are included in *Patient Counseling Information (17.6)* and in the *Medication Guide*. If additional assistance is required, call PAR PHARMACEUTICAL at 1-800-828-9393.

16.3 How Supplied

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied in six dosage strengths. Each unit is individually wrapped in a child-resistant, protective blister package. These blister packages are packed 30 per shelf carton for use when patients have been titrated to the appropriate dose.

Each dosage unit has a white to off-white color. Each individual solid drug matrix is marked with "Fentanyl" and the strength of the unit ("200 mcg", "400 mcg", "600 mcg", "800 mcg" ,"1200 mcg", or "1600 mcg"). The dosage strength is also marked on the handle tag, the blister package and the carton. See blister package and carton for product information.

Oral Transmucosal Fentanyl Citrate (OTFC) is supplied as white to off-white, round cylindrical shaped lozenges attached to a fracture resistant plastic handle, as:

200 mcg: Imprinted Fentanyl over 200 mcg in blue ink, debossed with 1 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

400 mcg: Imprinted Fentanyl over 400 mcg in blue ink, debossed with 2 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

600 mcg: Imprinted Fentanyl over 600 mcg in blue ink, debossed with 3 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

800 mcg: Imprinted Fentanyl over 800 mcg in blue ink, debossed with 4 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

1200 mcg: Imprinted Fentanyl over 1200 mcg in blue ink, debossed with 5 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

1600 mcg: Imprinted Fentanyl over 1600 mcg in blue ink, debossed with 6 on the convex (top) side and flat on the other (bottom) side.

30 Units (10 x 3 Blisters)

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide)*.

17.1 Patient/Caregiver Instructions

- Before initiating treatment with Oral Transmucosal Fentanyl Citrate (OTFC), explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time OTFC is dispensed because new information may be available.
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive OTFC.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding OTFC or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access Program, prescribers must review the contents of the OTFC Medication Guide with every patient before initiating treatment with OTFC.
  - Advise the patient that OTFC is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug
  - Advise the patient that only enrolled healthcare providers may prescribe OTFC.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of OTFC.
  - Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program.

- **Patients and their caregivers must be instructed that children exposed to OTFC are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep OTFC out of the reach of children [*See How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.2 and 5.3) and Medication Guide for specific patient instructions.*]
- Provide patients and their caregivers with a *Medication Guide* and review it with them each time OTFC is dispensed because new information may be available.
- Instruct patients and their caregivers to keep both used and unused dosage units out of the reach of children. Partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible [*see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3), and Patient Counseling Information (17.5)*].
- Instruct patients not to take OTFC for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and that OTFC is only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.

- Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take OTFC.
- Instruct patients that, if the breakthrough pain episode is not relieved 15 minutes after finishing the OTFC unit, they may take **ONLY ONE ADDITIONAL UNIT OF OTFC USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take no more than two units of OTFC for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with OTFC.
- Instruct patients NOT to share OTFC and that sharing OTFC with anyone else could result in the other individual's death due to overdose.
- Make patients aware that OTFC contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in OTFC, fentanyl, is a drug that some people abuse. OTFC should be taken only by the patient it was prescribed for, and it should be protected from theft or misuse in the work or home environment.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking OTFC.
- Instruct patients to use OTFC exactly as prescribed by their doctor and not to take OTFC more often than prescribed.
- Caution patients that OTFC can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking OTFC of these dangers and counsel them accordingly.
- Warn patients to not combine OTFC with alcohol, sleep aids, or tranquilizers except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
- Inform female patients that if they become pregnant or plan to become pregnant during treatment with OTFC, they should ask their doctor about the effects that OTFC (or any medicine) may have on them and their unborn children.
- Physicians and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

17.2 Dental Care

Because each OTFC unit contains approximately 2 grams of sugar, frequent consumption may increase the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medications (such as fentanyl) may add to this risk.

Postmarketing reports of dental decay have been received in patients taking OTFC [*see Adverse Reactions (6.2)*]. In some of these patients, dental decay occurred despite reported routine oral hygiene. As dental decay in cancer patients may be multi-factorial, patients using OTFC should consult their dentist to ensure appropriate oral hygiene.

17.3 Diabetic Patients

Advise diabetic patients that OTFC contains approximately 2 grams of sugar per unit.

17.4 OTFC Child Safety Kit

Provide patients and their caregivers who have children in the home or visiting with an Oral Transmucosal Fentanyl Citrate (OTFC) Child Safety Kit, which contains educational materials and safe interim storage containers to help patients store OTFC and other medicines out of the reach of children. To obtain a supply of Child Safety Kits, healthcare professionals can call PAR PHARMACEUTICAL at 1-800-391-5974.

17.5 Disposal of Used OTFC Units

Patients must be instructed to dispose of completely used and partially used OTFC units.

1. After consumption of the unit is complete and the matrix is totally dissolved, throw away the handle in a trash container that is out of the reach of children.
2. If any of the drug matrix remains on the handle, place the handle under hot running tap water until all of the drug matrix is dissolved, and then dispose of the handle in a place that is out of the reach of children.
3. Dispose of handles in the child-resistant container (as described in steps 1 and 2) at least once a day.

If the patient does not entirely consume the unit and the remaining drug cannot be immediately dissolved under hot running water, the patient or caregiver must temporarily store the OTFC unit in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

17.6 Disposal of Unopened OTFC Units When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened units remaining from a prescription as soon as they are no longer needed.

To dispose of the unused OTFC units:

1. Remove the OTFC unit from its blister package using scissors, and hold the OTFC by its handle over the toilet bowl.
2. Using wire-cutting pliers cut off the drug matrix end so that it falls into the toilet.
3. Dispose of the handle in a place that is out of the reach of children.
4. Repeat steps 1, 2, and 3 for each OTFC unit. Flush the toilet twice after 5 units have been cut and deposited into the toilet.

Do not flush the entire OTFC units, OTFC handles, blister packages, or cartons down the toilet. Dispose of the handle where children cannot reach it [*see How Supplied/Storage and Handling (16.1)*].

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of OTFC are provided in the OTFC *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable units that remain in the home after a patient has expired, instruct them to call the toll-free number for PAR PHARMACEUTICAL (1-800-828-9393) or seek assistance from their local DEA office.

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt) Lozenge CII
(OTFC)

200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**

- You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
- You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**

4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

   OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.
   - **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
7. OTFC is available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of OTFC
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.

- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS ACCESS program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions

- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

- Your healthcare provider will explain the TIRF REMS ACCESS program to you.
- You will sign the TIRM REMS ACCESS program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS ACCESS program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC during each episode of breakthrough cancer pain:

- Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
- If your breakthrough cancer pain is not relieved 15 minutes after you finished the OTFC unit, use **only 1** more unit of OTFC at this time.
- If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**

- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:

   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**

2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088**.**

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
    - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
    - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-391-5974 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

- **A child-resistant lock that** you use to secure the storage space where you keep OTFC (See **Figure 1**).

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
    - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See **Figure 2**).

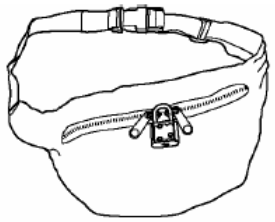


Figure 2

- **A child-resistant temporary storage bottle** (See **Figure 3**).

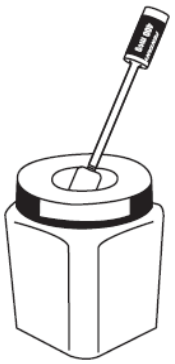


Figure 3

- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.
- **Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.**
- Keep OTFC dry.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.**

After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If **any** medicine remains on the used OTFC unit after you have finished:

- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See **Figure 4**).

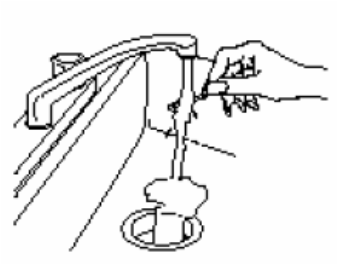


Figure 4

<u>Temporary Storage of Used OTFC Units</u>:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

<u>Disposing of Used OTFC Units from the Temporary Storage Bottle</u>:

You must dispose of all used OTFC units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See **Figure 6**).

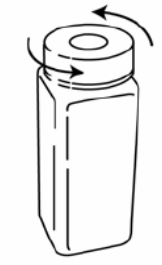


Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

Disposing of unopened OTFC units: Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all OTFC from the locked storage space (See **Figure 7**).

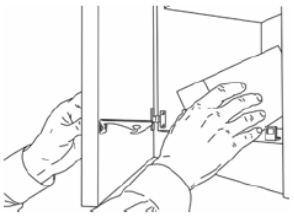


Figure 7

2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See **Figures 8A** and **8B**).

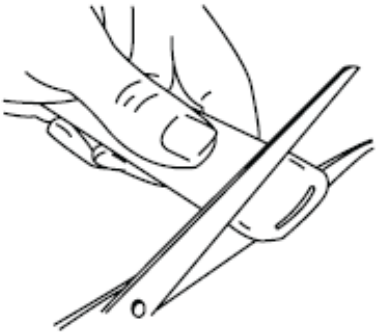


Figure 8A

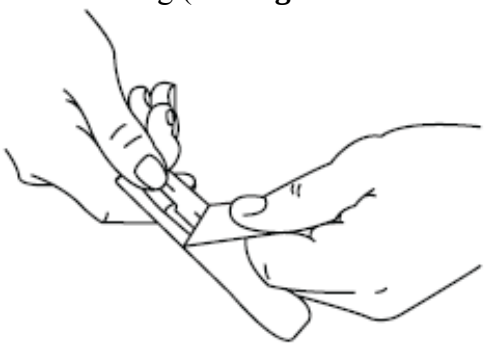


Figure 8B

3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See **Figures 9A** and **9B**).

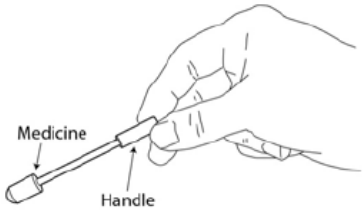


Figure 9A

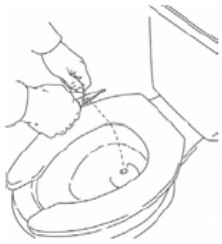


Figure 9B

4. Throw the handle away in a place that is out of the reach of children (See **Figure 10**).

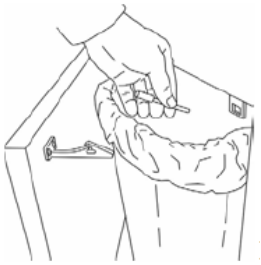


Figure 10

5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See **Figure 11**). Do not flush more than 5 OTFC units at a time.

Figure 11

• Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have**. OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.

For more information about the TIRF REMS ACCESS program, go to www.TIRFREMSaccess.com or call 1-866-822-1483.

What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

Active Ingredient: fentanyl citrate
Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See **Figure12**). **Do not open the blister package until you are ready to use OTFC.**

Figure 12

- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See **Figures 13A** and **13B**). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See **Figure 14**).

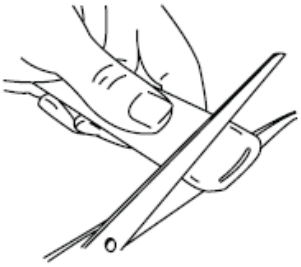


Figure 13A

Figure 13B

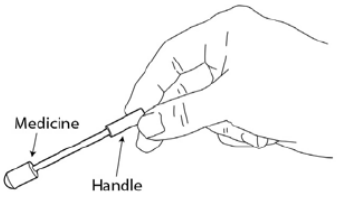


Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See **Figure 15**).

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured By:
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Manufactured For:
PAR PHARMACEUTICAL
Spring Valley, NY 10977

U.S. Patent No. 7,908,729 Rev. 12/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH O WEBBER
12/28/2011

Teleconference with TIRF Generic Firms
Meeting Minutes
February 7, 2012

Attendees:
FDA - Darrell Jenkins, Jane Axelrad, Adolph Vezza, Koung Lee, Megan Moncur, Kristen Miller, Carrie Lemley, Tamika White and Marcia Britt Williams
Par Pharmaceuticals – Jaime Reid, Michelle Bonomi-Huvala, Anthony Guacci, William Giglio, Sokie Mogul, Suraya Zikria
Mallinckrodt – Jason Wallace and Diane Servello

Question to Firms: How are they ensuring that after 3/12/12 (go live date) that the product is only being sold by pharmacies that are part of the TIRF program?

Both firms replied that McKesson and Relay-Health are taking the lead on this issue and both companies have supplied a list of their distributors to McKesson so that they can be sure all distributors are enrolled by the go live date.

Action
The firms had the following three questions:

1. The enforcement letters issued to all TRIF REMS sponsors, state a report on the progress towards full implementation of the TIRF REMS must be filed every 30 days, beginning 30 days from the date of the TIRF REMS approval (December 28, 2011); however, the firms just received the correspondence on February 1, 2012. Is it acceptable to submit this report 30 days from the date of receipt of the enforcement discretion letter? If so, should each company submit a report or should it be a joint report from the TRIG? What information would the FDA like to be included in the report?

> FDA responded that submission 30 days from receipt of the enforcement discretion letter would be acceptable. Information that should be contained includes steps being taken to ensure full implementation of the REMS by 3/12/12, how many pharmacies are currently enrolled, etc.
>
> Post-meeting note: We agreed that this report is not necessary. All sponsors that received the enforcement discretion letter should be informed.

2. Is it necessary to relabel all products that are in distribution centers on 3/12/12? Will the sponsors need to recall products that do not have the new labeling? Based on current demand, the sponsors anticipate it will take a few months to exhaust the supply.

> FDA responded that they will discuss this internally and hope to respond to the sponsors during the week of February 13.

3. Under the RiskMap, assessments are due at the end of January, and a bridging assessment (briefing document) to cover February 1 through implementation of the TIRF REMS. The TIRF REMS will require an assessment from December 28 through April 30. Is that adequate, and therefore the RiskMap assessment will not be necessary?

FDA will discuss how the assessments should be aligned to eliminate duplication of efforts. FDA confirmed that an additional survey would not need to be conducted at this time, and will send an email to the firms to that effect.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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02/16/2012

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Submitted to FDA via ESG

April 5, 2012

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Rockville, Maryland 20855

CORRESPONDENCE
REMS-RELATED INFORMATION REQUEST
PHARMACY DATA

RE: ANDA 077312 Oral Transmucosal Fentanyl Citrate Lozenge, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Webber:

Reference is made to our abbreviated new drug application for Oral Transmucosal Fentanyl Citrate Lozenge, ANDA -77312. This correspondence is being submitted to provide pharmacy data requested by FDA during their March 16, 2012 teleconference with the TIRF REMS Industry Group ("TRIG").

FDA requested the TRIG to provide data on the number of pharmacies dispensing Transmucosal Immediate Release Fentanyl (TIRF) medicine for a period prior to implementation of the class-wide REMS. In response, each NDA/ANDA holder is submitting this information to their respective drug applications, while also providing a copy to Mr. Darrell Jenkins, Regulatory Health Project Manager, OSE.

Accordingly, the following PDF documents are included with this correspondence.

- Par's Fentanyl Total Indirect Sales listed by end customer for the period covering 10/31/2011 to 03/26/2012
- Par's Fentanyl Indirect Sales listed by individual brand ID for the period covering 10/31/2011 to 03/26/2012
- Memo from Par explaining the Pharmacy Data

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

Should you have any questions regarding this submission, please contact the undersigned by phone at 845-573-5778, by email at karen.a.rocco@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Karen Rocco

Karen A. Rocco RAC
Director, Regulatory Affairs

ATTACHMENT TO FDA 356h FORM

STRENGTHS:
eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg of Fentanyl base
CII

INDICATION(S) FOR USE:

Only for the management of breakthrough cancer pain in patients 16 and older with malignancies **who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.**

Par Pharmaceutical, Inc.
One Ram Ridge
Spring Valley, NY 10977
Tel 201 802 4000
Fax 201 391 5217
www.parpharm.com

MEMO

DATE: April 2, 2012

SUBJECT: Pharmacy Data

From: Drug Safety and Pharmacovigilance Department

"Unfortunately, pharmacy sales data is not information that is available to us through the normal course of business. Although there are certain types of sales that are subject to contracts with wholesalers that we can identify through our finance systems, Par does not have visibility into any sales that occur outside of those contracts. As these non-contract sales are not subject to routine reporting, we are not certain of the availability of the data; and, if available, we would most likely be required to purchase the data at an additional cost to Par.

Additionally, although EDI 867 Product Transfer and Resale Reports ("867 reports") contain some of this data in theory, not all customers utilize this reporting capability. Furthermore, the data is often blinded at the request of the end customer, and therefore not useful."

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Submitted to FDA via ESG

May 16, 2012

Keith Webber, Ph.D., Deputy Director
Office of Generic Drugs
CDER/FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

REMS-OTHER
SURVEY METHODOLOGY

RE: ANDA 077312
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Webber:

Reference is made to the Fentanyl Citrate risk management program for Oral Transmucosal Fentanyl Citrate as required by the approval of ANDA 077312.

Reference is also made to the transfer of ownership of this ANDA from Barr Laboratories, Inc. (an indirect, wholly owned subsidiary of Teva Pharmaceuticals USA) to Par Pharmaceutical, Inc., effective October 14, 2011.

As one of the sponsors involved in the class-wide REMS consortium (TIRF Industry Group or TRIG), Par is submitting the enclosed protocols pursuant to FDA's request and agreement with the TRIG. We recognize that an important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers', prescribers', and pharmacists' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines, as described in the product-specific Medication Guide. The enclosed protocols describe the administration of the surveys that will be conducted among these groups. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS. The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at the agreed upon intervals.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, Par was granted a renewal of our eCTD Waiver from the eCTD Specifications requirements through May 9, 2013 by the CDER eSUBS group on May 9, 2012.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5778, by email at karen.a.rocco@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Karen Rocco

Digitally signed by Karen Rocco
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Reason: I am the author of this document
Date: 2012.05.16 16:13:36 -0 '00'

Karen A. Rocco RAC
Director, Regulatory Affairs

Attachments

Par Pharmaceutical, Inc.
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Submitted to FDA via ESG

June 22, 2012

Keith Webber, Ph.D.
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TIRF REMS 6-MONTH ASSESSMENT REPORT

RE: ANDA 077312
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Webber:

Reference is made to the Fentanyl Citrate risk management program for Oral Transmucosal Fentanyl Citrate as required by the approval of ANDA 077312.

Par Pharmaceuticals, Inc, as one of the sponsors involved in the class-wide REMS consortium (TIRF Industry Group or TRIG), is hereby submitting the TIRF REMS 6-month Assessment Report, as required, for the TIRF REMS Access Program that was approved December 28, 2011. The TIRF REMS Access Program is administered by McKesson Specialty Health and RelayHealth. The assessment report has been prepared by United Biosource Corporation (UCB) and contains data through April 27, 2012 in order to allow a 60 day preparation period for filing by June 28, 2012.

Please note that there are no ongoing post-marketing studies and/or clinical trials being conducted for this application at this time.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, Par was granted a renewal of our eCTD Waiver from the eCTD Specifications requirements through May 9, 2013 by the CDER eSUBS group on May 9, 2012.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Krista Richardson

Digitally signed by Krista Richardson
DN: o=VeriSign Inc ou=VeriSign Trust Network ou=www verisign com/repository/RPA Incorp by Ref LIAB LTD(c)98 ou=Persona Not Validated ou=Digital ID Class 1 - Microsoft Full Service cn=Krista Richardson email=krista richardson@parpharm com
Date: 2012 06 22 14:11:32 04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Attachment

Title: Transmucosal Immediate Release Fentanyl (TIRF)
Risk Evaluation and Mitigation Strategy (REMS) Access Program
6-month Assessment Report

Document Number: Version 1.0 FINAL

Product Name: Transmucosal Immediate Release Fentanyl

Sponsor: TIRF REMS Industry Group (TRIG) of Companies:

Archimedes Pharma US Inc.
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceuticals)
Insys Therapeutics Inc.
Meda Pharmaceuticals
Mallinckrodt Inc. (a Covidien Company)
Par Pharmaceutical, Inc.
ProStrakan, Inc.

Confidentiality Statement

6-MONTH REPORT PRODUCED AS FDA_5 TO FDA_74

Par Pharmaceutical, Inc.
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Submitted to FDA via ESG

December 21, 2012

Gregory P. Geba, M.D., M.P.H.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

TIRF REMS 12-MONTH ASSESSMENT REPORT

RE: ANDA 077312; *Sequence 0013*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Geba:

Reference is made to Par's Abbreviated New Drug Application for Oral Fentanyl Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg of Fentanyl base, CII.

Par Pharmaceuticals, Inc, as one of the sponsors involved in the class-wide REMS consortium (TIRF Industry Group or TRIG), is hereby submitting the TIRF REMS 12-month Assessment Report, as required, for the TIRF REMS Access Program that was approved December 28, 2011. The TIRF REMS Access Program is administered by McKesson Specialty Health and RelayHealth. The initial REMS Assessment report was submitted on 28 June 2012 (cut-off date of 27 April 2012). This REMS Assessment report covers the period from 27 April 2012 to 28 October 2012. The assessment report has been prepared by United Biosource Corporation (UCB).

Please note that there are no ongoing post-marketing studies and/or clinical trials being conducted for this application at this time.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, Par was granted a renewal of our eCTD Waiver from the eCTD Specifications requirements through May 9, 2013 by the CDER eSUBS group on May 9, 2012.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

Krista Richardson

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DN: o=VeriSign, Inc., ou=VeriSign Trust Network, ou=www.verisign.com/repository/RPA Incorp. by Ref.,LIAB.LTD(c)98, ou=Persona Not Validated, ou=Digital ID Class 1 - Microsoft Full Service, cn=Krista Richardson, email=krista.richardson@parpharm.com
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Krista Richardson
Senior Manager, Regulatory Affairs

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Submitted to FDA via ESG

May 15, 2013

Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

Request for Information Response
TIRF REMS 12-MONTH ASSESSMENT REPORT

RE: ANDA 077312; *Sequence 0014*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to Par's Abbreviated New Drug Application for Oral Fentanyl Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg of Fentanyl base, CII.

Reference is made to the TIRF REMS 12-Month Assessment Report dated December 21, 2012, and to the email correspondence from Carrie Lemley, FDA/OGD dated April 15, 2013, which contained additional requests for information in relation to the Assessment Report. The requests have been excerpted from the email and are in bold font below, followed by Par's responses:

As part of the TIRF REMS Assessment Report, public FAERS post-marketing reports of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental pediatric exposures/ingestion were submitted. Provision of line listings or individual PTs is insufficient for a thorough analysis of safety data as it relates to the effectiveness of the REMS. The nearly 6 month gap in these data also does not allow a timely analysis of safety data. In order to better assess safety, and to determine whether the REMS is meeting its goals, an analysis of individual Sponsor's internal adverse event data is needed.

REQUEST FOR INFORMATION

For the time period between December 28, 2011 and October 20, 2012:

- **Provide an overall summary analysis describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, overdose).**

  Response:
  As requested above, an overall summary analysis report is provided in Module 1.16 describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, over dose). The report is entitled, "Summary Analysis of Fentanyl Citrate [ANDA 077312]; Adverse Event Reports from Par Safety Database (December 28, 2011 – October 20, 2012".

- **In tabular form, for each US case reported from December 28, 2011 to October 20, 2012 that includes one or more of the following events: (death, overdose, misuse, abuse, addiction, inappropriate prescribing*, medication error, accidental pediatric exposures/ingestion), provide at a minimum, the following information if available:** ***Manufacturer control number; patient age; patient gender; event date; report date; description of the event, root cause of AE or error if known; TIRF product name; TIRF product dose; TIRF product duration use; concurrent extended-release or long-action opiod and dose; concurrent CNS depressant medications; concurrent illicit drugs or alcohol, if recorded; pertinent patient medical history; outcome of event.***

  Response:

  The overall summary analysis report referenced in the response above contains the requested information in tabular form. Please note that the referenced table also contains the drug NDC number if available, since Par acquired ownership of the ANDA from Barr/Teva effective October 14, 2011. The table annotates, via NDC number, which product the patient was taking at the time of adverse event occurrence.

- **For clarity in the final report, provide a total number of unique cases. Also note within each table which cases contain more than one event, (e.g. inappropriate prescribing and overdose), with a notation such as an asterisk, so that there is no duplication in case count.**

  Response:
  Based on Par's assessment, there were a total of two unique cases, only one of which contains more than one event. The details of these cases are explained on page 11 of the summary analysis report, in the 5th paragraph.

- **Include the working definitions for the event term by which each case was classified.**

  Response:
  The working definitions for the event term by which each case was classified is provided in Section 1 of the overall summary analysis report provided in Module 1.16.

- **Append MedWatch forms for the events listed in the table.**

  Response:
  The relevant MedWatch forms are provided in Module 1.16.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson
@parpharm.com
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Date: 2013.05.15 10:46:17 -04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

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Submitted to FDA via ESG

September 11, 2013

Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
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Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT

- *Proposed REMS Modification #2*

RE: ANDA 077312; *Sequence 0015*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to Par's Abbreviated New Drug Application for Oral Fentanyl Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg of Fentanyl base, CII.

Further reference is made to the Prior Approval Supplement submitted September 27, 2012, for proposed REMS Modification #2. As discussed with FDA over the past several months, the shared TIRF REMS is now being submitted to DMF #027320 rather than each TIRF REMS sponsor's NDA/ANDA. All previous approved REMS submissions will be included in the DMF to provide the full history of the REMS. The initial DMF submission was sent to the Agency on September 4, 2013. As one of the sponsors involved in the class-wide REMS consortium (TIRF Industry Group or TRIG), Par is hereby submitting this amendment to the Prior Approval Supplement to provide a DMF Letter of Authorization to DMF#027320. The letter is provided in Module 1.4.1.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

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Date: 2013 09 11 11:16:29 04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Accenture LLP
585 East Swedesford Road
Wayne, PA 19087
Tel: (610) 535-6500
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accenture

Date: August 28, 2013

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

DMF#: 027320
Holder: McKesson Specialty Health (McKesson)
Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Letter of Authorization for: Not applicable because DMF does not cover multiple items.

McKesson hereby authorizes Par Pharmaceutical, Inc. to incorporate by reference information regarding the Transmucosal Immediate Release Fentanyl (TIRF) Access Program in DMF Number 027320 into any application filed by Par Pharmaceutical, Inc. We also authorize the FDA to review the aforementioned specific information in DMF Number 027320 when considering any application filed by Par Pharmaceutical, Inc.

The entire DMF can be referenced, which was submitted on August 20, 2013.

McKesson states that DMF Number 027320 is current and McKesson will comply with the statements made within it. McKesson will notify FDA through an amendment to DMF Number 027320 of any addition, change, or deletion of information in the DMF. McKesson will also notify in writing Par Pharmaceutical, Inc. that an addition, change, or deletion of information has been made to the DMF.

Sincerely,

Jann A. Kochel

Jann A. Kochel, U.S. Agent
Associate Director, Regulatory Affairs
Accenture, LLP
610-535-6500, ext. 5572
610-535-6515 (Fax)
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Par Pharmaceutical, Inc.
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Submitted to FDA via ESG

October 23, 2013

Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs
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Food and Drug Administration
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Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT

- *Proposed REMS Modification #2*

RE: ANDA 077312; *Sequence 0016*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to Par's Abbreviated New Drug Application for Oral Fentanyl Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg of Fentanyl base, CII.

Further reference is made to Par's Prior Approval Supplement for a Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2012. Reference is also made to the Prior Approval Supplement submitted on September 26, 2012 for Proposed REMS Modification #2. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted to this application on September 11, 2013.

As instructed by FDA, the shared TIRF REMS was submitted to DMF #027320 rather than each TIRF REMS sponsor's NDA or ANDA. All previous REMS submissions were included in the DMF to provide the full history of the REMS. Please refer to Sequence 0006 to DMF #027320, submitted on September 23, 2013 for the final documentation pertaining to REMS Modification 2.

Please refer to section 1.14.2 for the FPL of the most recent Medication Guide for Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII. Par had to revise the Medication Guide only to update the telephone number to call in order to request a Child Safety Kit. For ease of review, Par has also included a PDF version of a Microsoft Word document of Medication Guide, with highlights showing where changes were made.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.
krista.richardson@parpharm.com
Digitally signed by krista richardson@parpharm com
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Date: 2013 10 23 10 53:57 04'00'
Krista Richardson
Senior Manager, Regulatory Affairs

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt)
Lozenge [C]
(OTFC)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC). These are medical emergencies that can cause death. It possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.**

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC is available only through a program called the Transmucosal Immediate Release Fentanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of OTFC
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC during each episode of breakthrough cancer pain:
  - Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
  - If your breakthrough cancer pain is not relieved 15 minutes after you finished the OTFC unit, use **only 1** more unit of OTFC at this time.
  - If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See **"What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:
   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt)
Lozenge [C]
(OTFC)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC). These are medical emergencies that can cause death. It possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.**

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC is available only through a program called the Transmucosal Immediate Release Fentanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of OTFC
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

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How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

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- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
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- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
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- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See **"What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:
   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
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The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt)
Lozenge [C]
(OTFC)
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
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- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC). These are medical emergencies that can cause death. It possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.**

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3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
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6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

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What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
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- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
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  - available through the TIRF REMS Access program
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It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
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- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
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Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

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Before you can begin to use OTFC:

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Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
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- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See **"What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:
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   - have drowsiness with slowed breathing
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2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
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   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC is available only through a program called the Transmucosal Immediate Release Fentanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of OTFC
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
  - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-828-9393 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

- **A child-resistant lock that** you use to secure the storage space where you keep OTFC (See **Figure 1**).

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See **Figure 2**).

Figure 2

- **A child-resistant temporary storage bottle** (See **Figure 3**).

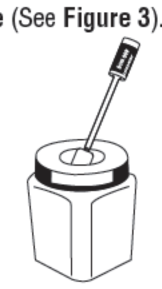

Figure 3

- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.
- **Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.**
- Keep OTFC dry.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.**

After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If **any** medicine remains on the used OTFC unit after you have finished:

- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See **Figure 4**).

Figure 4

Temporary Storage of Used OTFC Units:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

Disposing of Used OTFC Units from the Temporary Storage Bottle:

You must dispose of all used OTFC units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See **Figure 6**).

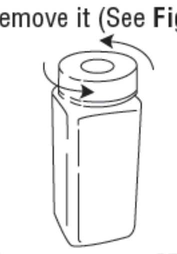

Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

Disposing of unopened OTFC units: Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all OTFC from the locked storage space (See **Figure 7**).

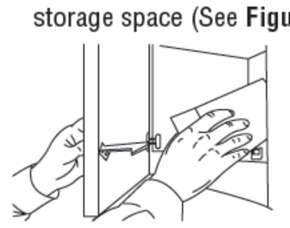

Figure 7

2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See **Figures 8A** and **8B**).

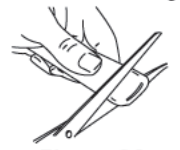

Figure 8A

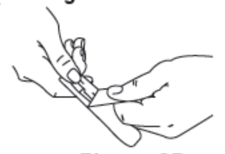

Figure 8B

3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See **Figures 9A** and **9B**).

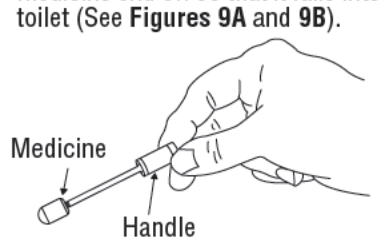

Figure 9A

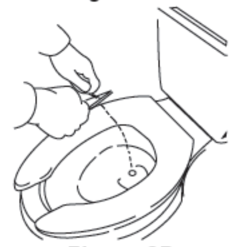

Figure 9B

4. Throw the handle away in a place that is out of the reach of children (See **Figure 10**).

Figure 10

5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See **Figure 11**). Do not flush more than 5 OTFC units at a time.

Figure 11

- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have.** OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See **Figure 12**). **Do not open the blister package until you are ready to use OTFC.**

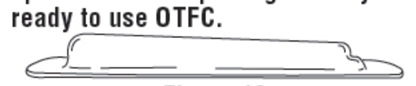

Figure 12

- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See **Figures 13A** and **13B**). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See **Figure 14**).

Figure 13A

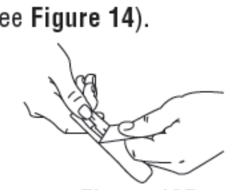

Figure 13B

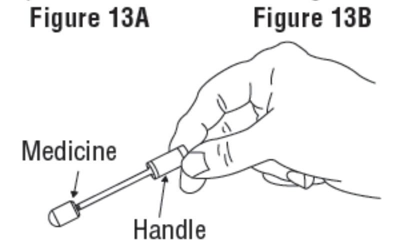

Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See **Figure 15**).

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Manufactured For:
PAR PHARMACEUTICAL COS., INC.
Spring Valley, NY 10977

U.S. Patent No. 7,908,729 Rev. X 3/2013
MG459-01-61-04

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- Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed. Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
  - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-828-9393 to request one.
The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.
The Child Safety Kit includes:
- A child-resistant lock that you use to secure the storage space where you keep OTFC (See Figure 1).
Figure 1
- A portable locking pouch for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See Figure 2).
Figure 2
- A child-resistant temporary storage bottle (See Figure 3).
Figure 3
- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
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After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.
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5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.
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Figure 8A Figure 8B
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Medicine
Handle
Figure 9A
Figure 9B
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Figure 10
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Flush 2 Times
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Figure 13A Figure 13B
Medicine
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Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.
Patient Instructions for Use
Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.
When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See Figure 12). Do not open the blister package until you are ready to use OTFC.
Figure 12
- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See Figures 13A and 13B). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See Figure 14).
Figure 13A Figure 13B
Medicine
Handle
Figure 14
1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See Figure 15).
Figure 15
3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.
- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See Figure 16).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.
Figure 16
See "How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?" for proper disposal of OTFC.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Manufactured For:
PAR PHARMACEUTICAL COS., INC.
Spring Valley, NY 10977
U.S. Patent No. 7,908,729 Rev. X 3/2013
MG459-01-61-04

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?
- Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed. Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
  - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-828-9393 to request one.
The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.
The Child Safety Kit includes:
- A child-resistant lock that you use to secure the storage space where you keep OTFC (See Figure 1).
Figure 1
- A portable locking pouch for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See Figure 2).
Figure 2
- A child-resistant temporary storage bottle (See Figure 3).
Figure 3
- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.
- Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.
- Keep OTFC dry.
How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?
Disposing of OTFC units after use:
Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.
After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.
If any medicine remains on the used OTFC unit after you have finished:
- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See Figure 4).
Figure 4
Temporary Storage of Used OTFC Units:
- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. Never leave unused or partially used OTFC units where children or pets can get to them (See Figure 5).
Figure 5
Disposing of Used OTFC Units from the Temporary Storage Bottle:
You must dispose of all used OTFC units in the temporary storage bottle at least one time each day, as follows:
1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See Figure 6).
Figure 6
2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.
Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.
Disposing of unopened OTFC units: Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:
1. Remove all OTFC from the locked storage space (See Figure 7).
Figure 7
2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See Figures 8A and 8B).
Figure 8A Figure 8B
3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See Figures 9A and 9B).
Medicine
Handle
Figure 9A
Figure 9B
4. Throw the handle away in a place that is out of the reach of children (See Figure 10).
Figure 10
5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See Figure 11). Do not flush more than 5 OTFC units at a time.
Flush 2 Times
Figure 11
- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.
If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.
General information about Oral Transmucosal Fentanyl Citrate (OTFC)
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have. OTFC can harm other people and even cause death. Sharing OTFC is against the law.
This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.
For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.
What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?
Active Ingredient: fentanyl citrate
Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.
Patient Instructions for Use
Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.
When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See Figure 12). Do not open the blister package until you are ready to use OTFC.
Figure 12
- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See Figures 13A and 13B). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See Figure 14).
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1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See Figure 15).
Figure 15
3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.
- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See Figure 16).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.
Figure 16
See "How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?" for proper disposal of OTFC.
This Medication Guide has been approved by the U.S. Food and Drug Administration.
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U.S. Patent No. 7,908,729 Rev. X 3/2013
MG459-01-61-04

MEDICATION GUIDE

Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt) Lozenge CII
(OTFC)

200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:

Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.

Get emergency medical help right away if:

- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause life-threatening breathing problems which can lead to death:

1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**

- You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
- You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**

4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. OTFC is available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:

- talk to your healthcare provider
- understand the benefits and risks of OTFC
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?

- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.

- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?

Do not use OTFC:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?

Before using OTFC, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions

- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.

- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?

Before you can begin to use OTFC:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:

- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC during each episode of breakthrough cancer pain:
    - Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.

- If your breakthrough cancer pain is not relieved 15 minutes after you finished the OTFC unit, use **only 1** more unit of OTFC at this time.
- If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**

- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?

OTFC can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about OTFC?"**

   Call your healthcare provider or get emergency medical help right away if you:

   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**

2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:

- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.

OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
    - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items

in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.

- If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-828-9393 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

- **A child-resistant lock that** you use to secure the storage space where you keep OTFC (See **Figure 1**).

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See **Figure 2**).

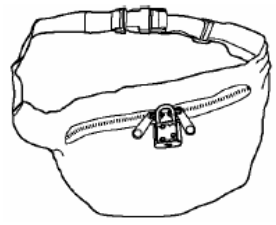


Figure 2

- **A child-resistant temporary storage bottle** (See **Figure 3**).

Figure 3

- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.

- **Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.**
- Keep OTFC dry.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.**

After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If **any** medicine remains on the used OTFC unit after you have finished:

- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See **Figure 4**).

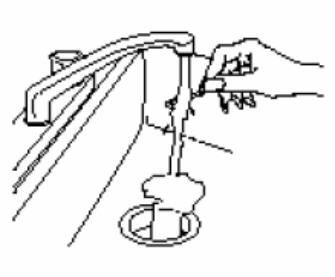


Figure 4

<u>Temporary Storage of Used OTFC Units</u>:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

<u>Disposing of Used OTFC Units from the Temporary Storage Bottle</u>:

You must dispose of all used OTFC units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See **Figure 6**).

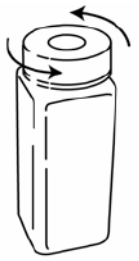


Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

Disposing of unopened OTFC units: Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all OTFC from the locked storage space (See **Figure 7**).

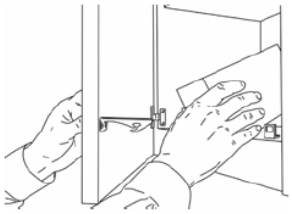
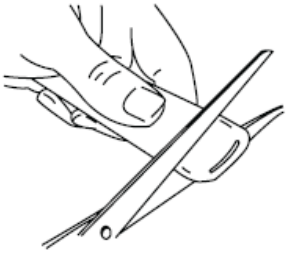


Figure 7

2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See **Figures 8A** and **8B**).



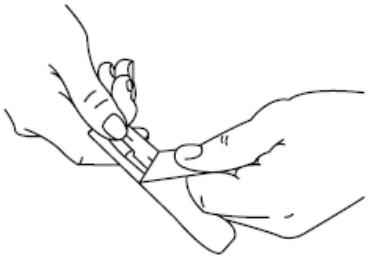
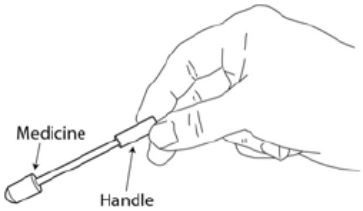


Figure 8A **Figure 8B**

3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See **Figures 9A** and **9B**).



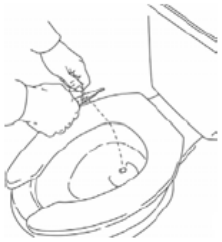


Figure 9A **Figure 9B**

4. Throw the handle away in a place that is out of the reach of children (See **Figure 10**).

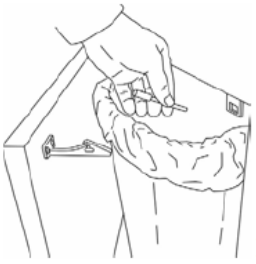


Figure 10

5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See **Figure 11**). Do not flush more than 5 OTFC units at a time.

Figure 11

• Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have**. OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.

- Each unit of OTFC is sealed in its own blister package (See **Figure12**). **Do not open the blister package until you are ready to use OTFC.**

Figure 12

- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See **Figures 13A** and **13B**). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See **Figure 14**).

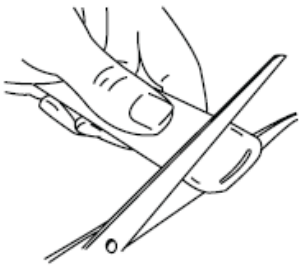


Figure 13A

Figure 13B

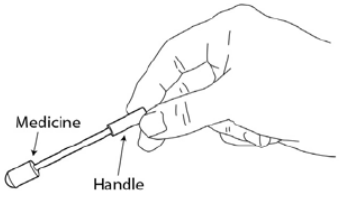


Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See **Figure 15**).

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Manufactured For:
PAR PHARMACEUTICAL
Spring Valley, NY 10977

U.S. Patent No. 7,908,729 Rev. X 3/2013

MG-459-01-61-04

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312/S-005

SUPPLEMENTAL APPROVAL

Par Pharmaceutical, Inc.
Attention: Krista Richardson
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

Please refer to your Supplemental Abbreviated New Drug Application (sANDA) dated and received October 1, 2012, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

We acknowledge receipt of your amendments dated September 11 and October 23, 2013 and your risk evaluation and mitigation strategy (REMS) assessment dated December 21, 2012 and amended May 15, 2013.

This supplemental new drug application provides for modifications to the approved REMS for Oral Transmucosal Fentanyl Citrate, which is part of the single shared system REMS, the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access Program.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Oral Transmucosal Fentanyl Citrate was originally approved on December 28, 2011. The REMS was last modified on June 8, 2012. The REMS consists of a Medication Guide, elements to assure safe use, and an implementation system.

Your proposed modification to the TIRF REMS, including appended REMS materials as applicable, consists of the following:

- Revised terminology, processes, and definitions for outpatient pharmacies
- Revised attestations for physicians and patients to address concerns regarding patient access
- Revised Program Overview and Frequently Asked Questions to improve clarity and content
- Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program

Your proposed modified REMS, submitted on October 1, 2012, jointly amended on September 11 and October 23, 2013, by the TIRF REMS Industry Group (TRIG), and appended to this letter, is approved.

The TIRF REMS Access Program includes the following products:

NDA 020747 Actiq (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 021947 Fentora (fentanyl buccal tablets)
NDA 022266 Onsolis (fentanyl buccal soluble film)
NDA 022510 Abstral (fentanyl) sublingual tablets
NDA 022569 Lazanda (fentanyl) nasal spray
NDA 202788 Subsys (fentanyl) sublingual spray
ANDA 077312 Fentanyl Citrate Oral Transmucosal Lozenge
ANDA 078907 Fentanyl Citrate Oral Transmucosal Lozenge

Other products may be added in the future if additional TIRF NDAs or ANDAs are approved.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy.

Prominently identify any submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

ANDA 077312
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 077312
PROPOSED REMS MODIFICATION

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.80 and 314.81).

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal

Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, contact Carrie Lemley, Labeling Project Manager, at (240) 276-8986 or carrie.lemley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kathleen Uhl, M.D.
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
REMS

Initial REMS approval: 12/2011

Most recent modification: 11/2013

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**
  - i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.
  - ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
  - iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form.* In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for <u>all</u> patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form.* In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS

Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

   ii. The patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.
2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:
   a. Review the distributor TIRF REMS Access program materials
   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:
      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.
      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.
      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.
   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.
   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.
   e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.
   f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.
   g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:
      - *Dear Distributor Letter*
      - *Distributor Enrollment Form*
      - *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.
4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.
5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.
6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.
7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will

update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program.

b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.

13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is listed in attachment 1.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and Enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This education program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program Overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guides for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are

knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

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Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines

- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
    - children,
    - individuals for whom it is not prescribed, and
    - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are not equivalent to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora and Actiq to Subsys you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Always 100 mcg.	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge and generic equivalents	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per breakthrough cancer pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Products Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information)	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.

Patient Counseling

Tell the patient (cont.):

- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?

Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?

Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?

Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?

Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Lazanda to Actiq
B. Actiq to Fentora
C. Actiq to Subsys
D. Both B & C

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** _____ **DEA Number*** _____
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

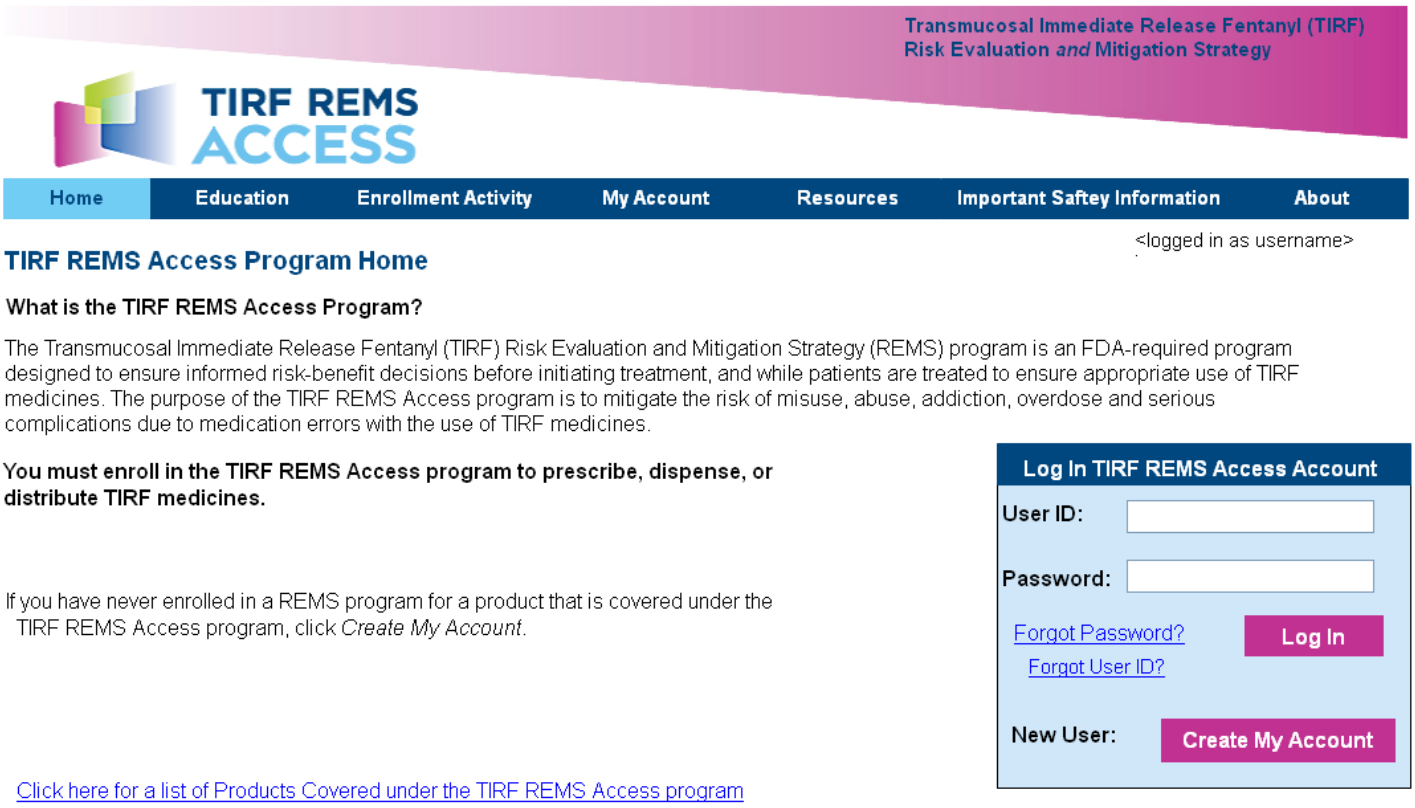
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

HOME PAGE



Click here for a list of Products Covered under the TIRF REMS Access program hyper link will open the document in a pdf window

Attachment 1

List of TIRF medicines Available Only through the TIRF REMS Access program

- **ABSTRAL®** (fentanyl) sublingual tablets
- **ACTIQ®** (fentanyl citrate) oral transmucosal lozenge
- **FENTORA®** (fentanyl buccal tablet)
- **LAZANDA®** (fentanyl) nasal spray
- **ONSOLIS®** (fentanyl buccal soluble film)
- **SUBSYS®** (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is listed in attachment 1.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
    - To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim: Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is listed in attachment 1.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,

- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is listed in attachment 1.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Chain Outpatient Pharmacies”, “An Overview for Independent Outpatient Pharmacies” or “An Overview for Inpatient Pharmacies” for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**.

- **To confirm enrollment confirmation by phone:**
    - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
    - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

        - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
        - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
    - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1:

List of TIRF Medicines Available through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is listed in attachment 1.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Pharmacist Name* (please print):_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65,
0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-01, 20482-002-01, 20482-004-01, 20482-006-01, 20482-008-01, 20482-001-10, 20482-002-10,
20482-004-10, 20482-006-10, 20482-008-10, 20482-001-30, 20482-002-30, 20482-004-30, 20482-006-30,
20482-008-30, 20482-012-15, 20482-016-15,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55
57881-331-12, 57881-331-32, 57881-332-12, 57881-332-32, 57881-333-12, 57881-333-32, 57881-334-12,
57881-334-32, 57881-336-32, 57881-338-32

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of

Pharmacist Name* (please print):_____

Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of the TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*: _____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s:

42747-221-32, 42747-222-32, 42747-223-32, 42747-224-32, 42747-226-32, 42747-228-32
63459-502-30, 63459-504-30, 63459-506-30, 63459-508-30, 63459-512-30, 63459-516-30,
63459-541-28, 63459-542-28, 63459-544-28, 63459-546-28, 63459-548-28,
51772-311-01, 51772-314-01, 0037-5200-30, 0037-5400-30, 0037-5600-30, 0037-5800-30, 0037-5120-30,
00093-5370-65, 00093-5371-65, 00093-5372-65, 00093-5373-65, 00093-5374-65, 00093-5375-65, 0406-9202-30, 0406-9204-30, 0406-9206-30, 0406-9208-30, 0406-9212-30, 0406-9216-30,
55253-0070-30, 55253-0071-30, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-01, 20482-002-01, 20482-004-01, 20482-006-01, 20482-008-01, 20482-001-10, 20482-002-10,
20482-004-10, 20482-006-10, 20482-008-10, 20482-001-30, 20482-002-30, 20482-004-30, 20482-006-30,
20482-008-30, 20482-012-15, 20482-016-15,
49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55
57881-331-12, 57881-331-32, 57881-332-12, 57881-332-32, 57881-333-12, 57881-333-32, 57881-334-12, 57881-334-32, 57881-336-32, 57881-338-32

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports

Chain ID*:_____

may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of the TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

Attachment 1

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl buccal tablet)
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
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- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

- Patient First Name..... TIRFREMSTEST
- Patient Last Name..... Smithers
- Date of Birth..... 19841105
- Patient ZIP/Postal Zone..... 07921
- Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
- Quantity Dispensed..... 12
- Days Supply..... 4
- Prescriber ID..... BA1111119
- Prescriber Last Name..... REMSTEST

- Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

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- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
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- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

11/07/2013

Deputy Director, Office of Generic Drugs, for
Kathleen Uhl, M.D.

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

Submitted to FDA via ESG

December 30, 2013

Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

24 MONTH ASSESSMENT REPORT

- *Reference to DMF Submission*

RE: ANDA 077312; *Sequence 0018*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII. Reference is also made to the 24-Month Assessment Report submitted to DMF #027320 on December 27, 2013. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted to this application on September 11, 2013 (Sequence 0016).

Please refer to DMF #027320 for the TIRF REMS 24-month REMS Assessment Report. The Assessment Report was included in eCTD sequence 0007 to DMF #027320.

We are also confirming that we will submit an amendment to this Assessment Report no later than January 31, 2014 providing safety information for our product, consisting of CIOMS II line listings (including all of the data elements requested by FDA) along with MedWatch forms/narratives for deaths, overdoses and pediatric exposures.

Please note that there are no ongoing post-marketing studies and/or clinical trials being conducted for this application at this time.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson
@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm.com, email=krista.richardson@parpharm.com
Date: 2013.12.30 10:28:48 -05'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

January 30, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

AMENDMENT TO REMS ASSESSMENT REPORT

RE: ANDA 077312; *Sequence 0019*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII.

Reference is also made to the 24 month Assessment Report submitted to DMF #027320 on December 30, 2013.

In response to the Agency's request during a teleconference held on November 14, 2013, Par is hereby providing safety information for our product in Module 5.3.6 "*Reports of Post-Marketing Experience*". The data consist of CIOMS II line listings with narrative (including all of the data elements requested by FDA) for deaths, overdoses and pediatric exposures.

Please note that all TIRF REMS sponsors provided safety data to their individual applications in May 2013 covering the period 28-DEC-2011 to 20-OCT-2012. Our 24 month assessment report covers the period from 29-OCT-2012 to 28-OCT-2013. In order to cover the "gap", we are submitting reports covering 21-OCT-2012 to 28-OCT-2013 for this assessment report. Future submissions will revert to the 12 month reporting period covered by our assessment reports.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson
@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm.com
email=krista.richardson@parpharm.com
Date: 2014.01.30 14:38:21 -05'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

April 1, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

AMENDMENT TO REMS ASSESSMENT REPORT

RE: ANDA 077312; *Sequence 0020*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII.

Reference is also made to the 24 month Assessment Report submitted to DMF #027320 on December 27, 2013. Additional reference is made to the Letter of Authorization (LOA) for DMF 027320 submitted to this application on September 11, 2013.

On March 31, 2014, in response to the Agency's request in an email dated December 5, 2013, the sponsors of TIRF products submitted a report providing an analysis of risks drawn from databases capturing abuse, addiction, overdose and death. This analysis covers the period of July 1, 2012 to September 30, 2013. Please refer to DMF 027320, Sequence 0008 for the report.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson
@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm.com, email=krista.richardson@parpharm.com
Date: 2014.04.01 10:32:41 -04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

May 22, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT

- *REMS Modification #3*

RE: ANDA 077312; *Sequence 0022*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Prior Approval Supplement dated May 21, 2014, which was submitted in conjunction with the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII, contained in DMF #027320.

Par is hereby submitting this amendment to the above-mentioned supplement in order to provide the Generic Drug User Fee Cover Sheet indicating the required payment for this Prior Approval Supplement. This was inadvertently omitted in the original submission and is provided herein in Module 1.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm.com, email=krista.richardson@parpharm.com
Date: 2014.05.22 10:13:22 -04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

June 2, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE

RE: ANDA 077312; *Sequence 0023*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF 027320 submitted to this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of the submission to the TIRF REMS DMF #027320 in sequence 0010 [May 30, 2014] of its response to the FDA Information Request dated May 16, 2014 concerning cash transactions. The e-mail correspondence from FDA to the TRIG on May 16, 2014 is provided herein for reference.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson
@parpharm.com
Digitally signed by krista.richardson@parpharm.com
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Date: 2014.06.02 15:42:54 -04'00'

Krista Richardson
Senior Manager, Regulatory Affairs

From: Jarral, Vaishali
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: TIRF REMS Modification #3 proposals
Date: Friday, May 16, 2014 8:28:17 AM

Hello Karla,

Reference is made to your April 15, 2014 response to our inquiry about your proposed "TRIG Recommendations for Programs Enhancements" sent March 24, related to the addition of information in TIRF REMS materials related to Cash Claim FAQs. In your response you clarified that per your 24-month assessment report Table 29 (page 72 of 131), 7 instances of non-compliance occurred where TIRF medicines were dispensed without verifying stakeholder enrollment through the TIRF REMS pharmacy management system and that the pharmacies involved "were either not aware of the requirement to process cash claims through the TIRM REMS Program or were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway." Your response also stated that to address "apparent prescription processing knowledge deficit" the proposed Cash Claim FAQ information would be added to emphasize that "all claims, highlighting cash claims specifically, must be submitted to the TIRF REMS Access Program to verify the enrollment status of the stakeholders before dispensing a TIRF medicine to a patient and to clearly provide the proper BIN number for transmission of cash claims data."

Prior to the information you provided, our understanding of the TIRF REMS Switch system transmission process was that the transaction is adjudicated through the switch automatically, whether the transaction was an insurance or cash claim. It appears that this is not the case and that, in fact, the process involves additional manual steps at the pharmacy level to enter the Cash BIN # into the system in order for the transaction to be adjudicated. We are concerned that the switch system is not a failsafe process for adjudication of TIRF REMS safety verifications prior to dispensing the product.

We have the following information request (IR) for the TRIG, in response to the information you have provided:

1. Provide a proposal to mitigate this failure mode to assure the Switch System cannot be bypassed prior to dispensing of TIRF products. Describe any ways that participating pharmacies' systems can be modified in order to automatically:
    a. adjudicate of cash claims and eliminate the required pharmacist manual entry of a BIN # and/or
    b. prevent the dispensing of a prescription if the cash claim is not transmitted to the TIRF REMS Access program.
    c. To what extent have certified pharmacies implemented such automated systems?

2. Please explain the method used to identify the 7 cases/7 pharmacies reported in your 24-month REMS assessment. Is the method used to identify these cases comprehensive in identifying all such cases?

3. Since the 24-month REMS assessment, have you identified any additional cases?

4. Provide the root cause analysis of how these cases occurred along with the TRIG's proposed plan for future detection/identification of cases such as these.

5. In your proposed modified FAQ, you ask pharmacists to transmit TIRF REMS CASH claims to the TIRF REMS Access Program using the REMS CASH BIN 014780. FDA has heard that pharmacies may be using other processes to transmit their TIRF REMS cash claims. Please confirm that these instructions will work in all pharmacies that participate in the REMS, and that they will not interfere with those pharmacies standard REMS operating procedures.

Please submit the response to DMF by May 27, 2014.

Thank you

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Tuesday, April 15, 2014 12:34 PM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Dear Vaishali,
Thank you for your inquiry about the TRIG's change proposal regarding the TIRF REMS Cash Claims requirements. TRIG's responses are as follows:

- Are cash transaction prescriptions currently being routed through the TIRF REMS System?
  - Yes.
- What prompted the TRIG to propose this modification?
  - As provided in Table 29 (page 72 of 131) of the 24-month assessment report, during this reporting period the non-compliance review team identified 7 instances where a TIRF medicine was dispensed without verifying stakeholder enrollment through the TIRF REMS pharmacy management system. A total of 7 pharmacies involved in these non-compliant events indicated they were either not aware of the requirement to process cash claims through the TIRF REMS Access Program (3); or, were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway (4).
- Please provide any additional information to help inform our understanding of this proposal.
  - To alleviate this apparent prescription processing knowledge deficit, the TRIG opted to propose a modification to the FAQ for "Chain and Independent Outpatient Pharmacy Cash Claim" to emphasize that all claims, highlighting cash claims specifically, must be submitted to the TIRF REMS Access Program to verify the enrollment status of the stakeholders before dispensing a TIRF medicine to a patient and to clearly provide the proper BIN number for transmission of cash claims data.

Please let us know if you have additional questions.

Best regards,

Kindest regards,
Karla

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs, Specialty Generics
Mallinckrodt Pharmaceuticals
675 McDonnell Boulevard
Hazelwood MO, 63042 USA
T: 314.654.3517
M: 314.229.7895
karla.werre@mallinckrodt.com

www.mallinckrodt.com

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Monday, April 14, 2014 9:55 AM
To: Werre, Karla L
Subject: RE: TIRF REMS Modification #3 proposals

Thank you.

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Monday, April 14, 2014 10:46 AM
To: Jarral, Vaishali
Subject: RE: TIRF REMS Modification #3 proposals

Vaishali,
Yes, definitely before Friday, likely to be tomorrow.

Regards,
Karla

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Monday, April 14, 2014 9:30 AM
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Karla,

In regards to the information request below, kindly let me know if you will able to respond by this Friday.

Thanks,
Vaishali

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Wednesday, April 09, 2014 11:12 AM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: FW: TIRF REMS Modification #3 proposals

Vaishali,
Thank you for your inquiry. I will pose your question to the TRIG and get back to you promptly.

Kindest regards,

Karla
Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs, Specialty Generics
Mallinckrodt Pharmaceuticals
675 McDonnell Boulevard
Hazelwood MO, 63042 USA

T: 314.654.3517
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karla.werre@mallinckrodt.com
www.mallinckrodt.com

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Wednesday, April 09, 2014 9:57 AM
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Karla,

The Division of Risk Management (DRISK) would like to better understand the TRIG proposal included in your March 24, 2014 email (your email below) document titled 'TRIG Recommendations for Program Enhancements' that relates to TIRF REMS Cash claims requirements. Are cash transaction prescriptions currently being routed through the TIRF REMS System? What prompted the TRIG to propose this modification? Please provide any additional information to help inform our understanding of this proposal.

Thank you,

Vaishali Jarral, M.S., M.B.A
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4472
Silver Spring, MD 20993

301.796.4248
Vaishali.Jarral@fda.hhs.gov

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Monday, March 24, 2014 2:00 PM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: TIRF REMS Modification #3 proposals

Vaishali,

In addition to the previously communicated modifications to the TIRF REMS provided in our e-mail dated February 18th (remove NDC numbers, remove Attachment A, remove reference to individual generics in Education program), the TRIG proposes to further enhance the program per the attachment entitled, "TRIG Recommendations for Program Enhancements."

Additionally to clarify, in our March 13th conversation, you stated that changes to the assessment metrics and the RSD do not necessarily trigger a modification. Should the changes in the attachment to this e-mail be included in Modification 3?

Kindest regards,

Karla
Karla Werre, MBA, RAC(US) | Manager, Regulatory Affairs
Specialty Generics | **Mallinckrodt Pharmaceuticals**
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DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 077312/MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment REMS ASSESSMENT PLAN REVISION
Communication ID:	(COR-SEC901REMS-10) (COR-SEC901REMS-17)
Drafted by:	M.Liberatore 7/25/14, 8/6/14, 8/12/14
Clearance History:	JRacoosin 7/27/14 K. Lehrfeld 8/6/14 P. Jani/8-12-14 SRT
Finalized:	M. Liberatore
Filename:	
Use Statement:	
Notes:	

Version: DARRTS 06/03/2012

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT
REMS ASSESSMENT PLAN REVISION

Par Pharmaceuticals, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

Attention: Krista Richardson
Senior Manager, Regulatory Affairs

Dear Ms. Richardson:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg.

We also refer to your December 30, 2013, submission containing the 24-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. In your one-year assessment report, information regarding the number of enrolled pharmacies from government agencies as well as other integrated systems/mail order data were presented. These categories are absent from your 24-month assessment report. In light of the REMS compliance issues experienced by at least two federal closed systems (the VA and DOD), in future assessment reports, report on the number of enrolled pharmacies in federal and other integrated systems.

2. Although the percentage of Patient-Provider Agreement Forms (PPAFs) received in the 10-day window between patient enrollment and receipt by the REMS program improved from the 12-month report figure (46% vs. 37%), continue to employ strategies that will improve the percentage of PPAFs received in the 10-day window.

3. A total of 73 outpatient pharmacies are described as having an "*incomplete configuration*," though no reasons are provided as to why these 73 pharmacies remain in this status. In all subsequent assessment reports, provide complete information regarding why certain pharmacies are not able to configure their systems.

4. In future assessment reports, provide the most recent American Association of Poison Control Centers (AAPCC) case narratives.

5. Regarding RADARS data submissions in the future provide:
    a. information about the protocols used to generate these data
    b. data from the RADARS Drug Diversion Program
    c. the numbers of patients identified to have taken TIRFs for all of the programs for which you present data.

6. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

7. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

8. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

9. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

Our December 28, 2011, REMS approval letter described the REMS assessment plan. During the review of the first and second year TIRF REMS assessment reports, changes to some of the metrics in the assessment plan were discussed both internally as well as with the TIRF REMS Industry Group (TRIG). The revisions provided in this letter serve to further tailor the metrics to those that are most informative regarding the operation and effectiveness of the TIRF REMS program. In brief, the revised REMS assessment plan comprises:

- Scaled back reporting of TIRF utilization data that focuses on the stakeholders enrolled, inactivated, and the numbers of stakeholders affected by enrollment delays

- Refocused dispensing activity data that includes stratification by closed/non-closed systems.
- A plan to assess non-compliance with the REMS that includes annual audits of randomly selected closed systems and inpatient systems.
- Safety surveillance that will consist of one comprehensive report that includes spontaneous adverse event data from all of the drugs under the TIRF REMS and that will focus on four categories of adverse events: addiction, overdose, death, and pediatric exposures.
- Continued use of stakeholder knowledge surveys to help inform whether the goals of the REMS are being met.

The complete revised REMS assessment plan is attached (see Appendix).

If you have any questions, contact Katherine Won, REMS Coordinator, at (301) 796-7568 or Katherine.Won@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

CAPT Jason J.Y. Woo, M.D., M.P.H.
Acting Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Revised Assessment Plan

APPENDIX: REVISED ASSESSMENT PLAN

Assessment Plan for TIRF REMS

1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively)
    a. Patient Enrollment:
        i. Number of unique patients enrolled
        ii. Number of patients inactivated
    b. Prescriber Enrollment:
        i. Number of prescribers enrolled
        ii. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
        iii. Number of prescribers inactivated
    c. Pharmacy Enrollment:
        i. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities);
        ii. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
        iii. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);
    d. Distributor enrollment:
        i. Number of distributors enrolled
        ii. Number of distributors inactivated

2. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)
    a. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity

b. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)

c. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons

d. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized

e. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF

f. Number of prescriptions dispensed after ten days without a PPAF in place

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described

b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

c. Call center report with

i. Overall number of contacts

ii. Summary of frequently asked questions

iii. Summary of REMS-related problems reported

d. Description of corrective actions taken to address program/system problems

4. TIRF REMS Access Non-Compliance Plan: The TIRF sponsors should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Numbers of prescription authorizations per closed system

iii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program. Data to include the 12 month

period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).

iv. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

b. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period
These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program

iii. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

c. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:

i. Description of how the NCRT defines a non-compliance event

ii. Description of how non-compliance information is collected and tracked

iii. Criteria and processes the Team uses to make decisions

iv. Summary of decisions the Team has made during the reporting period

v. How the Team determines when the compliance plan should be modified

d. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action

e. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences

f. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified

h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

i. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

5. Safety Surveillance (data collected per reporting period):

a. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures

b. TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:

i. Line listings under each category of adverse events of interest as listed above

ii. Line listings should provide at a minimum the following information (see sample table provided):

1. Identifying case number
2. Age and Gender of the patient
3. Date of the event as well as of the report
4. The Preferred Terms
5. Indication of TIRF use
6. Duration of TIRF therapy
7. Concomitant medications
8. Event Outcome

iii. Other metrics of interest include:

1. Number of event reports in each event category of interest
2. Counts of adverse events related to inappropriate conversions between TIRF products
3. Counts of adverse events related to accidental and unintentional exposures
4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients

iv. Duplicate cases are identified and eliminated

v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events

vii. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs
ii. Surveys conducted at substance abuse treatment programs
iii. College surveys
iv. Poison control center data
v. Impaired health care workers
vii. Drug-related hospital emergency department visits
viii. Drug-related deaths
ix. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

6. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

08/21/2014

Associate Director for Review Quality, for
Jason Woo, M.D., M.P.H.

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT
TIRF REMS MODIFICATION 3

November 26, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 077312 – Sequence 0025
Oral Transmucosal Fentanyl Citrate,
eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in sequence 0012 [November 25, 2014].

The modifications to the TIRF REMS program included in this submission are comprised of changes requested by the FDA in e-mails dated October 20th, November 6th, and November 18th, 2014 and furthermore, consist of changes proposed and accepted by the TIRF REMS Industry Group ("TRIG") and FDA, respectively on November 7th, 2014. All updated TIRF REMS documents are submitted as both red-lined and clean versions in MS Word format. In addition, PDF documents of the RSD with Appendices and REMS with Supporting Materials are provided. Please note that unchanged TIRF REMS documents are not being resubmitted, but are referenced in the Reviewer's Guide and hyperlinked to the current version. All changes to the TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a MS Word file with screen prints in the clean versions.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
Digital y signed by krista richardson@parpharm com
DN: cn=krista richardson@parpharm com
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Date: 2014 11 26 11:15:32 05 00

Krista Richardson
Associate Director, Regulatory Affairs

Par Pharmaceutical Inc.
One Ram Ridge Rd.
Spring Valley, NY 10977
Tel 845-425-7100
Fax 845-573-5795

December 11, 2014

Kathleen Uhl, MD
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT

- *TIRF REMS Modification 3*

RE: ANDA 077312 – Sequence 0026
Oral Transmucosal Fentanyl Citrate,
eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in sequence 0013 [December 10, 2014]. Prior amendments to the REMS for Modification #3 were submitted on April 1, 2014, May 21, 2014 and November 25, 2014. (The last REMS Assessment for the TIRF REMS Access Program was submitted on December 27, 2013.).

In conjunction with the correspondence received November 26, 2014 from Vaishali Jarral of your office, provided herein is the complete documentation of the TIRF REMS Access program including the requested "Dear" letters which were previously omitted. Please note that for the ease of review, this submission (DMF Sequence # 0013) contains the updated TIFR REMS documents in both red-lined and clean versions in MS Word format that were previously submitted via Sequence 0012 on November 25, 2014. All documents are referenced in the Reviewer's Guide and hyperlinked to their current version. All changes to the TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a MS Word file with screenprints in the clean versions. No new changes requiring additional FDA review are proposed at this time. Additionally, enclosed for the reference in Module 1.16 is the current medication guide for the drug product.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm.com, email=krista.richardson@parpharm.com
Date: 2014.12.11 12:06:29 -05'00'

Krista Richardson
Associate Director, Regulatory Affairs

MEDICATION GUIDE
Oral Transmucosal
Fentanyl Citrate (FEN ta nil SIT rayt)
Lozenge
(OTFC) **C II**
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg

IMPORTANT:
Do not use Oral Transmucosal Fentanyl Citrate (OTFC) unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means that you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.
Keep Oral Transmucosal Fentanyl Citrate (OTFC) in a safe place away from children.
Get emergency medical help right away if:
- **a child takes Oral Transmucosal Fentanyl Citrate (OTFC). Oral Transmucosal Fentanyl Citrate (OTFC) can cause an overdose and death in any child who uses it.**
- **an adult who has not been prescribed Oral Transmucosal Fentanyl Citrate (OTFC) uses it.**
- **an adult who is not already taking opioids around-the-clock, uses Oral Transmucosal Fentanyl Citrate (OTFC).**

These are medical emergencies that can cause death. If possible, remove Oral Transmucosal Fentanyl Citrate (OTFC) from the mouth.

Read this Medication Guide completely before you start using OTFC and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about Oral Transmucosal Fentanyl Citrate (OTFC)?
OTFC can cause life-threatening breathing problems which can lead to death:
1. **Do not use OTFC if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using OTFC. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use OTFC exactly as prescribed by your healthcare provider.**
   - You must not use more than 1 unit of OTFC at a time and no more than 2 units of OTFC during each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain. **See the Medication Guide section "How should I use OTFC?" and the Patient Instructions for Use at the end of this Medication Guide about how to use OTFC the right way.**
4. **Do not switch from OTFC to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of OTFC is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of OTFC that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use OTFC for short-term pain that you would expect to go away in a few days, such as:
   - pain after surgery
   - headache or migraine
   - dental pain
6. **Never give OTFC to anyone else,** even if they have the same symptoms you have. It may harm them or even cause death.

OTFC is a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.
- **Prevent theft, misuse or abuse. Keep OTFC in a safe place** to protect it from being stolen. OTFC can be a target for people who abuse opioid (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**
7. OTFC is available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive OTFC, you must:
- talk to your healthcare provider
- understand the benefits and risks of OTFC
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form

What is Oral Transmucosal Fentanyl Citrate (OTFC)?
- OTFC is a prescription medicine that contains the medicine fentanyl.
- OTFC is used to manage breakthrough pain in adults (16 years of age and older) with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- OTFC is started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use OTFC if you are not opioid tolerant.
- OTFC is a lozenge (attached to a handle) that you place between your cheek and lower gum and suck on to dissolve.
- You must stay under your healthcare provider's care while using OTFC.
- OTFC is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if OTFC is safe and effective in children under 16 years of age.

Who should not use Oral Transmucosal Fentanyl Citrate (OTFC)?
Do not use OTFC:
- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain
- if you are allergic to any of the ingredients in OTFC. See the end of this Medication Guide for a complete list of ingredients in OTFC.

What should I tell my healthcare provider before using Oral Transmucosal Fentanyl Citrate (OTFC)?
Before using OTFC, tell your healthcare provider if you:
- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse or addiction problem, or a family history of a drug abuse problem or addiction problem
- have diabetes. Each OTFC unit contains about ½ teaspoon (2 grams) of sugar.
- have any other medical conditions
- are pregnant or plan to become pregnant. OTFC may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. OTFC passes into your breast milk. It can cause serious harm to your baby. You should not use OTFC while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with OTFC. Sometimes, the doses of certain medicines and OTFC may need to be changed if used together.
- Do not take any medicine while using OTFC until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using OTFC.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use Oral Transmucosal Fentanyl Citrate (OTFC)?
Before you can begin to use OTFC:
- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- OTFC is only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your OTFC prescription filled.

Using OTFC:
- **Use OTFC exactly as prescribed. Do not use OTFC more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Patient Instructions for Use at the end of this Medication Guide for information about how to use OTFC the right way.**
- Finish the OTFC unit completely in 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
- **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**
- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- You must not use more than 2 units of OTFC during each episode of breakthrough cancer pain:
  - Use **1** unit for an episode of breakthrough cancer pain. Finish the unit over 15 minutes.
  - If your breakthrough cancer pain is not relieved 15 minutes after you finished the OTFC unit, use **only 1** more unit of OTFC at this time.
  - If your breakthrough pain does not get better after the second unit of OTFC, call your healthcare provider for instructions. **Do not use another unit of OTFC at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with OTFC.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using OTFC.
- Talk to your healthcare provider if your dose of OTFC does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of OTFC needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before OTFC is completely dissolved, remove OTFC from your mouth.
- If you use too much OTFC or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room right away.

What should I avoid while using Oral Transmucosal Fentanyl Citrate (OTFC)?
- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how OTFC affects you. OTFC can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using OTFC.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of Oral Transmucosal Fentanyl Citrate (OTFC)?
OTFC can cause serious side effects, including:
1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about OTFC?**"
   Call your healthcare provider or get emergency medical help right away if you:
   - have trouble breathing
   - have drowsiness with slowed breathing
   - have slow shallow breathing (little chest movement with breathing)
   - feel faint, very dizzy, confused, or have other unusual symptoms

   These symptoms can be a sign that you have used too much OTFC or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not use any more OTFC until you have talked to your healthcare provider.**
2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop taking OTFC or any other opioid, without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have ever been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.

The most common side effects of OTFC are:
- nausea
- vomiting
- dizziness
- sleepiness
- weakness
- headache
- anxiety
- confusion
- depression
- rash
- trouble sleeping

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including OTFC and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking OTFC.
OTFC contains sugar. Cavities and tooth decay can happen in people taking OTFC. When taking OTFC, you should talk to your dentist about proper care of your teeth.

NOTE(S):

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of OTFC. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oral Transmucosal Fentanyl Citrate (OTFC)?

- **Always keep OTFC in a safe place away from children and from anyone for whom it has not been prescribed.** Protect OTFC from theft.
  - You can use the OTFC Child Safety Kit to help you store OTFC and your other medicines out of the reach of children. It is very important that you use the items in the OTFC Child Safety Kit to help protect the children in your home or visiting your home.
  - If you were not offered a Child Safety Kit when you received your medicine, call PAR PHARMACEUTICAL at 1-800-828-9393 to request one.

The OTFC Child Safety Kit contains important information on the safe storage and handling of OTFC.

The Child Safety Kit includes:

- **A child-resistant lock that** you use to secure the storage space where you keep OTFC (See **Figure 1**).

Figure 1

- **A portable locking pouch** for you to keep a small supply of OTFC nearby. The rest of your OTFC must be kept in a locked storage space.
  - Keep this pouch secured with its lock and keep it out of the reach and sight of children (See **Figure 2**).

Figure 2

- **A child-resistant temporary storage bottle** (See **Figure 3**).

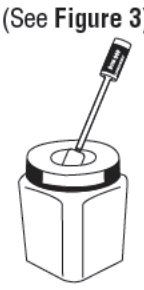


Figure 3

- Store OTFC at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use.
- Do not freeze OTFC.
- **Keep OTFC in the original sealed child-resistant blister package. Do not open the blister package until you are ready to use OTFC.**
- Keep OTFC dry.

How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?

Disposing of OTFC units after use:

Partially used OTFC units may contain enough medicine to be harmful or fatal to a child or other adults who have not been prescribed OTFC. **You must properly dispose of the OTFC handle right away after use even if there is little or no medicine left on it.**

After you have finished the OTFC unit and the medicine is totally gone, throw the handle away in a place that is out of the reach of children.

If **any** medicine remains on the used OTFC unit after you have finished:

- Place the used OTFC unit under hot running water until the medicine is gone, and then throw the handle away out of the reach of children and pets (See **Figure 4**).

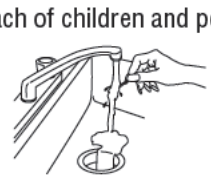


Figure 4

Temporary Storage of Used OTFC Units:

- If you did not finish the entire OTFC unit and you cannot dissolve the medicine under hot running water right away, put the used OTFC unit in the temporary storage bottle that you received in the OTFC Child Safety Kit. Push the used OTFC unit into the opening on the top until it falls completely into the bottle. **Never leave unused or partially used OTFC units where children or pets can get to them** (See **Figure 5**).

Figure 5

Disposing of Used OTFC Units from the Temporary Storage Bottle:

You must dispose of all used OTFC units in the temporary storage bottle **at least one time each day**, as follows:

1. To open the temporary storage bottle, push down on the cap until you are able to twist the cap to the left to remove it (See **Figure 6**).

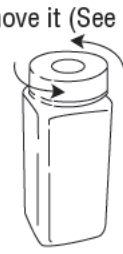


Figure 6

2. Remove one OTFC unit from the temporary storage bottle. Hold the OTFC by its handle over the toilet bowl.
3. Using wire-cutting pliers, cut the medicine end off so that it falls into the toilet.
4. Throw the handle away in a place that is out of the reach of children.
5. Repeat these 3 steps for each OTFC handle that is in the storage bottle. There should not be more than 4 handles in the temporary storage bottle for 1 day.
6. Flush the toilet twice.

Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

Disposing of unopened OTFC units:

Dispose of any unopened OTFC units remaining from a prescription as soon as they are no longer needed, as follows:

1. Remove all OTFC from the locked storage space (See **Figure 7**).

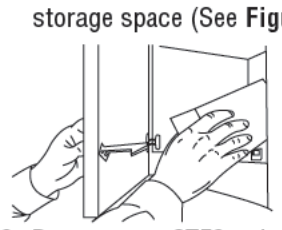


Figure 7

2. Remove one OTFC unit from its blister package by using scissors to cut off the marked end and then peel back the blister backing (See **Figures 8A** and **8B**).

Figure 8A

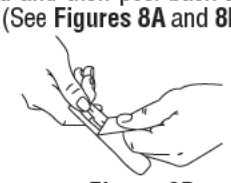


Figure 8B

3. Hold OTFC by its handle over the toilet bowl. Use wire-cutting pliers to cut the medicine end off so that it falls into the toilet (See **Figures 9A** and **9B**).

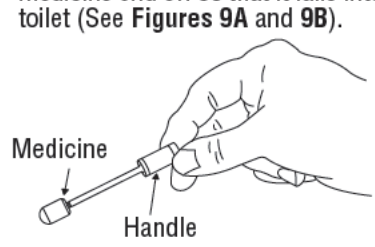


Figure 9A

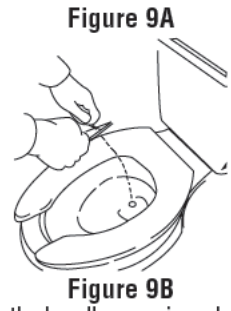


Figure 9B

4. Throw the handle away in a place that is out of the reach of children (See **Figure 10**).

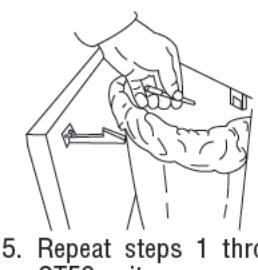


Figure 10

5. Repeat steps 1 through 4 for each OTFC unit.
6. Flush the toilet twice after the medicine ends from 5 OTFC units have been cut off (See **Figure 11**). Do not flush more than 5 OTFC units at a time.

Figure 11

- Do not flush entire unused OTFC units, OTFC handles, or blister packages down the toilet.

If you need help with disposal of OTFC, call PAR PHARMACEUTICAL, at 1-800-828-9393, or call your local Drug Enforcement Agency (DEA) office.

General information about Oral Transmucosal Fentanyl Citrate (OTFC)

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use OTFC only for the purpose for which it was prescribed. Do not give OTFC to other people, even if they have the same symptoms you have.** OTFC can harm other people and even cause death. Sharing OTFC is against the law.

This Medication Guide summarizes the most important information about OTFC. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about OTFC that is written for healthcare professionals.

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients of Oral Transmucosal Fentanyl Citrate (OTFC)?

Active Ingredient: fentanyl citrate

Inactive Ingredients: Anhydrous citric acid, artificial raspberry flavor, confectioner's sugar, dextrates, dibasic sodium phosphate, FD&C blue no. 1, magnesium stearate, pregelatinized starch, propylene glycol and purified shellac.

Patient Instructions for Use

Before you use OTFC, it is important that you read the Medication Guide and these Patient Instructions for Use. Be sure that you read, understand, and follow these Patient Instructions for Use so that you use OTFC the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use OTFC.

When you get an episode of breakthrough cancer pain, use the dose of OTFC prescribed by your healthcare provider as follows:

- You may drink some water before using OTFC but you should not drink or eat anything while using OTFC.
- Each unit of OTFC is sealed in its own blister package (See **Figure 12**). **Do not open the blister package until you are ready to use OTFC.**

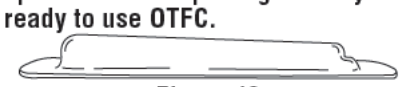


Figure 12

- When you are ready to use OTFC, cut open the package using scissors. Peel back the blister backing, and remove the OTFC unit (See **Figures 13A** and **13B**). The end of the unit printed with "OTFC" and the strength number of the unit ("200", "400", "600", "800", "1200", or "1600") is the medicine end that is to be placed in your mouth. Hold the OTFC unit by the handle (See **Figure 14**).

Figure 13A

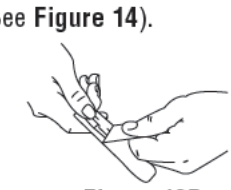


Figure 13B

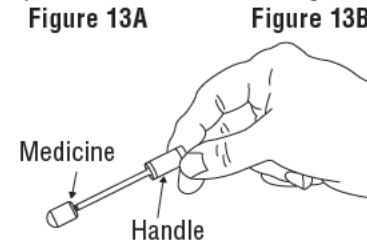


Figure 14

1. Place the medicine end of the OTFC unit in your mouth between your cheeks and gums and actively suck on the medicine.
2. Move the medicine end of the OTFC unit around in your mouth, especially along the inside of your cheeks (See **Figure 15**).

Figure 15

3. Twirl the handle often.
4. Finish the OTFC unit completely over 15 minutes to get the most relief. If you finish OTFC too quickly, you will swallow more of the medicine and get less relief.
5. **Do not bite or chew OTFC. You will get less relief for your breakthrough cancer pain.**

- If you cannot finish all of the medicine on the OTFC unit and cannot dissolve the medicine under hot tap water right away, immediately put the OTFC unit in the temporary storage bottle for safe keeping (See **Figure 16**).
  - Push the OTFC unit into the opening on the top until it falls completely into the bottle. You must properly dispose of the OTFC unit as soon as you can.

Figure 16

See "**How should I dispose of Oral Transmucosal Fentanyl Citrate (OTFC) units when they are no longer needed?**" for proper disposal of OTFC.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960
Manufactured For:
PAR PHARMACEUTICAL COS., INC.
Spring Valley, NY 10977

U.S. Patent No. 7,908,729 Rev. X 3/2013
MG459-01-61-04

FDA_12110

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 077312/S006
CommunicationType:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	C.Phillips/11-10-14
Clearance History by:	M. Liberatore 11/20/14; C. Miller 12/3/14
Finalized:	
Filename:	
Use Statement:	Use to notify applicant of an approval action for a supplemental application that includes changes to the labels or labeling
Notes:	USE "sNDA Approval [OTC ONLY]" template for Over-the-Counter sNDA Approvals USE COR-SNDAACTION-06 FOR sNDA CMC APPROVALS USE COR-SNDAACTION-09 FOR sNDA TENTATIVE APPROVALS If supplement approval also fulfills a PMR/PMC, this letter will need to be double-coded as PMR-PMC Fulfilled.

Version: DARRTS 04/30/2014

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312/S-006

SUPPLEMENT APPROVAL

Par Pharmaceutical, Inc.
Attention: Krista Richardson
Senior Manager, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Ms. Richardson:

Please refer to your Supplemental Abbreviated New Drug Application (ANDA) dated May 21, 2014, received May 21, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

We acknowledge receipt of your amendments dated May 22, 2014, July 17, 2014, November 26, 2014, and December 11, 2014. We also refer to the May 20, 2014, November 25, 2014 and December 10, 2014, submissions to DMF 27320, which contain the proposed modifications to your shared risk evaluation and mitigation strategy (REMS) program.

This "Prior Approval" supplemental abbreviated new drug application provides for modifications to the approved REMS for Oral Transmucosal Fentanyl Citrate, which is part of the single shared system REMS, the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access Program.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for TIRF Products, of which Oral Transmucosal Fentanyl Citrate is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on November 7, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the TIRF REMS, including appended REMS materials as applicable, consist of the following:

1. Removal of NDC Numbers from the following:
    i. Independent Outpatient Pharmacy Enrollment Form;
    ii. Chain Outpatient Pharmacy Enrollment Form, and;

iii. TIRF REMS Website

2. Removal of reference to generic equivalents of specific products and replacement with a footnote in the following:
   i. Education Program for Prescribers and Pharmacists, and;
   ii. TIRF REMS Website
3. Removal of “Attachment 1: List of TIRF Medicines Available Only through the TIRF REMS Access Program," and replacement with a hyperlink to the new TIRF REMS Webpage in the following:
   i. TIRF REMS Document;
   ii. Overview for Prescribers;
   iii. Prescriber Enrollment Form;
   iv. Overview for Patients and Caregivers;
   v. Independent Outpatient Pharmacy Overview ;
   vi. Chain Outpatient Pharmacy Overview;
   vii. Closed System Outpatient Pharmacy Overview;
   viii. Independent Outpatient Pharmacy Enrollment Form;
   ix. Chain Outpatient Pharmacy Enrollment Form;
   x. Closed System Outpatient Enrollment Form;
   xi. Inpatient Pharmacy Enrollment Form;
   xii. Distributor Enrollment Form, and;
   xiii. TIRF REMS Website and Website Landing Page
4. Revised criteria for inactivation of Patient-Prescriber Agreement Form (PPAF) in the TIRF REMS Document
5. Revisions to enhance knowledge about conversion of TIRF Medicines in the following:
   i. Education Program for Prescribers and Pharmacists, and;
   ii. TIRF REMS Website
6. Information clarifying the process to electronically transmit TIRF REMS Cash Claims in the following:
   i. TIRF REMS Document;
   ii. TIRF REMS Access Program Frequently Asked Questions (FAQ);
   iii. Independent Outpatient Pharmacy Overview;
   iv. Chain Outpatient Pharmacy Overview, and;
   v. Closed System Outpatient Pharmacy Overview

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed modified REMS, submitted on May 21, 2014, and amended on December 11, 2014, and appended to this letter, is approved.

The TIRF REMS Access Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM309784.pdf

Other products may be added in the future to the TIRF REMS Access Program if additional TIRF NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. There are no changes to the revised REMS assessment plan attached to our August 21, 2014, REMS Assessment Acknowledgment/REMS Assessment Plan Revisions letter.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 077312
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 077312
PROPOSED REMS MODIFICATION

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.98, 314.80 and 314.81).

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, call Chantal Phillips, REMS Coordinator, at 301-796-2259.

Sincerely,

John R. Peters -S

Digitally signed by John R. Peters -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John R. Peters -S, 0.9.2342.19200300.100.1.1=1300383953
Date: 2014.12.24 11:54:15 -05'00'

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
REMS

Initial REMS approval: 12/2011

Most recent modification: 12/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**
    i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.
    ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
    iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys ® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Additional Prescriber Information (All Fields Required)

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued* _____
DEA Number* _____

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/ProductList.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

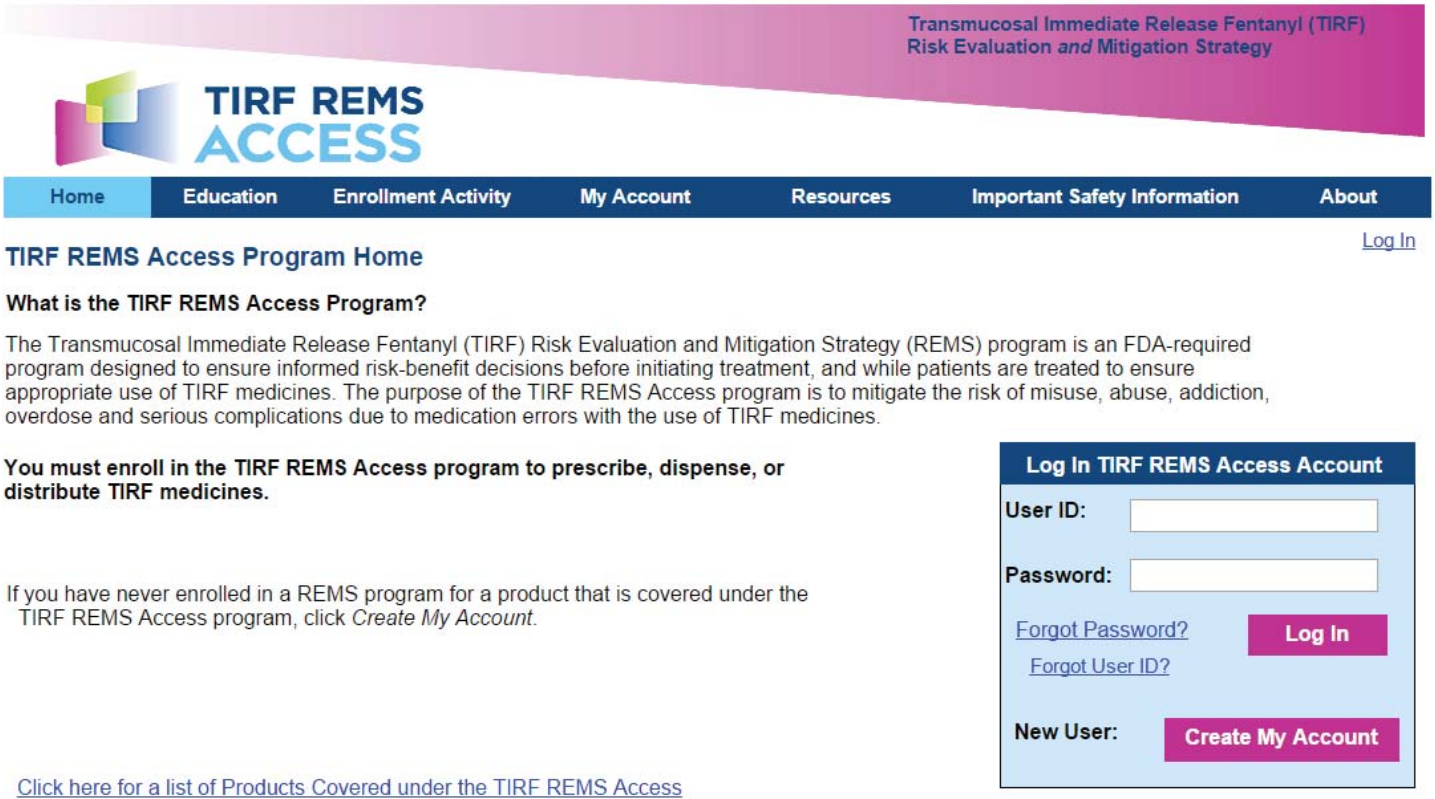
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

- Patient First Name,
- Patient Last Name,
- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

*Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Chain Outpatient Pharmacies”, “An Overview for Independent Outpatient Pharmacies” or “An Overview for Inpatient Pharmacies” for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

- Patient First Name..... TIRFREMSTEST
- Patient Last Name..... Smithers
- Date of Birth..... 19841105
- Patient ZIP/Postal Zone..... 07921
- Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
- Quantity Dispensed..... 12
- Days Supply..... 4
- Prescriber ID..... BA1111119
- Prescriber Last Name..... REMSTEST

- Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... “P” (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = “A” (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: *“Invalid test transaction sequence”*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
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- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

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- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

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TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

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When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Distributor Responsibilities in the TIRF REMS Access Program:

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

From: Phillips, Chantal
To: krista.richardson@parpharm.com
Cc: Phillips, Chantal
Subject: ANDA 77312
Date: Friday, January 23, 2015 10:00:17 AM

Hi Ms. Richardson,

We have discovered an error in our letter which was sent to you on December 24, 2014. In the "RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS" section, we inadvertently referred to a document that was not included in the attached REMS materials. Under section 6, we should not have included item "v. Closed System Outpatient Pharmacy Overview." The REMS materials attached to the December 24, 2014, letter are correct and do not include this document.

Thank you,

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
REMS Coordinator
Food and Drug Administration
Office of Generic Drugs
BLDG 75, Rm 2514

chantal.phillips@fda.hhs.gov
(301) 796-2259

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHANTAL N PHILLIPS
01/23/2015

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 077312 MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment
Communication ID:	(COR-SEC901REMS-10)
Drafted by:	C.Phillips/7-16-15; J. Sarchet 7-28-2015; C. Phillips 7-28-2015
Clearance History:	Based off NDA clearance
Finalized:	J. Sarchet 8-3-2015
Filename:	
Signatory Authority:	DDS, Division Director, or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	
Notes:	

Version: 10/28/2014

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077312
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, New York 10977

Attention: Krista Richardson
Associate Director, Regulatory Affairs

Dear Ms. Richardson:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 1200 mcg, and 1600 mcg.

We also refer to your December 29, 2014, submission containing the 36-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. We are not able to assess whether the REMS is meeting its goals. The absence of spontaneous adverse event reports citing either use of a TIRF in opioid non-tolerant individuals or inappropriate conversions between TIRF products is not informative because spontaneous reporting systems are subject to under-reporting of adverse events. In addition, the accidental pediatric exposure data presented in the Assessment Report are difficult to assess due to unequal assessment periods and small numbers of cases. Lastly, the survey results indicate areas of low awareness of some important safe use messages.

2. In order to assess the TIRF REMS goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients, conduct the following analysis: Identify a health care database that includes an adequate number of TIRF product users. Within that database, by year, provide the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting. Determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. Provide these data separately for patients receiving an opioid analgesic within the 7-days prior and within the 30-days prior to

the initial TIRF prescription. Before embarking on this analysis, provide to FDA your choice of database and the estimated number of TIRF users in the database so that we can determine if the number is adequate.

3. We are not able to establish whether the TIRF REMS is achieving the goal of preventing inappropriate conversion between TIRF medicines. In order to better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely. Conduct a persistency analysis based on the data available on the prescriptions processed through the switch system used by retail pharmacies. This analysis should demonstrate the number of patients starting on a TIRF and follow them over weeks and months to summarize their treatment course and change in therapy. The TIRF products can be grouped together, and the specific drug does not need to be disclosed. Following the discontinuation of the TIRF, the persistency analysis should also depict what treatment option the patient uses next. This will be either full discontinuation or switching to another TIRF product. There may be gaps in between prescriptions; propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF and provide a rationale for selection of that gap length.

4. Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues.

5. There has been a notable increase in mean and median prescription processing times during this reporting period versus the previous period. Investigate and identify the causes of these increasing delays in prescription processing and report the results in your next Assessment Report.

6. None of your reported spontaneous adverse events include a root cause analysis as specified in the Assessment Plan. In your subsequent Assessment Reports, include a root cause analysis of adverse events reported to the TRIG Sponsors.

7. The closed system pharmacies continue to struggle with the REMS authorization processes. Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report.

8. Your presentation of the non-compliance data in the submitted report is disorganized. Various events are described in Assessment Report Section 6.1.1 and in the Report's Tables 21 and 22. Events found in one of these areas often sound similar to events reported in other areas, and thus it is unclear whether these different sources are referring to distinct events or are describing the same event. In addition, while your Report's Table 21 indicates seven instances where closed system pharmacies dispensed drugs without obtaining authorization, the audit conducted by the TRIG reports 513 such incidents. Organize and harmonize these

various components into one clear presentation that is comprehensive and eliminates duplication.

9. Provide the criteria as to how compliance decisions are made by the NCRT and include your non-compliance protocol with your next Assessment Report.

10. In subsequent Assessment Report submissions of RADARS data, provide the following:

    a. A more detailed data analysis section that presents the statistical methods used, how calculations were performed, and the assumptions made, at the level of detail as provided in your April 2, 2015, response to the March 19, 2015, FDA Information Request. In addition, include a pre-post REMS means analyses and trend analyses (e.g. segmented regression analyses), statistically comparing event rates for a time-period immediately prior to full implementation of the TIRF REMS with an equivalent period of time after REMS implementation.

    b. Present the data at the dosage unit level as well as population and URDD levels.

    c. The RADARS treatment center data (Opioid Treatment Program and Survey of Key Informants Patients) programs are confounded by the fact that the number of treatment centers participating in each quarter fluctuates (although the overall numbers are generally increasing). In subsequent submissions, limit the presentation of treatment center data to centers that have contributed data in all of the time-periods assessed. In addition, provide the various versions of the survey instruments/pill cards in use throughout the time-periods assessed with dates provided indicating when each instrument was in use.

11. We remind you that the following comments related to the stakeholder surveys were provided in the August 21, 2014, letter to the TRIG. These revisions should be implemented in subsequent surveys along with the new survey revisions described in item 12 below:

    a. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

    b. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

    c. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist

survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

d. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

12. Additional comments and recommended revisions to the stakeholder surveys that should be implemented in subsequent surveys follow below:
    a. Patient survey
        i. In subsequent Assessment Reports, provide an analysis of how the demographics of the patient survey respondents compare to the demographics of actual TIRF patients.
        ii. For Question 4, remove Onsolis as a response option because it is no longer available.
        iii. Move Question 13b: *It is okay for patients to take TIRF medicines for headache pain* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.
        iv. Add Question 10a-e: *For which of the following conditions should you use a TIRF medicine?* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.

    b. Pharmacist survey
        i. For Question 26, remove Onsolis as a response option because it is no longer available.
        ii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.
        iii. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.
        iv. Move Question 13c: *TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product* to Key Risk Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

c. Prescriber survey

i. In subsequent Assessment Reports, provide an analysis of how the demographics of the prescriber survey respondents compare to the demographics of actual TIRF prescribers.

ii. For Question 30, remove Onsolis as a response option because it is no longer available.

iii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

iv. Move Question 7b: *Death has occurred* in opioid non-tolerant patients treated with some fentanyl products to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients.*

v. Move Question 10d: *Dosing of TIRF medicines is not equivalent on a microgram to microgram basis* to Key Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

vi. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.

vii. Move Question 18b*: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

viii. Move Question 18c: *Instruct patients that if they stop taking their around the clock opioid medicine, they can continue to take their TIRF medicine* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

ix. Remove Question 19: *Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*

If you have any questions, call Wendy Brown, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-9140.

Sincerely,

{See appended electronic signature page}

Trueman W. Sharp, M.D., M.P.H.
Acting Deputy Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRUEMAN W SHARP
08/03/2015

Par Pharmaceutical, Inc.
One Ram Ridge Road
Chestnut Ridge, NY 10977
tel 845-573-5500
fax 845-573-5795
www.parpharm.com

October 13, 2015

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE

- *Consolidated Responses to Information Requests from the 36-month Assessment Report*

RE: ANDA 077312; *Sequence 0031*
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par's Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF 027320 submitted to this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par Pharmaceutical, Inc. hereby notifies FDA of submission of its Consolidated Responses to Information Requests from the 36-month REMS Assessment to DMF #027320 in eCTD sequence 0018 on October 12, 2015.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
Digitally signed by krista.richardson@parpharm.com
DN: cn=krista.richardson@parpharm com, email=krista.richardson@parpharm com
Date: 2015.10.13 08:43:47 -04'00'

Krista Richardson
Associate Director, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Chestnut Ridge, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

December 29, 2015

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

48-MONTH ASSESSMENT REPORT

- *Reference to DMF Submission*

RE: ANDA 077312 – Sequence 0034
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of submission of the 48-month REMS Assessment Report to DMF #027320 in eCTD sequence 0019 on December 28, 2015.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
Digitally signed by krista richardson@parpharm com
DN: cn=krista richardson@parpharm com
email=krista richardson@parpharm com
Date: 2015 12 29 08:18:43 05'00'

Krista Richardson
Associate Director, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-573-5500
fax 845-573-5795
www.parpharm.com

May 5, 2016

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
48-MONTH REMS SUPPLEMENTAL ASSESSMENT REPORT

RE: ANDA 077312 – Sequence 0035
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical, Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013 (sequence 0015).

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par Pharmaceutical, Inc. hereby notifies FDA of submission of the 48-month REMS Supplemental Assessment Report to DMF #027320 in eCTD sequence 0023 on May 04, 2016.

The current medication guide may be referenced in Sequence 0026 dated December 11, 2014.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

[*see attached signature page*]

Krista Richardson
Associate Director, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845-573-5500
fax 845-573-5795
www.parpharm.com

August 19, 2016

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 077312 – Sequence 0037
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

DMF Annual Report (Reporting Period: August 21, 2015 – August 20, 2016)

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical, Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII, which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 on September 11, 2013 (sequence 0015).

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par Pharmaceutical, Inc. hereby notifies FDA of submission of the DMF Annual Report for the reporting period August 21, 2015 – August 20, 2016, to DMF #027320 in eCTD sequence 0024 on August 18, 2016.

The current medication guide may be referenced in Sequence 0026 dated December 11, 2014.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

[*see attached signature page*]

Krista Richardson
Associate Director, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Chestnut Ridge, NY 10977
tel 845-425-7100
fax 845-573-5795
www.parpharm.com

December 29, 2016

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

60-MONTH ASSESSMENT REPORT

- *Reference to DMF Submission*

RE: ANDA 077312 – Sequence 0039
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of submission of the 60-month REMS Assessment Report to DMF #027320 in eCTD sequence 0027 on December 28, 2016.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
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Krista Richardson
Associate Director, Regulatory Affairs

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January 31, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
CONSOLIDATED RESPONSES TO INFORMATION REQUESTS
FROM THE 48-MONTH ASSESSMENT REPORT

RE: ANDA 077312 – Sequence 0041
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of submission of Consolidated Responses to the Information Request dated January 23, 2017 in relation to the 48-month REMS Assessment Report via the DMF. DMF #027320 was updated via eCTD sequence 0026 on January 30, 2017 with this information.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

krista.richardson@parpharm.com
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Krista Richardson
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February 20, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
60-MONTH SUPPLEMENTAL ASSESSMENT REPORT

RE: ANDA 077312 – Sequence 0042
Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Par Pharmaceutical Inc.'s Oral Transmucosal Fentanyl Citrate, eq. to 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg of Fentanyl base CII which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Par hereby notifies FDA of submission of the 60-Month Supplemental Assessment Report to DMF #027320 in eCTD sequence 0028 on February 17, 2017.

The current medication guide may be referenced in Sequence 0026 dated December 11, 2014.

This submission is being submitted in electronic format via the Electronic Submissions Gateway. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc.

Should you have any questions regarding this application, please do not hesitate to contact the undersigned by phone at 845-573-5558, by email at krista.richardson@parpharm.com, or by fax at 845-573-5795.

Sincerely,
PAR PHARMACEUTICAL, INC.

[*see attached signature page*]

Krista Richardson
Associate Director, Regulatory Affairs

Multi-Sponsor Industry Meeting to Discuss Transmucosal Immediate Release Fentanyl (TIRF) REMS Single Shared System

MEETING DATE/TIME: October 28, 2010/ 12 NOON

LOCATION: White Oak Campus
10903 New Hampshire Avenue
Bldg 2, CSU Room 2047 W
Silver Spring, MD 20903

MINUTES RECORDER: Abolade (Bola) Adeolu, RPh., MS, MBA

Panel Members	Title
Douglas Throckmorton, MD*	Deputy Director; Center for drug Evaluation and Research (CDER)
John Jenkins, MD	Director; Office of New Drugs (OND); CDER
Jane Axelrad, JD	Associate Director for Policy; CDER
Bob A. Rappaport, MD	Director; Division of Anesthesia and Analgesia Products (DAAP); Office of Drug Evaluation 2 (ODE2); OND; CDER
Sharon Hertz, MD	Deputy Director; DAAP, ODE2; OND; CDER
Gerald Dal Pan, MD,MHS	Director; Office of Surveillance and Epidemiology (OSE); CDER
Claudia Karwoski, PharmD	Director; Division of Risk Evaluation (DRISK), OSE; CDER
Megan Moncur,	Risk Management Analyst, Acting Team Leader; DRISK, OSE; CDER

Company Name	Attendee
Archimedes/SciLucent	Stephen Kanovsky, General Counsel
Archimedes/SciLucent	Michael Perelman, Chief Development Officer
Cephalon, Inc.	Randy Bradway, Vice President, Commercial Operations
Cephalon, Inc.	Susan Franks, Director, Regulatory Affairs
Cephalon, Inc.	James Ottinger, Vice President, Regulatory Affairs*
Covidien	Stuart K. Kim, Legal Department
Covidien	Sherice Mills, Patient and Product Safety
Covidien	Diane Servello, Regulatory Affairs
Endo Pharmaceuticals	Lauren Tornetta, Associate Director, Regulatory Affairs*
Insys Therapeutics	Michael Babich, President and Chief Operating Officer
Insys Therapeutics	Willene Brondum, SeniorManager, Regulatory

	Affairs
Insys Therapeutics	Larry Dillaha, MD; Chief Medical Officer
Meda Pharmaceuticals	Richard Fosko, RPh., MPH; Senior Director, Regulatory Affairs
Meda Pharmaceuticals	Harry Sacks, MD, FAAP; Vice President of Medical and Scientific Affairs, and Chief Medical Officer
Meda Pharmaceuticals	Mark Sirgo, PharmD.; President & CEO BioDelivery Sciences International, Inc. (BDSI is Meda's development partner for Onsolis)
Nycomed	Martin Lessem, JD; Director, Alliance US Regulatory, US Agent for Nycomed
ProStrakan	Nelson M. Alfonso, MBA; Senior Director, US Marketing
ProStrakan	Nigel Atherton, Head of Development*
ProStrakan	Dalena DeGrezia, MBA; Director, US Regulatory Affairs*
ProStrakan	Ian Duguid, PhD., MRPharmS; Senior Vice President, Head of Regulatory Affairs
ProStrakan	Anthony G. Oladipo, Pharm.D., MPH, BCPS; Vice President, Global Drug
Sandoz	Brian Watson, RPh.,MBA; Director, Drug Safety
Sandoz	Laura M. Pethick, RPh.; Manager, Pharmacovigilance & Risk Management
Sandoz	Justin Uthup, Senior Associate, Regulatory Affairs*
Sandoz	Alison Sherwood, Manager, Regulatory Affairs*
Teva Pharmaceuticals	Kishore Gopu, Associate Director REMS program
Watson Laboratories	Gary Kozloski, Vice President
Watson Laboratories	Joannie Jung, Manager
Watson Laboratories	Janet Vaughn, Director of Regulatory Affairs

* Telephone Participants

Background:

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

The Agency has determined that the transmucosal immediate-release fentanyl (TIRF) products will be required to have Risk Evaluation and Mitigation Strategies (REMS) to ensure that the benefits of the drugs continue to outweigh the serious risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors. The REMS will include a Medication Guide, elements to assure safe use including prescriber certification or training, dispenser certification, and documentation of safe-use conditions, an implementation system, and a timetable for submission of assessments.

The provisions in FDAAA state that elements to assure safe use must be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not be unduly burdensome on patient access to the drug, and be designed to be compatible with established distribution, procurement, and dispensing systems. With limited exceptions, FDAAA requires generic and innovator products to use a single shared system to implement the elements to assure safe use.

Because of the challenges and burdens of implementing multiple stand-alone REMS for each product, the Agency is working with the manufacturers of TIRF products to develop a single, shared REMS for the TIRF class.

Introduction:

The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRFs only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRFs

In the interest of public health and to reduce the burden on the healthcare system, a uniform approach for implementing a REMS across TIRF products is needed.

Agenda:

I. Introduction (*John Jenkins, MD)*

II. Background *(John Jenkins, MD & Jane Axelrad, JD)*

III. TIRF REMS Overview & Framework *(Presentation: Megan Moncur)*

IV. Next Steps *(Presentation: Megan Moncur)*

V. Questions

Meeting minutes:

The meeting opened with welcoming comments by Dr. Jenkins and Ms. Axelrad. The Background discussion followed and included an overview of the Agency's development of the TIRF REMS and a description of the Agency's expectations of sponsors. The following points were emphasized:

- A REMS for TIRFs is necessary to ensure that the benefits of these products outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.
- A single, shared REMS for the TIRFs is critical to minimize burden on the healthcare system.
- FDA worked to develop a REMS template that will support a single-shared REMS for the TIRF products; the resulting REMS template incorporates many aspects of the programs submitted by sponsors as well as stakeholder input
- FDA is not entertaining changes in the framework of the REMS template but is open to discussing the details and challenges involved in the implementation of the REMS.
- Sponsors were asked to adopt this framework as soon as possible with a goal to have all products under an approved REMS within 6 months and all REMS programs in a single-shared system within 12 months
- FDA noted that there are examples where sponsors have successfully worked together on a single-shared system, and acknowledged the importance of developing a governance/financial framework to facilitate that collaboration

Megan Moncur then provided a presentation of the TIRF REMS Overview & Framework as well as next steps. The meeting then continued with the following questions and answers.

Questions and Answers:

1. **Industry Question/Comment:** Is a REMS system that is solely electronic acceptable?

   Agency Response: Sponsors should consider whether a solely electronic system will have an impact on patient access, especially in remote areas.

2. **Industry Question/Comment:** Meda Pharmaceuticals noted they have an existing REMS submission. Will they need an additional submission that conforms to the TIRF REMS?

   Agency Response: Yes, anything already in house for review will need to be revised.

3. **Industry Question/Comment**:
   a. Concern was expressed that patients will receive their first prescription before it is determined that a Patient-Prescriber Agreement (PPA) is in place'.
   b. For patients on titration schedules of 10 days or less, how will we ensure they get their second /maintenance dose on time since prescribers have up to 10 working days to submit the PPA to the system?

   Agency Response: (addresses both a and b) The REMS template was designed this way to prevent patients from being denied access to their prescribed medications and to allow prescribers some flexibility in determining the most efficient way to incorporate the REMS into their workflow. To maintain this flexibility, enrolled prescribers will need to be accountable. Therefore, it is up to the prescriber to ensure adequate initial supply of the medication and to submit the PPA in time. It is important that the Prescriber Educational Materials reinforce this.

4. **Industry Question/Comment:** Pharmacy chains will not tolerate any impedance to work flow; can chain pharmacies be responsible for the training of pharmacists?

   Agency Response: Yes, pharmacy chains will be able to develop their own mechanism to train pharmacists. However they will be required to document that the training has occurred for audit purposes.

5. **Industry Question/Comment:** With the REMS submission due to FDA in 120 days, and the tight timelines for approval, will there be an accelerated time frame for review by the Agency?

   Agency Response: The review team will work expeditiously to review the submissions with the goal of meeting the timelines above, assuming there are no modifications and that the initial submissions are complete and generally consistent with each other.

6. **Industry Question/Comment:** Will FDA take regulatory action against companies that don't have the REMS approved within the 6 month time frame?

   Agency Response: Yes, we intend to follow through on regulatory action if needed. Products with an approved REMS could be looked at differently than products without a REMS. FDA will provide public awareness of the REMS requirements for the TIRF products when the first TIRF REMS is approved.

7. **Industry Question/Comment:** When will we get a REMS Notification letter?

Agency response: within the next week or two

8. **Industry Question/Comment:** Will FDA be soliciting comments on the REMS draft?

   Agency Response: Yes, as sponsors work on implementation, we are open to comments, but you should all work together starting today.

9. **Industry Question/Comment:** Who owns the single, shared REMS and who will police it?

   Agency response: Details of the REMS will be left to the sponsors. A number of companies have worked together including the isotretinoin sponsors and sponsors of Cellcept and mycophenolate. One sponsor will need to take the lead initially to facilitate collaboration.

10. **Industry question/Comment:** Is it only physicians that can issue the PPA or will the nurse be able to?

    Agency Response: It is up to the physician; they can choose to delegate but they retain full responsibility

11. **Industry question/Comment:** If the pharmacist on duty is not trained on the REMS program, will the prescription still be able to be filled?

    Agency response: This should not be a problem as it is the pharmacy that is enrolled in the program.

12. **Indusrty Question/comment:** Will the REMS be approved as they come into the FDA?

    Agency response: Individual submissions will be reviewed as they come in and will be approved when they meet the requirements. Sponsors will need to work together to harmonize the system.

13. **Industry question/comment:** What happens on weekends in terms of the 10 business days?

    Agency Response: The physician will need to be educated about the need to send in the PPA sooner, if needed and the impact of not sending PPAs in a timely fashion. A system that will remind physicians to submit the PPAs can be built to assist them.

14. **Industry Question/Comment:** Covidien will volunteer to convene first meeting and be ready to execute in 2-3 weeks

    Agency Response: FDA will be happy to be a part of this process.

15. Industry Question/Comment: We need to know all the players who need to be involved in this process.

Agency response: Sponsors of pending applications will need to identify themselves to Covidien and others.

Summary of Meeting Discussion:

Closing by FDA:

- We are very serious about the need for a single shared REMS program for the class of TIRF products
- We have considered all of the proposed REMS programs when developing this REMS template and have spent considerable time on the process
- No undue burden is intended,
- We strongly encourage you to work on individual programs to get approved within the next 6 months, and begin working together soon so that a single shared system can be implemented within 12 months.
- FDA will hold additional meetings to field questions from sponsors.
- A REMS IR letter will be sent with the next week or two.
- Reviews of the proposed REMS will be completed as quickly as possible.

Action Items: REMS IR letter to be sent in 1 to 2 weeks.

Follow up: Telecons to be scheduled between FDA and the TIRF-sponsor Working Group once the letters have been issued.

Transmucosal Immediate- Release Fentanyl (TIRF) REMS: Single-Shared System

Meeting

October 28, 2010

12 noon

Agenda

I. Introduction

II. Background

III. TIRF REMS Overview & Framework

IV. Next Steps

V. Questions

TIRF REMS
Overview & Framework

REMS Goals

The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRFs only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRFs

Overview of REMS Elements

1. **Medication Guide**
2. **ETASU***
   - A: Prescriber is certified
   - B: Pharmacy is certified
   - D: Dispensed only with documentation of safe-use-conditions
3. **Implementation System**
4. **Timetable for Submission of Assessments**

* ETASU=Elements to Assure Safe Use

ETASU A:
Prescribers are Certified (1 of 3)

- Prescribers who prescribe to outpatients* must enroll in the TIRF REMS Program

  a) Review education materials and Full Prescribing Information

  b) Successfully complete knowledge assessment

  c) Complete enrollment form and acknowledgements

*outpatient: e.g. patient, not hospitalized, who is being treated in an office, clinic, or other ambulatory care facility

ETASU A:
Prescribers are Certified (2 of 3)

- Prescribers are required to:

  a) Counsel patient & provide Medication Guide

  b) Ensure that a patient-prescriber-agreement (PPA) is completed with each new patient, and again every 2 years

  c) Submit completed PPAs to the REMS program administrator within 10 business days

  d) Re-enroll every 2 years

ETASU A:
Prescribers are Certified (3 of 3)

Note: Prescribers who prescribe to inpatients*:

- Are not required to enroll, **if** prescribing for inpatient use only
- Are required to enroll, **if** discharging a patient with a prescription, intended to be filled by an outpatient pharmacy

*inpatient: e.g. patients in hospitals, hospices, or long-term care facilities

ETASU B:
Pharmacies are Certified (1 of 2)

- All pharmacies must enroll in the TIRF REMS Program
  - A subset of requirements differ for **outpatient*** and **inpatient**** pharmacies
- Core Requirements that apply to both:

a) Designate an authorized pharmacist

b) Review educational materials & Full Prescribing Information

c) Successfully complete knowledge assessment

d) Complete enrollment form with acknowledgements

e) Train relevant staff

f) Re-enroll every 2 years

* outpatient pharmacy: e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use

** inpatient pharmacy: e.g. hospitals, hospices, and long-term care facilities that dispense for inpatient use

ETASU B:
Pharmacies are Certified (2 of 2)

Outpatient Requirements:

a) Successfully enable pharmacy management system (PMS) to support communication with the REMS system using established telecommunication standards
b) Enroll patients (passive, via PMS)
c) Verify documentation of safe-use-conditions
d) Provide Medication Guide & Encourage to Counsel
e) Agree to process all TIRF prescriptions through their PMS
f) Agree to appropriately respond to REMS program messages and alerts in order to comply with program requirements

Inpatient Requirements:

a) Establish a system, order sets or protocols to help ensure appropriate dosing and compliance with the REMS requirements
b) Only dispense for inpatient use

ETASU D:
Dispensed only with documentation of safe-use-conditions

- TIRFs are dispensed for outpatient use only with documentation of safe-use-conditions in the REMS system: prescriber, pharmacy, and patient are enrolled
  - Patients are passively enrolled when their first prescription is processed
- Required enrollments are electronically verified via the pharmacy management system, as part of the standard prescription processing workflow
- ***Note*:** verification of safe-use conditions is not required for prescriptions ordered within an inpatient healthcare setting for inpatient use

Distributors are Enrolled

- Complete enrollment form
- Train relevant staff on REMS Program
- Distribute only to enrolled pharmacies
- Re-enroll every 2 years

Implementation Requirements for TIRF Sponsors (1 of 2)

- Ensure PPAs can be submitted and enrollment completed via website, mail, fax or by scan/e-mail
- Validate & activate enrollment requests
  - Notify enrollees when enrollment is activated
- Maintain a call center and website to support REMS Program activities
- Also ensure REMS materials are available via website or call center

Implementation Requirements (2 of 2)

- Develop a REMS system for outpatient pharmacies to enroll patients and verify safe-use-conditions:
  - Use existing pharmacy management systems
  - Use established telecommunication standards
- Maintain a database of all enrolled entities
  - Notify enrollees of impending enrollment expirations
  - Notify enrollees of substantive changes to REMS program
- Monitor and evaluate implementation of, and compliance with, the REMS requirements
  - Institute corrective actions for non-compliance
  - Improve implementation/compliance, as applicable

Minimum Required REMS Materials

TIRF Class Materials

- Patient-Prescriber-Agreement
- Prescriber and Pharmacy (OP and IP):
  - Educational Program*
  - Knowledge Assessment*
  - Enrollment Form (with Acknowledgements)
- Distributor:
  - Program Information
  - Enrollment Form (with Acknowledgements)

Product-specific materials

- Medication Guide
- Prescriber and Pharmacy:
  - Educational Program*
  - Knowledge Assessment*

* The educational program and knowledge assessment contain both TIRF and product-specific components

Summary

- In the interest of public health and to reduce the burden on the healthcare system, a uniform approach for implementing a REMS across TIRF products is needed

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/s/

CLAUDIA B KARWOSKI
12/03/2010
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/s/

ABOLADE A ADEOLU
12/27/2010
Meeting Minutes from TIRF

CLAUDIA B KARWOSKI
01/03/2011
concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907

REMS NOTIFICATION

Mallinckrodt Inc.
675 McDonnell Blvd.
Hazelwood, MO 63042

Attention: Stacie M. Winter
Senior Regulatory Affairs Associate

Dear Ms. Winter:

Please refer to your abbreviated new drug application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Fentanyl Citrate to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.

We further refer to the meeting held on October 28, 2010, at the FDA White Oak Campus, at which we discussed that in the interest of public health and to reduce the burden on the healthcare system of having multiple unique REMS programs, we have determined that a single, shared system should be used to implement the REMS for all members of the class. The necessary REMS elements should be implemented across the class of transmucosal immediate release fentanyl (TIRF) products to address the serious risks described above.

At the October 28, 2010 meeting we informed the sponsors of the TIRF products of our development of standardized REMS materials that could be used in the development of a single shared system to implement the REMS for all TIRF products. At that meeting, we told sponsors that we intend to move rapidly to review and approve REMS for each of the TIRF products that include the standardized program, and we encouraged sponsors to work together to implement a single shared system to reduce the burden on the healthcare system of individual programs. This letter is a follow up to that meeting discussion.

Attachment 1 contains a REMS program that can be implemented as a single shared system across all TIRF products, and we recommend that your proposed REMS conform to this program. The program includes standardized elements and enrollment forms that can be used by all sponsors of TIRF products and can be implemented using existing pharmacy systems.

Your proposed REMS must include the following:

Medication Guide: FDA previously approved a Medication Guide for distribution with Fentanyl Citrate in accordance with 21 CFR Part 208. The Medication Guide must be revised to incorporate information about the above-described risks. Under 21 CFR Part 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fentanyl Citrate.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions, including a plan to ensure that a Child Safety Kit will be available to patients within 48 hours of filling the initial Fentanyl Citrate prescription, and that this kit contains an interim container for incompletely used Fentanyl Citrate units, a locking fanny pack, and a cabinet/drawer lock.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include all elements listed in Attachment 1.

In accordance with section 505-1, within 120 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

This submission should include two parts: a “proposed REMS” and a “REMS supporting document.” Attached is a template for the proposed REMS that includes information that we believe is pertinent across the class of TIRF products (see Attachment 1). Additionally, all relevant proposed REMS materials including: enrollment forms, educational, and communication materials should be appended to the proposed REMS. These appended

documents should also be standardized across the class of TIRF products, with the exception of the product-specific information that will be included in the training program for prescribers and information about the Child Safety Kit. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Attachment 2).

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT**." To facilitate review of your submission, please provide labeling in Final Printed Labeling (FPL) and Microsoft Word format.

If you have any questions, please contact Melaine Shin, Labeling Reviewer, at melaine.shin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA #
Drug Name and Dosage Form
Opioid Analgesic
[SPONSOR].
[ADDRESS]
[PHONE]
[FAX]

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the Fentanyl Citrate REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing Fentanyl Citrate only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Fentanyl Citrate prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe Fentanyl Citrate for <u>outpatient</u> use are specially certified.

a. Mallinckrodt will ensure that healthcare providers who prescribe Fentanyl Citrate for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe Fentanyl Citrate, prescribers will be required to enroll in the Fentanyl Citrate REMS program. Prescribers must complete the following requirements to be enrolled:

i. Review the Fentanyl Citrate REMS prescriber educational materials (*Prescriber Education Program*), including the Full Prescribing Information, and successfully complete the knowledge assessment (*Prescriber Knowledge*

Assessment).

ii. Complete and sign the *Prescriber Enrollment Form*. In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I understand the responsible use conditions for Fentanyl Citrate and the risks and benefits of chronic opioid therapy.

b) I understand that Fentanyl Citrate can be abused, and that this risk should be considered when prescribing or dispensing Fentanyl Citrate in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that Fentanyl Citrate is indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that Fentanyl Citrate must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.

f) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose, and that patients must be titrated individually.

g) I understand that Fentanyl Citrate is not bioequivalent with any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to Fentanyl Citrate must not be converted on a microgram-per-microgram basis.

h) I will complete and sign a Fentanyl Citrate REMS *Patient-Prescriber Agreement* with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.

In signing the *Patient-Prescriber Agreement*, the prescriber documents the following:

1) Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.

2) Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral

oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) The Fentanyl Citrate Medication Guide has been provided to and reviewed with the patient or their caregiver

4) The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of Fentanyl Citrate including communication of the following safety messages:

   A. If patients stop taking their around-the-clock opioid medication, they must stop taking Fentanyl Citrate.

   B. NEVER share Fentanyl Citrate

   C. Giving Fentanyl Citrate to someone for whom it has not been prescribed can result in a fatal overdose.

   D. Fentanyl Citrate can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

In signing the *Patient-Prescriber Agreement*, the patient and/or their caregiver document the following:

1) My prescriber has given me a copy of the Fentanyl Citrate Medication Guide and has reviewed it with me.

2) I understand that before I can take Fentanyl Citrate, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking Fentanyl Citrate.

4) I understand how I should take Fentanyl Citrate, including how much I can take, and how often I can take it.

5) I understand that Fentanyl Citrate can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take Fentanyl Citrate <u>exactly</u> as my prescriber has directed me to take it.

6) I agree to contact my prescriber if Fentanyl Citrate does not relieve my pain. I will not change my dose of Fentanyl Citrate myself or take Fentanyl Citrate more often than my prescriber has directed.

7) I agree that I will never give Fentanyl Citrate to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store Fentanyl Citrate in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of unused and remaining Fentanyl Citrate and will dispose of Fentanyl Citrate as soon as I no longer need it.

10) I understand that selling or giving away Fentanyl Citrate is against the law.

11) I have asked my prescriber all the questions I have about Fentanyl Citrate. If I have any additional questions or concerns in the future about my treatment with Fentanyl Citrate, I will contact my prescriber.

12) [placeholder for sponsor to add HIPAA/privacy statement language]

i) I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the Fentanyl Citrate REMS program (by fax, scan and e-mail, mail or through the Fentanyl Citrate REMS website) within ten (10) working days.

j) At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.

k) I understand that Fentanyl Citrate is only available through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for prescribers.

b. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new *Patient-Prescriber Agreement* at least every two (2) years.

c. Mallinckrodt will:

i. Ensure that prescriber enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, prescribers receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Prescriber Education Program*
- *Prescriber Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement*

iii. Ensure that prescribers have successfully completed the knowledge assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the Fentanyl Citrate REMS program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, are certified to prescribe Fentanyl Citrate.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

2. Fentanyl Citrate will only be dispensed by pharmacies that are specially certified.

a. Mallinckrodt will ensure that Fentanyl Citrate will only be dispensed by certified pharmacies. To become certified to dispense Fentanyl Citrate, each pharmacy must be enrolled in the Fentanyl Citrate REMS program.

b. Each pharmacy will be required to designate an authorized pharmacist to complete enrollment on behalf of the pharmacy.

c. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals, hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to enroll their **outpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program)* and successfully complete the *Pharmacy Knowledge Assessment*.

ii. Ensure the pharmacy enables their pharmacy management system to support communication with the Fentanyl Citrate REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I understand the risks and benefits associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing Fentanyl Citrate have been educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program*. This training should be documented and is subject to audit.

c) I understand that Fentanyl Citrate is not bioequivalent with other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for <u>all</u> patients is the lowest dose.

f) I understand the importance of discussing the risks and benefits of Fentanyl Citrate with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the Fentanyl Citrate Medication Guide must be given to the patient or their caregiver each time Fentanyl Citrate is dispensed.

h) I understand that Fentanyl Citrate will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL Fentanyl Citrate prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the Fentanyl Citrate REMS program to dispense Fentanyl Citrate.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program and successfully complete the enrollment requirements every two (2) years.

n) I understand that Fentanyl Citrate is only available through the REMS program. I understand that the pharmacy must comply with the Fentanyl Citrate REMS program requirements for outpatient pharmacies.

e. ***Inpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program*) and successfully complete the *Pharmacy Knowledge Assessment*

ii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form* the authorized pharmacist is required to acknowledge the following:

a) I understand the benefits and risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program*.

c) I understand that Fentanyl Citrate is not bioequivalent to other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the Fentanyl Citrate REMS program to dispense Fentanyl Citrate to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy is not to dispense Fentanyl Citrate for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with an Fentanyl Citrate prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the REMS program, as described in section B.1 of this REMS.

i) I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the Fentanyl Citrate REMS.

j) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program every two (2) years.

m) I understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years

g. Mallinckrodt will:

i. Ensure that pharmacy enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, pharmacies receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Pharmacy Education Program*
- *Pharmacy Enrollment Form*
- *Pharmacy Knowledge Assessment*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the knowledge assessment before activating a pharmacy's enrollment in the Fentanyl Citrate REMS program. For outpatient pharmacies only, Mallinckrodt will also ensure that the upgrades to the pharmacy management system have been validated before enrolling a pharmacy in the Fentanyl Citrate REMS program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, certified to dispense Fentanyl Citrate.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

3. Fentanyl Citrate will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. Mallinckrodt will ensure that Fentanyl Citrate will only be dispensed for outpatient use if there is documentation in the Fentanyl Citrate REMS system that the dispensing pharmacy, prescriber, and patient are all enrolled and active in the Fentanyl Citrate REMS program.

b. Patients are passively enrolled in the Fentanyl Citrate REMS program when their first Fentanyl Citrate prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the Fentanyl Citrate REMS system. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2.a-d, respectively.

c. Prior to dispensing Fentanyl Citrate, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the Fentanyl Citrate prescription through their pharmacy management system.

i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient

ii. If one or more of the required enrollments can not be verified, the Fentanyl Citrate REMS system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

i. The patient has not filled a prescription for more than six (6) months

ii. The patient receives prescriptions for Fentanyl Citrate from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the Fentanyl Citrate REMS program cannot fill the prescription for Fentanyl Citrate until the new prescriber is active in the Fentanyl Citrate REMS program.

f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for Fentanyl Citrate are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. Mallinckrodt will ensure that wholesalers/distributors who distribute Fentanyl Citrate are enrolled in the Fentanyl Citrate REMS program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving Fentanyl Citrate inventory for distribution:

a. Review the distributor Fentanyl Citrate REMS program materials

b. Complete and sign the *Distributor Enrollment Form* and send it to the Mallinckrodt (by fax, scan and e-mail, mail or through the TIRF website). In signing the *Distributor Enrollment Form*, each distributor is required to indicate they understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program and that they must comply with program requirements, and acknowledge that:

i. I will ensure that relevant staff are trained on the Fentanyl Citrate REMS program procedures and will follow the requirements of the Fentanyl Citrate REMS program.

ii. I will ensure that Fentanyl Citrate is only distributed to pharmacies whose enrollment has been validated in the Fentanyl Citrate REMS program.

iii. I will provide data to the Fentanyl Citrate REMS program including information on shipment to enrolled pharmacies.

iv. I will cooperate with periodic audits or non-compliance investigations to ensure that Fentanyl Citrate is distributed in accordance with the program requirements.

c. Mallinckrodt will ensure that all forms are complete, prior to enrolling a distributor in the Fentanyl Citrate REMS program.

d. Mallinckrodt will notify distributors when they are enrolled in the Fentanyl Citrate REMS program, and therefore, able to distribute Fentanyl Citrate.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the Fentanyl Citrate REMS program every two (2) years.

g. The following distributor materials are part of the Fentanyl Citrate REMS program and are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*

2. Mallinckrodt will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the Fentanyl Citrate REMS requirements.

3. Mallinckrodt will develop a REMS system that uses existing pharmacy management systems that allow for the transmission of REMS information using established telecommunication standards. The REMS system should incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the REMS requirements, if deemed necessary in the future.

4. Mallinckrodt will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing Fentanyl Citrate. Additionally, Mallinckrodt will monitor to ensure that Fentanyl Citrate is only being dispensed for outpatient use to actively enrolled patients of

actively enrolled prescribers. Corrective action or inactivation will be instituted by Mallinckrodt if non-compliance is found.

5. Mallinckrodt will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement* with each Fentanyl Citrate patient, and to submit it to the REMS program within ten (10) business days. This will be accomplished through patient surveys and by reconciling the *Patient-Prescriber Agreements* submitted to the REMS program with patient enrollment data captured through the pharmacy management system.

6. Mallinckrodt will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the Fentanyl Citrate REMS program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

7. Prostraken will evaluate enrolled inpatient pharmacies' compliance with REMS requirements through surveys.

8. Mallinckrodt will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the Fentanyl Citrate REMS program.

9. Mallinckrodt will ensure that all materials listed in or appended to the Fentanyl Citrate REMS will be available through the Fentanyl Citrate website www. Fentanyl CitrateREMS.com or by calling the Fentanyl Citrate REMS call center at XXX-XXX-XXXX.

10. Mallinckrodt will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the REMS program. Notifications for patients will be sent to the patient's prescriber.

11. If there are substantive changes to the Fentanyl Citrate REMS Program, Mallinckrodt will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the Fentanyl Citrate REMS program are defined as:

    a. Significant changes to the operation of the Fentanyl Citrate REMS program for outpatient pharmacies.

    b. Changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of Fentanyl Citrate.

12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, Mallinckrodt will take reasonable steps to improve implementation of these elements and to maintain compliance with the Fentanyl Citrate REMS program requirements, as applicable.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System

4. Information Needed for Assessments

5. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

11/12/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

Multi-Sponsor Industry Meeting to Discuss Transmucosal Immediate Release Fentanyl (TIRF) REMS Single Shared System

MEETING DATE/TIME: December 16, 2010/ 9:00 am

LOCATION: White Oak Campus
10903 New Hampshire Avenue
Bldg 22, Room 4270
Silver Spring, MD 20903

MINUTES RECORDER: Darrell Jenkins, OSE

Panel Members	Title
Abolade Adeolu, M.S., M.B.A.	Safety Regulatory Health Project Manager, OSE; CDER
Jane Axelrad, JD	Associate Director for Policy; (CDER)
Suzanne Barone, Ph.D.	Team Leader, Risk Management & Strategic Problem Solving Team, Division of Compliance Risk Management and Surveillance
Sammie Beam, R.Ph.	Acting Director, Safety Regulatory Health Project Manager, OSE; CDER
Carla Cartwright, JD	Attorney, Office of Chief Counsel, CDER
Lauren Choi, Pharm.D.	Team leader for DPVII, OSE, CDER
Kimberly Compton, R.Ph.	Senior Regulatory Project Manager, DAAP, ODE2; OND; CDER
Gerald Dal Pan, MD, MHS	Director; Office of Surveillance and Epidemiology (OSE); CDER
Kristen Everett, RN	FDAAA Project Manager, ORP, CDER
Ellen Fields, MD, MPH	Clinical Team Leader, DAAP, ODE2; OND; CDER
Kathleen Frost. B.S.	Associate Director for Regulatory Policy, OSE
Sharon Hertz, MD	Deputy Director; DAAP, ODE2; OND; CDER
Shawnetta Jackson, M.S.	Project Specialist, OSE; CDER
Darrell Jenkins	Safety Regulatory Health Project Manager, Team Leader, OSE; CDER
John Jenkins, MD	Director; Office of New Drugs (OND); (CDER)
Claudia Karwoski, PharmD	Director; Division of Risk Evaluation (DRISK), OSE; CDER
Elizabeth Kilgore, M.D.	Medical Officer/Clinical Reviewer, (DAAP), ODE2, OND, CDER
Cynthia LaCivita, Pharm.D	Risk Management Analyst, DRISK, OSE, CDER

Megan Moncur, MS	Risk Management Analyst, Acting Team Leader; DRISK, OSE; CDER
Agnes Plante, BSN	Consumer Safety Officer, OC, CDER
Frank Pucino, M.D.	Clinical Analyst, DAAP, ODE2; OND; CDER
Bob A. Rappaport, MD	Director; Division of Anesthesia and Analagesia Products (DAAP); Office of Drug Evaluation 2 (ODE2); OND; CDER
Matthew Sullivan	Senior Regulatory Project Manager, DAAP, ODE2; OND; CDER
Stephen Sun, M.D.	Medical Officer, Controlled Substance Staff, Center for Drug Evaluation and Research (CDER)
Douglas Throckmorton, MD*	Deputy Director; Center for Drug Evaluation and Research (CDER)
Chris Wheeler, PharmD Katherine Won, PharmD, MBA	Safety Regulatory Health Project Manager, Team Leader, OSE; CDER Safety Regulatory Project Manager, DAAP, ODE2, OND, CDER

Company Name	Attendee
Archimedes/SciLucent	Michael Perelman, Chief Development Officer
Cephalon, Inc.	Randy Bradway, Vice President, Commercial Operations
Cephalon, Inc.	Susan Franks, Director, Regulatory Affairs
Cephalon, Inc.	James Ottinger, Vice President, Regulatory Affairs
Covidien	Diane Servello, Senior Director, Regulatory Affairs
Endo Pharmaceuticals	Michael Clark, Director, PVRM
Insys Therapeutics, Inc.	Lauren H. Wind, Senior Consultant
Insys Therapeutics, Inc.	Michael Babich, President and Operating Officer
Insys Therapeutics, Inc.	Larry Dillaha, Chief Medical Officer
Insys Therapeutics, Inc.	Willene Brondum, Senior Manager, Regulatory Affairs
Meda Pharmaceuticals	Harry J. Sacks, Vice President, Medical and Scientific Affairs, Chief Medical Officer
Meda Pharmaceuticals	Richard Fosko, Senior Director, Regulatory Affairs
Meda Pharmaceuticals (BioDelivery Sciences International-BDSI)	David T. Wright, Vice President, Regulatory Affairs
ProStrakan, Inc.	Dalena DeGrezia, Director, US Regulatory Affairs

ProStrakan, Inc.	Ian Duguid, Head of Regulatory Affairs
ProStrakan, Inc.	Bridget O'Mahony, REMS Manager
Sandoz Inc.	Laura M. Pethick, Manager, Pharmacovigilance & Risk Management
Sandoz Inc.	Brian Watson, Director, Drug Safety
Sandoz Inc.	Allison Sherwood, Manager, Regulatory Affairs
Teva Pharmaceuticals	Mona Morey, Manager, Regulatory Affairs
Teva Pharmaceuticals	Kishore Gopu, Associate Director, REMS Programs
Teva Pharmaceuticals	Christopher Uhrn, Senior Manager, Regulatory Affairs
Watson Laboratories, Inc.-Florida	Janet Vaughn, Director, Regulatory Affairs
Watson Laboratories, Inc.-Florida	Gary Kozloski, Vice President Medical Affairs
Watson Laboratories, Inc.-Florida	Janie Gwinn, Director, Regulatory Affairs

Agenda

1. Introduction
2. Status Update from TIRF Sponsors
3. Questions from FDA
4. Next Steps

Introduction

The meeting was opened and welcomed by Darrell Jenkins. The first TIRF Meeting was held on October 28, 2010. This meeting was the follow up of that first meeting.

Meeting Minutes

The meeting started with discussion around the charter. The formalized charter was a point of discussion as it needed to be in place for the January 2011 meeting. Issues covered in charter included voting rights and decision making; process and frequency of meetings; how meetings occur; confidentiality; group participation and group withdrawal; antitrust issues and expenses; making changes and tweaks as obstacles occur; commitment to deliver REMS and manage it going forward. Additionally, the charter discussion included managing the REMS program and process.

FDA requested that questions from the sponsors should be submitted first week of January. FDA requested that the sponsors coordinate questions through one industry participants. FDA provided details on upcoming and future meeting and stated that an email notification would be forthcoming to provide this information.

The meeting ended with the sponsors extending an invitation to the meeting in January in Philadelphia on January 7, 2011, as well as future TIRF sponsor meetings. The sponsors suggested providing FDA a copy of the agenda, should FDA wish to attend, before FDA attendance confirmation in an effort appropriately address coordination of questions to FDA for a collective answer from FDA. Finally, the sponsors asked for clarification on the following points:

- Timeline for shared portion of the REMS?
- Clarification of group effort of 120 day letter (submission of approval from sponsors)

FDA would provide a timeline for the shared portion of the REMS and would offer clarification on the 120 day letter at the January 2011 meeting.

The meeting ended.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAWNETTA M JACKSON
03/18/2011

CLAUDIA B KARWOSKI
03/18/2011
concur

MALLINCKRODT INC.

COVIDIEN

PRIOR APPROVAL SUPPLEMENT: PROPOSED REMS

December 5, 2011

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

RE: ANDA 078907: Oral Transmucosal Fentanyl Citrate Lozenges
(200 mcg; 400 mcg; 600 mcg; 800 mcg; 1200 mcg; 1600 mcg)

Dear Sir or Madam:

Reference is made to the REMS notification letter dated November 12, 2010, whereby FDA discussed that in the interest of public health and to reduce the burden on the healthcare system of having multiple unique REMS programs, a single, shared system should be used to implement the REMS for all members of the class of transmucosal immediate release fentanyl (TIRF) products.

Our proposed REMS is modeled after the template included in the REMS notification letter dated November 12, 2010. The submission includes two parts: a "proposed REMS" and a "REMS supporting document". Please note all relevant proposed REMS materials including enrollment forms, educational, and communication materials are appended to the proposed REMS. The appended documents are standardized across the class of TIRF products. Draft Labeling is also provided in this submission in Microsoft Word format. As directed by FDA in an email dated December 2, 2011, the package insert, medication guide, and carton labeling will be submitted as an amendment to the TIRF REMS once finalized.

This application, which has been organized according to the June 2008 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications,* is approximately 30 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0028. It has been checked and found free from virus infection using McAfee VirusScan Enterprise 8.7*i* Antivirus Software. For technical assistance, please contact Jeremy Grise, Manager, Regulatory Operations at 314-654-8259.

Correspondence related to this application should be addressed to Jasen Wallace, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-3157, or Rebecca Welton, Manager, Regulatory Affairs, at 314-654-5607.

Sincerely,

Jasen Wallace
Senior Regulatory Affairs Specialist
Email: jasen.wallace@covidien.com
Fax: 314-654-3157

Transmucosal Immediate Release Fentanyl (TIRF)

Sponsors:

TIRF REMS Industry Group (TRIG) of Companies

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) SUPPORTING DOCUMENT

1. TABLE OF CONTENTS

2. BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended release and immediate release products. Extended release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic [Biedrzycki et al, 2009]. Secondary effects of fentanyl on central nervous system, respiratory and gastro-intestinal functions are typical of opioid analgesics and are considered to be an effect [Simpson et al, 2007].

TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, BTP). All the TIRF medicines as such, are short acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and on occasion fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

In order to mitigate these risks, TIRF Sponsors will implement a Risk Evaluation and Mitigation Strategy (REMS) for the transmucosal immediate release fentanyl products (or "TIRF medicines"), intended for use in breakthrough pain (BTP) in patients with cancer, while ensuring treatment access for patients who would benefit from this therapy.

The TIRF medicines which are the subject of this proposed TIRF REMS are shown in Table 1 below. Table 1 shows the products and dosage forms. These products are currently used for the treatment of BTP in adult patients with cancer who are already receiving, and are tolerant to, around-the-clock (ATC) routine opioid therapy. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

Table 1: TIRF Medicines

Product Name (active ingredient)/formulation	Applicant/Sponsor	Availability	Initial Dose
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg	100 mcg
ACTIQ® (fentanyl citrate) oral transmucosal lozenge*	Cephalon, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg 200 mcg 400 mcg 600 mcg 800 mcg	100 mcg**
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg 400 mcg	100 mcg
ONSOLIS® (fentanyl), buccal soluble film	Meda Pharmaceuticals	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg

Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Mallinckrodt Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg

*Can be used in patients aged 16 and older
**Unless substituting from an Actiq dose of 600 mcg or greater. Please see full prescribing information.

The TIRF REMS Access proposal presented here addresses the current requirements set forth by the FDA provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

A. Clinical Features of BTP

BTP is a transient exacerbation of pain of moderate to severe intensity that occurs on a background of otherwise stable pain in a patient receiving regular, continuous opioids. It is characterized by rapid onset, with pain reaching maximal intensity within 3 minutes and lasting approximately 30 minutes [Laverty, 2007]. Often classified by its relationship to specific events or spontaneous onset, BTP arises as a consequence of the cancer, the anticancer treatment or a concomitant illness. BTP can affect up to two-thirds of patients with cancer, and can have a significant impact on patient quality of life [Breivik et al., 2009]. Moreover, a number of patients remain inadequately treated for their BTP or feel dissatisfied with their pain control [Fishbain, 2008]. There is therefore a need for effective pharmacologic treatments that will help relieve and control the symptoms of BTP. An ideal treatment for BTP is an analgesic with good efficacy, rapid onset and short duration of action, with minimal adverse effects in appropriately selected patients, and is easy and quick for a patient or caregiver to administer.

B. Assessment of Key Risks of TIRF Medicines

The TIRF REMS Access program will address the primary risks of overdose, misuse, abuse, addiction and serious complications due to medication errors. These are broad risks relating to the distribution, sale, use and misuse of opioids in the US and are not unique to TIRF medicines. However, TIRF medicines are absorbed transmucosally and partially bypass gastrointestinal absorption and first-pass metabolism, resulting in rapid onset of analgesic effect, and potentially, adverse effects. The key acute risk for any individual exposed to TIRF medicines is excessive respiratory depression which can be fatal if untreated. This risk is highest in opioid non-tolerant patients. Therefore, TIRF medicines must not be used by opioid non-tolerant patients. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

By restricting the use of TIRF medicines to opioid tolerant patients the risk of serious outcomes such as severe respiratory depression should be minimized. Opioid addiction arising in palliative care patients is rare [Hojsted et al, 2007**].**

3. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

4. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors will execute the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program including patients, prescribers, pharmacists and distributors will be enrolled in the TIRF program, educated on the requirements of the program and required to document that they understand and will abide by the "elements to assure safe use."

Program materials will be provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program will contain both TIRF medicine class and product-specific components. Enrollment forms, the Patient-Prescriber Agreement Form (PPAF), stakeholder letters and overview documents containing program information will be provided to stakeholders as TIRF medicine materials. In addition, the Medication Guides will be provided to stakeholders in product-specific material format unique to the respective TIRF medicine being prescribed / dispensed.

The program procedures will be monitored for adherence and will be modified as necessary to ensure optimal effectiveness. The TIRF Sponsors will conduct ongoing and retrospective analysis as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

A. Additional Potential Elements

a. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF medicine prescription. Every TIRF medicine will have a unique Medication Guide. There will be sufficient copies distributed by each Sponsor to ensure that every patient receives a copy with each prescription. Medication Guides will be available through individual TIRF Sponsors, the TIRF REMS Access website, and the TIRF REMS Access call center.

The Medication Guide contains FDA approved language including an explanation of the risks associated with the use or misuse of TIRF medicines, augmented with information on precautions for safe use of the product, a brief explanation of essential elements of the TIRF REMS Access program, and contact information for customer assistance (i.e., call center with toll-free number and website). The TIRF medicine Medication Guides are developed to enhance patient awareness and understanding of the potential serious risks associated with the use of TIRF medicines with the intent of increasing the patients' appropriate use of TIRF medicines. The Medication Guides include critical information that every patient and caregiver should know about TIRF medicines including, but not limited to:

- Patients should not use a TIRF medicine unless they are regularly using another opioid pain medicine around-the-clock for their constant cancer pain and their body is used to these medicines (opioid tolerant).
- TIRF medicines must be kept in a safe place away from children.
- If a child, or an adult who is not already taking opioids regularly, takes a TIRF medicine, this is a medical emergency and can cause death. Get emergency help right away.

A copy of each product specific Medication Guide is distributed with every TIRF medicine.

TIRF Sponsors will supply all enrolled prescribers and pharmacies with sufficient copies of the Medication Guides to ensure that every patient who is prescribed and dispensed a prescription will have access to the specific TIRF medicine Medication Guide each time it is prescribed or dispensed.

The Medication Guide will be available through the TIRF REMS Access website, www.TIRFREMSaccess.com. Copies can also be obtained by calling the TIRF REMS Access program at **1-866-822-1483**.

b. Other Information Materials for Patients

The prescriber will discuss the benefits and risks of TIRF medicines as outlined in the Medication Guide with the patient, including proper dosing and administration, appropriate use and handling and storage of TIRF medicines.

The prescriber will discuss enrollment in the TIRF REMS Access program. The prescriber and the patient will review and sign the TIRF REMS Access program Patient-Prescriber Agreement Form (not required for inpatients) and a copy will be provided to the patient or caregiver. The prescriber will also provide the patient or caregiver with a copy of the Medication Guide.

The patient or caregiver will be offered counseling on the specific TIRF medicine by the dispensing pharmacist on appropriate use, storage and disposal, and receive an additional copy of the Medication Guide each time a TIRF medicine is dispensed.

The prescriber will have access to the TIRF REMS Access Program: An Overview for Patients and Caregivers to utilize with patients during discussions regarding the use of TIRF medicines. In patient-friendly language, the materials will focus on a description of the TIRF REMS Access program, including enrollment details and contact information (call center with toll-free telephone number and website address). This overview will also be available for download on www.TIRFREMSaccess.com.

c. Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS is not required. However, TIRF Sponsors will send Dear Healthcare Professional letters to targeted stakeholders to support implementation of the TIRF REMS Access program. These communications will include Dear Healthcare Provider and Dear Pharmacy letters, and will inform prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means of reporting adverse events.

TIRF Sponsors will send letters to healthcare professionals approximately 2 weeks prior to first availability of TIRF REMS Access program.

The target audience for the *Dear Healthcare Provider* letter will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

Additional materials will be available via the TIRF REMS Access program website or through the TIRF REMS Access program toll-free number.

B. Elements to Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This can be achieved by prescriber's enrollment through a review of the TIRF REMS Access Education Program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the enrollment form.

TIRF medicines will only be available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies will be enrolled into the TIRF REMS Access program. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals that dispense for inpatient use only). For Long-Term Care (LTC) and Hospice patients whose prescriptions are obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access program.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to undergo enrollment through review of the *TIRF REMS Access Education Program* and successful completion of the *Knowledge Assessment* on behalf of the pharmacy. The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transactions to validate the system enhancements and submit a completed and signed TIRF REMS Access enrollment form. The authorized pharmacist will be responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training must be documented and is subject to audit. At a minimum this documentation should include the store name, the store number, the pharmacist/pharmacy staff member's name, and the date training was completed.

For inpatient pharmacy enrollment, the authorized pharmacist must undergo the *TIRF REMS Access Education Program*, successfully complete the *Knowledge Assessment*, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist must also acknowledge that they understand that outpatient pharmacies within their facility must be separately enrolled.

For chain pharmacies, an authorized chain pharmacy representative must complete enrollment. The authorized chain pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program

requirements by submitting a completed and signed enrollment form. Pharmacy sites that have been trained may be updated by the authorized chain pharmacy representative using an online dashboard.

Pharmacies will not be able to successfully order TIRF medicines from distributors unless they are enrolled in the TIRF REMS Access program.

All patients (excluding inpatients) must complete and sign a Patient-Prescriber Agreement Form (PPAF) with their healthcare provider, documenting safe-use conditions. Their healthcare provider will submit a copy of the PPAF to the TIRF REMS Access program via the website at www.TIRFREMSaccess.com, fax at 1-866-822-1487, or regular mail at (Address: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038). Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program. A completed *Patient-Prescriber Agreement Form* needs to be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

a. Prescriber Education and Enrollment

The TIRF REMS Access program education materials are the primary tool for educating prescribers about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The *Education Program* also includes information for prescribers on the requirement to complete a *Patient-Prescriber Agreement Form* before writing the first prescription for a TIRF medicine (not required for inpatients). For inpatient administration of TIRF medicines prescriber enrollment in the TIRF REMS Access program is not required.

The *TIRF REMS Access Educational Program* for prescribers comprises the Education Program and *Knowledge Assessment* that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available on the TIRF REMS Access website (www.TIRFREMSaccess.com):

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

If the prescriber does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded on the TIRF REMS Access website, or requested as a hardcopy from the TIRF REMS Access program call center.

Review of the Knowledge Assessment

Following review of the TIRF REMS Access Education Program, the program Knowledge Assessment must be successfully completed. A description of the process followed in reviewing the Knowledge Assessments is presented below, and this description applies equally to prescribers and pharmacists.

Manual Knowledge Assessment Review (i.e. on receipt of printed materials)

The prescriber should review the *TIRF REMS Access Education Program*, complete the paper *Knowledge Assessment* and return it by fax to the TIRF REMS Access program.

Upon receipt of a manual program *Knowledge Assessment*, a TIRF REMS specialist will review the assessment and determine the stakeholder type.

The TIRF REMS specialist will enter each answer to the assessment question in the validated TIRF REMS Access database.

If the answers are correct (the user has passed the assessment with a score of 100%) and all other enrollment criteria have been met, the user will be enrolled in the program by notice through email or fax.

If answers are incorrect a *Knowledge Assessment* feedback fax will be generated and sent to the enrolling user that only addresses the incorrect questions received. If answers are missing an "Incomplete" fax is generated and sent to the user advising them to resend a completed *Knowledge Assessment* to allow for successful processing of the assessment.

Website Knowledge Assessment Review (web-based materials)

Upon completion of the review of the *Education Program*, the user is required to successfully complete the *Knowledge Assessment* prior to enrolling in the program.

The user is presented with one question at a time and required to provide an answer.

Upon completion of all program assessment questions, the system calculates a score. The score is presented to the user.

If the score is 100%, then the user has passed the program assessment.

If the user's score is less than 100%, they will be presented with the incorrectly answered question that they will be required to retake, in addition to further feedback on the incorrect answer.

The Knowledge Assessment (manual or website) may be attempted up to three times. If a score of 100% is not achieved after three attempts, the TIRF REMS Access Education Program must be reviewed again before retaking the *Knowledge Assessment*. Having performed the training again, a further three unsuccessful attempts at the *Knowledge Assessment* are permitted before enrollment is denied.

Successful completion of the *Knowledge Assessment* is required in order for the prescriber to enroll in the TIRF REMS Access program. Prescribers may enroll online or by paper by completing the TIRF REMS Access Prescriber Enrollment Form.

Verification of prescribers having successfully enrolled will be recorded in the TIRF REMS Access program and will allow them to access the full TIRF REMS Access program and to prescribe TIRF medicines. Prescribers will receive a user ID and password as part of the enrollment process. In addition, these forms will also be available as printed materials and can be downloaded from the website for stakeholders that prefer not to enroll electronically. These forms along with the *Knowledge Assessment* may be completed on paper and faxed to the TIRF REMS Access call center at 1-866-822-1487.

Manual Enrollment

Upon receipt of a paper enrollment form, a TIRF REMS specialist will review the form for completeness and determine the enrolling stakeholder type (i.e., prescriber or pharmacy). The TIRF REMS specialist will enter all data on the form into the TIRF REMS Access database.

Required for successful enrollment form:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation
4. The program Knowledge Assessment has been passed successfully.
5. All enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation is sent to the stakeholder via the preferred method of communication (fax or email) that is indicated on the enrollment form.

An enrollment form is considered incomplete where:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

If the enrollment form is incomplete, a fax is generated clearly listing all incomplete fields and a description of the action required to resolve the issue. The fax is sent to the fax number provided by the enrolling user on the enrollment form (email or phone can be used to send/discuss the incomplete form if the fax number is not available). The enrolling user must provide the incomplete information and return it to the TIRF REMS Access program for reprocessing. The enrollment is not considered complete until all required fields have been received and validated.

Web-based Enrollment

The enrolling user will be required to review the TIRF REMS Access Education Program, complete the *Knowledge Assessment* with a score of 100%, and complete the appropriate enrollment form.

Required for successful enrollment:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.

3. Successful Identifier Authentication Validation.
4. The enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation and completed enrollment form are sent via the indicated preferred method of communication (fax or email) provided by the enrolling user on the enrollment form. In the case that email is not available, a fax confirmation will be sent. Enrollment confirmation is also provided via the website.

An enrollment form is considered incomplete when:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

Unsuccessful Enrollment: The field edit messages are displayed back to the enrolling user. The enrolling user cannot progress further with the enrollment process until errors are corrected. Only the user's initial registration information will be retained; no enrollment data are saved to the TIRF REMS Access database.

TIRF Sponsors will maintain a database containing a list of all enrolled prescribers and their status (i.e. active or inactive). Upon initial activation, prescribers remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate prescribers for non-compliance reasons.

If a previously active prescriber becomes inactive, the prescriber will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment form in its entirety.

While a prescriber is inactive, prescriptions from that prescriber can no longer be filled under the TIRF REMS Access program. If the prescriber is providing care for patients using TIRF medicines at the time of prescriber inactivation, it is the prescriber's responsibility to ensure that the patients continue to receive appropriate pain medication via referral to another prescriber in the TIRF REMS Access program.

Prescribers are re-educated and re-enrolled in the TIRF REMS Access program every two years. TIRF Sponsors will notify prescribers of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify prescribers of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of TIRF medicines.

All communication methods utilized by the TIRF REMS Access program will provide information on how to report any suspected adverse events, including reports of misuse and abuse to TIRF Sponsors.

b. Outpatient Pharmacy Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating pharmacists about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines.

The TIRF REMS Access education for pharmacists comprises the *TIRF REMS Access Education Program* and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

If the pharmacy does not want to perform the *Education Prog*ram and *Knowledge Assessment* online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested from the TIRF REMS Access program call center.

The *Education Program* will cover information regarding how to validate prescriptions via the TIRF REMS Access program before they are filled as well as information on appropriate dispensing and use of TIRF medicines. Following review of the *Education Program*, the authorized pharmacist may enroll the pharmacy by successful completion of the *Knowledge Assessment* and the appropriate TIRF REMS Access program pharmacy enrollment form. On receipt of a valid enrollment form, the pharmacy will be sent by fax or email the instruction guide on the test transactions they will be required to run to verify that their pharmacy management system has been configured. If the test transactions have been completed successfully, the pharmacy will be enrolled and confirmation will be sent to the pharmacy. If the test transactions are not completed successfully, the pharmacy will not be enrolled and a message will be sent to contact the call center in order to further explain the need to configure the pharmacy management system.

The authorized pharmacist will be responsible for educating all pharmacy staff that participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training should be documented and is subject to audit.

An authorized chain pharmacy representative may complete the TIRF REMS Access training, *Knowledge Assessment* and enrollment on behalf of all their pharmacies within the chain and then document and manage training of all pharmacy staff by the chains' internal processes. The authorized chain pharmacy representative would also ensure completion of system testing to verify that their pharmacy management system has been configured. Upon completion of enrollment, the authorized chain representative would update trained stores on their chain

pharmacy dashboards or would submit a list to the TIRF REMS Access program for uploading into the database.

Enrolled Pharmacies will be recorded in the system which will allow them access to the TIRF REMS Access program to dispense TIRF medicines. Following web-based enrollment and successful completion of the test transactions, the authorized pharmacist will receive a username and enrollment ID, where the user can then create a password for the TIRF REMS Access website.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the Knowledge Assessment and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled Pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, the pharmacy will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines or dispense TIRF medicines under the TIRF REMS Access program.

Pharmacies are re-educated and re-enrolled every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies, of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any TIRF medicine.

The pharmacist will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

c. Inpatient Pharmacies: Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating inpatient pharmacies about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The Education Program also includes information about the requirements of the TIRF REMS Access program in the inpatient setting.

The TIRF REMS Access education materials for inpatient pharmacies comprise the Educational Program and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies

An authorized pharmacist of the inpatient pharmacy is required to undergo the TIRF REMS Access Pharmacy Education Program. If the pharmacist does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested as a hardcopy enrollment from the TIRF REMS Access program call center.

The Education Program will cover information about the requirements of the TIRF REMS Access program. Following review of the Education Program, the authorized pharmacist may enroll the pharmacy by successfully completing of the Knowledge Assessment and the TIRF REMS Access Inpatient Pharmacy Enrollment Form.

Inpatient pharmacy enrollment will be recorded in the system. Upon successful enrollment the inpatient pharmacy will have the ability to order TIRF medicines for inpatient dispensing. Pharmacies will receive a user ID and password as part of the enrollment process.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the *Knowledge Assessment* and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled inpatient pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled inpatient pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, it will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines.

Inpatient pharmacies are re-educated and re-certified every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program.

b. Changes to the Prescribing Information and Medication Guides that affect the benefit-risk profile of any TIRF medicine.

The inpatient pharmacy will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

d. Patient Enrollment and Counseling

Patient enrollment is not required for inpatient use of TIRF medicines.

- Prescribers for outpatients will be provided with copies of a TIRF medicine Medication Guide and materials to use in counseling patients. Medication Guides are product specific and can be accessed from the specific TIRF Sponsor, the TIRF REMS Access website, or the TIRF REMS Access call center. Patients will be counseled on the TIRF REMS product by enrolled prescribers, supported by review of the Medication Guide and the overview of the TIRF REMS Access program for Patients and Caregivers. Patients will also have the opportunity to discuss any questions or concerns they have with their prescriber. Together the prescriber and patient will review and sign the Patient-Prescriber Agreement Form.
- The patient will be counseled by the prescriber and personally sign the *Patient-Prescriber Agreement Form* unless they are unable to act on their own behalf. For incapacitated patients, the patient counseling can be provided to and signed by the patient's legally authorized representative or medical guardian.
- Both the prescriber and patient must complete the *Patient-Prescriber Agreement Form* and the prescriber must provide a completed copy by fax or through the TIRF REMS Access website to the TIRF REMS Access program within 10 working days. Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program.

- The TIRF REMS Access Program: An Overview for Patients and Caregivers will be available for distribution to the patient by the prescriber or through the program website. This overview details the steps the patient must follow. Further information will be available on the TIRF REMS Access program website or at the TIRF REMS Access call center.
- Patients will be offered counseling by the dispensing pharmacist on the responsible use, handling and disposal of TIRF medicines. A copy of a specific TIRF medicine's Medication Guide will be provided by the pharmacist when their prescriptions are dispensed by the pharmacy.
- A database will be maintained containing a list of all enrolled patients and their status (i.e. active or inactive). Upon initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include: a prescription has not been filled for more than 6 months or the patient receives prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, overdose, or addiction.
- If a previously active patient becomes inactive, the patient can become active again by completing the standard patient counseling and re-evaluation by their prescriber (i.e. a complete review of the current TIRF medicine's Medication Guide) and completing a new Patient-Prescriber Agreement Form.
- If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot authorize the prescription for the TIRF medicines to be filled until the new prescriber is active in the TIRF REMS Access program.
- Patients will be re-counseled and required to complete a new *Patient-Prescriber Agreement Form* every 2 years. TIRF Sponsors will notify the patient's prescriber of forthcoming enrollment expiration and the need to complete a new *Patient-Prescriber Agreement Form*.
- If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify the patient's prescriber of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program
    b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any and all TIRF medicines.

e. Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies must verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

TIRF Sponsors will use a model that uses a pharmacy billing claim and engages a switch provider in the validation process. The switch provider provides information to pharmacists at point-of-dispensing via their pharmacy terminals. Their secure connectivity network provides a single point of access between pharmacies and payers so that transactions are routed quickly and reliably, instantly transmitting claims to the appropriate processor and returning the adjudicated response to the pharmacy within seconds.

Patients must complete a Patient-Prescriber Agreement Form (PPAF) prior to being given a prescription for a TIRF medicine. This may be done in two ways – online at www.TIRFREMSaccess.com or paper based. If conducted online, the PPAF will be recognized immediately. Paper based PPAFs must be faxed to the program within 10 working days to complete enrolment.

On receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the pharmacist will enter the prescription details in their pharmacy management systems and send the transaction to the TIRF REMS Access program via the Switch Provider. The TIRF REMS Access program will use this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the REMS database will then be interrogated, via the Switch Provider, in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, a billing request will be sent to the payer by the Switch. Once the payer authorizes payment the switch provider will then authorize the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will reject the claim (prior to the claim being forwarded to the payer) and the pharmacy will receive a rejection notice from the Switch Provider. This automated feedback will indicate the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notify the pharmacist to contact the TIRF REMS Access call center for further information. The current switch authorization process typically takes 3-5 seconds to complete. Interrogation of the TIRF REMS Access program enrollment database should add not more than 1 second to the overall process. This method of verification is designed to integrate into normal pharmacy workflow patterns and therefore minimize burden to the pharmacy while providing a robust control on ability to dispense TIRF medicines outside of the TIRF REMS Access program.

The TIRF REMS Access system communicates an authorization number when the submitted prescription billing request passes all qualification rules and the processor approves the billing request. The switch provider appends the authorization to a message field before delivering the response to the pharmacy practice management system.

If the pharmacy is enrolled and the electronic prescription verification process fails, prescription verification can be facilitated through the call center. The call center representative can enter the required fields necessary to provide prescription verification.

The 'back-up' process/system is not the primary method for verification, and will only be available to enrolled, active pharmacies. All instances where the back-up process is used will be adequately documented, including the specific reason it is being used. A report on back-up system use will be included in the REMS Assessment.

Back-up system utilization will be incorporated into compliance monitoring; if excessive use is observed corrective action will be implemented.

f. The TIRF REMS Access Program Website

- The TIRF REMS Access program website (www.TIRFREMSaccess.com) contains information about the TIRF REMS Access program and serves as one method by which prescribers can receive education and enroll themselves in the TIRF REMS Access program. The prescriber will also be able to complete and submit a Patient-Prescriber Agreement Form via the website.
- Pharmacies can use the website for education and enrollment, including a dashboard functionality to allow chain pharmacies to manage their stores.
- The website includes the TIRF REMS Access Education Program, Knowledge Assessment and enrollment forms that must be reviewed and completed before enrolling. The website is referenced in all TIRF REMS Access program and TIRF medicine related materials.
- Prescribers can use the website to inform patients of enrolled pharmacies that can dispense TIRF medicines.

The TIRF REMS Access program Website also serves as a resource for:

- Description of the TIRF REMS Access program
- Ordering TIRF REMS Access Medication Guides
- Full Prescribing Information for all TIRF medicines
- Medication Guides for all TIRF medicines
- Patient/Caregiver, Prescriber, Pharmacy and Inpatient Pharmacies TIRF REMS Access program overviews in on-screen and printer friendly format
- TIRF REMS Access program contact information
- Frequently Asked Questions

g. The Key Elements of this REMS that Mitigate the Risks Associated with the Use of TIRF medicines are:

i. A certified prescriber who has acknowledged and agreed to adhere to the conditions that must be met for the appropriate outpatient use of each TIRF medicines.

- Prescribers will be educated and certified on the risks of inappropriate patient selection, including non-opioid tolerant patients. In order to become enrolled, outpatient prescribers will be required to complete the TIRF REMS Access Education Program and Knowledge Assessment. Enrollment is contingent upon prescribers documenting that they understand the risks of TIRF medicines and agree to the appropriate use of TIRF medicines (See appended Prescriber Enrollment Form).
- Without this enrollment, patients, with prescriptions from outpatient prescribers will be unable to have TIRF medicine prescriptions filled by an enrolled pharmacy.
- The TIRF REMS Access program will maintain a database of all enrolled prescribers.

ii. The certified pharmacy has agreed to send all claims through the system to verify eligibility

- All pharmacies that intend to purchase and dispense TIRF medicines must be enrolled in the TIRF REMS Access program in order to receive product from distributors. Pharmacies will be enrolled only after an authorized pharmacist undergoes *TIRF REMS Access Education Program*, completes a *Knowledge Assessment* and submits an enrollment form.
- Pharmacies that are not enrolled will be unable to obtain supplies of TIRF medicines.
- The TIRF REMS Access program will maintain a database of all certified pharmacies.

Outpatient Pharmacies

- The outpatient pharmacy will ensure that the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- The authorized pharmacist will ensure that all pharmacy staff involved in dispensing TIRF medicines at their pharmacy have been educated on the risks associated with TIRF medicines, maintain auditable training records for pharmacy staff, and adhere to the requirements of the TIRF REMS Access program.
- The pharmacist must ensure that TIRF medicines have been dispensed under the following safe use conditions:
    - The pharmacist has dispensed TIRF medicines only to enrolled patients, based on a valid Schedule II prescription from an enrolled prescriber and receipt of an authorization message from the TIRF REMS Access program.
    - The pharmacist has offered counseling to patients on appropriate TIRF medicine use.
    - The pharmacist has provided each patient with a product specific Medication Guide for every TIRF prescription dispensed, instructed the patient to read it and has answered any questions the patient may have.

- Additionally, all TIRF medicine prescriptions will be tracked based on the following:
    - Prescription validation and dispensing steps performed by enrolled pharmacists;
    - Generation of a prescription authorization number from the TIRF REMS Access database upon confirming enrollment status. This tracking will enable identification of prescriptions, as well as provide utilization information used in the evaluation of the TIRF REMS Access program.

Inpatient Pharmacies

- The authorized pharmacist for an inpatient pharmacy will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program. The authorized inpatient pharmacist acknowledges that Pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
- An inpatient pharmacy is not to dispense TIRF medicines for outpatient use.
- A prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.

iii. An informed outpatient and/or caregiver should understand the inherent risks in the use of opioids and know how to administer TIRF medicines appropriately at home. Therefore, each patient must:

- Sign a TIRF REMS Access program *Patient-Prescriber Agreement Form* that documents appropriate use conditions and opioid tolerance (See appended Patient-Prescriber Agreement Form).
- Deliver the TIRF medicine prescription to an enrolled pharmacy.
- Understand that they must be regularly using another opioid pain medicine for their constant pain.
- Be counseled on responsible use and handling by the pharmacist at each dispensing when they receive an additional copy of the appropriate Medication Guide.
- These requirements do not apply to inpatient use of a TIRF medicine.

C. Implementation System

The Implementation System includes the following:

a. Wholesaler/Distributor Enrollment and Fulfillment

- TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

- For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors will be contacted and will receive a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies. The distributor's authorized representative reviews the distributor program materials. The distributor's authorized representative will complete and sign the *Distributor Enrollment Form* and fax it to the TIRF REMS Access program. TIRF Sponsors will not ship TIRF medicines to any distributor who has not completed and signed the enrollment form; by checking the status of the distributor prior to shipping the drug (See appended Distributor Enrollment Form).
- As part of the TIRF REMS Access program, distributors will need to enroll in the TIRF REMS Access program. Distributors will need to confirm their understanding of the distributor requirements in the TIRF REMS Access program, which includes verifying that pharmacies are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
- The distribution process for TIRF medicines as it relates to drug distributors will consist of:
    - Only those TIRF medicine Sponsor contracted distributors will be eligible for TIRF REMS Access program enrollment.
    - TIRF medicine distributors will be contacted and will receive a communication describing the TIRF REMS Access program.
    - TIRF medicine distributors must acknowledge receipt and understanding of the TIRF REMS communication, by completing the TIRF REMS Access Distributor Enrollment Form, in order to become a customer eligible to receive and/or distribute TIRF medicines from TIRF Sponsors. In addition to the TIRF REMS Access *Distributor Enrollment Form*, the distributor's authorized contact will receive communication on how to verify pharmacies that are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
    - The procedures for the TIRF REMS Access program will include the method for timely communications of newly enrolled as well as inactive pharmacies in the TIRF REMS Access program.
    - The procedures for the TIRF REMS Access program will also include the procedure for reporting and management of non-compliance with the TIRF REMS Access distribution program.
    - Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor

becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

- Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years. TIRF medicine Sponsors will notify distributors (based on contractual relationships in place between Sponsor and distributors) of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.
- If there are substantive changes to the TIRF REMS Access program, impacted TIRF Sponsor or TIRF Sponsor team will update all affected materials and notify distributors of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    i. Significant changes to the operation of the TIRF REMS Access program.
    ii. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of impacted TIRF medicine.

b. The TIRF REMS Access Program Database

- The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive).
- Management of the TIRF REMS Access database will be contracted to an appropriately qualified third party vendor and overseen by the TIRF Sponsors. Data for all users will be updated in the TIRF REMS Access database. This includes data received from both the call center manual process and web-based processes. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing their TIRF medicine. Additionally, TIRF Sponsors will monitor to ensure their TIRF medicine is only being dispensed for outpatient use to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by the TIRF Sponsors if noncompliance is found.
- TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a Patient-Prescriber Agreement Form with each TIRF medicine patient, and to submit it to the REMS program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This will be accomplished by reconciling the *Patient-Prescriber Agreement Forms* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.
- TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.

- TIRF Sponsors will monitor the prescribing and dispensing of TIRF medicines to enrolled patients. If non-compliance is found, TIRF Sponsors will institute corrective actions. Please refer to Section 5(B) for further details.
- TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

Based on monitoring and evaluation of these elements to ensure safe use, TIRF Sponsors will work to improve implementation of these elements and to ensure compliance with the TIRF REMS Access program requirements, as applicable.

c. TIRF REMS Access Program Call Center

The TIRF REMS Access program includes a call center component. The call center will be staffed by qualified and trained specialists, who will provide TIRF REMS Access program support to patients, prescribers, pharmacies and distributors.

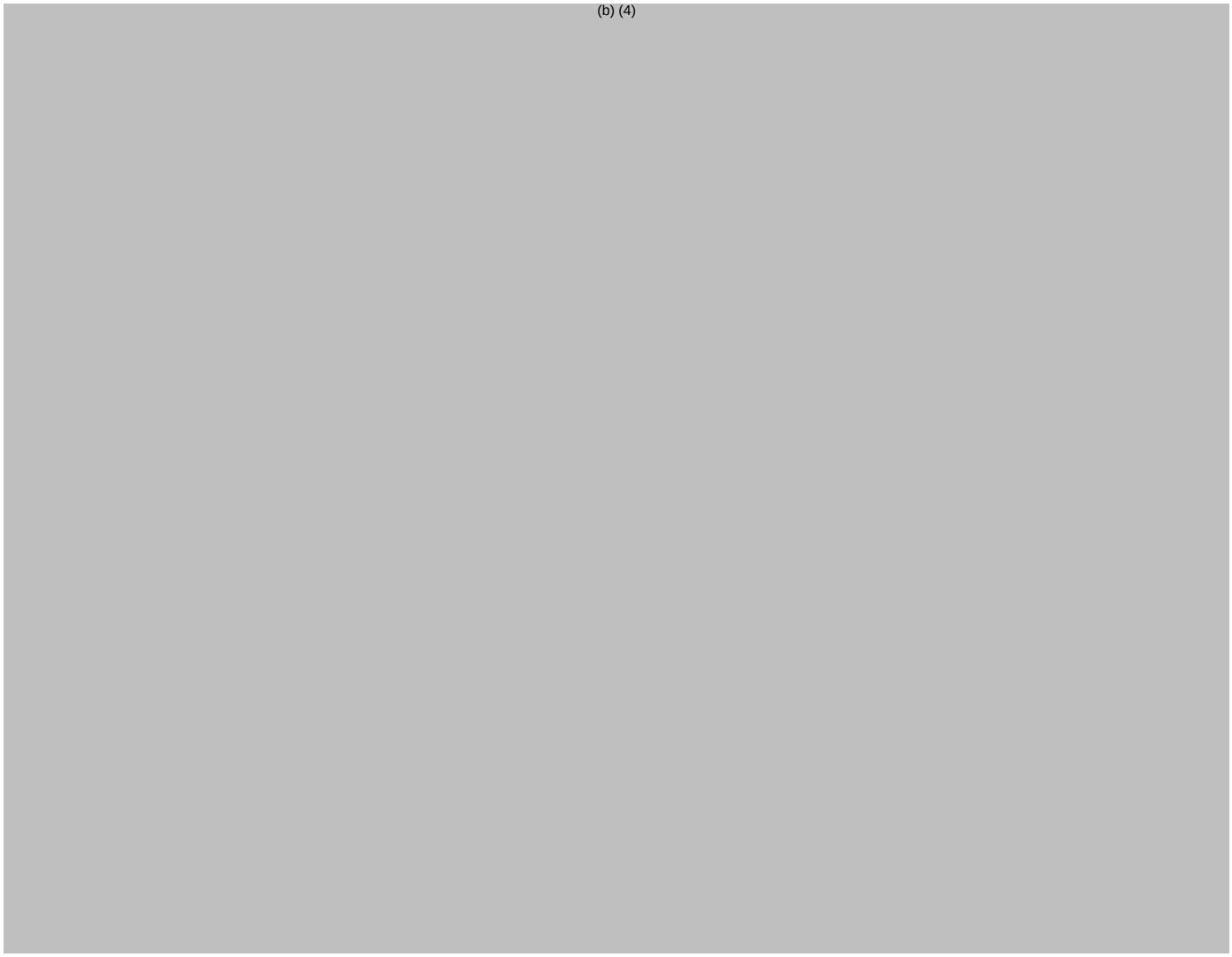
The call center specialists' responsibilities will include, but are not limited to, the following:

- Provide TIRF REMS Access program enrollment assistance to prescribers, pharmacies, distributors and patients
- Processing of prescriber, pharmacy and distributor enrollments and Knowledge Assessment forms
- Provide stakeholder enrollment verification in the TIRF REMS Access database
- Processing of Patient- Prescriber Agreements Forms
- Assist prescribers or patients in locating enrolled pharmacies
- Identify and transfer product complaints and potential adverse event information to TIRF Sponsors
- Provide general program information and technical assistance to stakeholders interacting with the TIRF REMS Access website

The TIRF REMS Access program call center hours of operation are Monday – Friday, 8:00am to 8:00pm EST. Callers outside of these hours are instructed to leave a message that will be addressed at the beginning of the next business day. TIRF medicine Medication Guides may include the TIRF Sponsor phone number and may be contacted. TIRF Sponsors may refer caller to Emergency Room.

The TIRF REMS Access program call center flow is show below in Figure 6.

Figure 6 TIRF REMS Access Program Call Center Flow



D. Timetable for Submission of Assessments of the REMS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. The knowledge, attitude, and behavior (KAB) surveys will be submitted at 12 and 24 months from the date of the REMS approval, and as needed thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

5. REMS ASSESSMENT PLAN

The aim of the TIRF REMS Access program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations will be used in an effort to improve the processes, over time, as needed.

A Data Sources

Data will be collected from the following main sources as described in detail below: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program infrastructure and performance, d) safety surveillance, e) periodic surveys of patients, healthcare providers, and pharmacies.

a. The TIRF REMS Access Program Outreach

The following metrics will be tabulated for every reporting period to assess program outreach efforts:

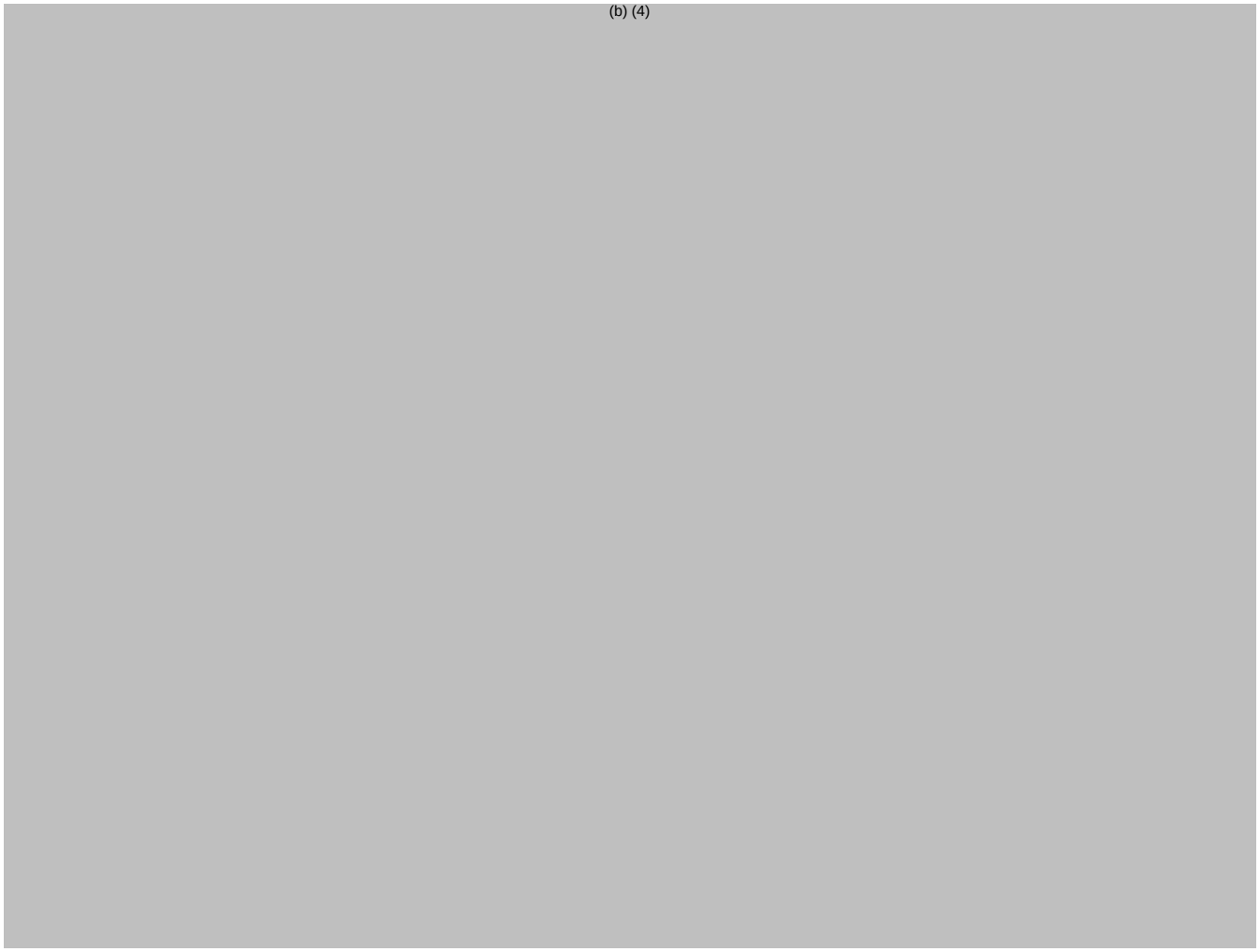
1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

b. The TIRF REMS Access Product and Program Utilization Statistics

The TIRF REMS Access program data flow is show in Figure 7 below.

Figure 7 TIRF REMS Access Program data flow

(b) (4)



For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following data will be tabulated for each reporting period and cumulatively:

5. Number of new patients enrolled by state
6. Number of patients inactivated
7. Number of attempts needed for prescribers to successfully complete Knowledge Assessments
    - Method of completion
8. Number of new prescribers enrolled by state
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
9. Number of prescribers who are inactivated
10. Number of new pharmacies enrolled by type (inpatient or outpatient), by state

- Method of enrollment
- Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

11. Number of pharmacies that are inactivated by type (inpatient or outpatient)
12. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments
13. Dispensing activity for enrolled outpatient pharmacies
    - Total number of prescriptions authorized
    - Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome)
15. Number of wholesalers/distributors inactivated, total
16. Number of new wholesalers/distributors enrolled
    - Method of enrollment
    - Number of incomplete forms
17. Number of days between passive enrollment and receipt of a Patient-Prescriber Agreement Form
    - Method of PPA submission
18. Number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment with and without a PPAF in place.

c. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be tabulated for each reporting period and cumulatively:

19. Assessment of process for pharmacies to upgrade their pharmacy management systems (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems)
20. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem)
21. Call center report
    - Summary of frequently asked questions
    - Problems reported
22. Description of corrective actions taken to address program/system problems.
23. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area
24. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays

The following reports for unintended system interruptions will be provided for each reporting period:

25. Reports identified of inadvertent enrollment deactivations
26. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code)
27. Reports of failure of re-enrollment notifications to reach stakeholders
28. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection.

d. Safety Surveillance

- TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures.
- Surveillance data from the following sources will be included in the REMS Assessment Reports:
    - FDA AERS database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion
    - Other external databases.

e. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Survey results will be reported at 12 months and 24 months after the TIRF REMS Access program approval. TRIG will discuss with the FDA if additional surveys are needed after 24 months. The results from the surveys will be analyzed together with other REMS assessment data, and a report on any corrective actions taken and the outcome of those actions will be provided.

B. TIRF REMS Access Non-Compliance Plan

GOALS & OBJECTIVES

The TIRF REMS Access program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the non-compliance plan is to ensure that TRIG monitors the functioning of TIRF REMS Access and identifies and investigates deviations and non compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program.

TIRF REMS ACCESS NON-COMPLIANCE REVIEW TEAM

A TIRF REMS Access Non-Compliance Review Team will be created. The team will have membership from the companies of the TRIG. A detailed plan for the TIRF REMS Access program will be created and implemented by the team.

The TIRF REMS Access Non-Compliance Review Team's responsibility will be to:

- Evaluate the compliance of patients, healthcare providers, distributors and pharmacies (stakeholders) with the TIRF REMS Access program
- Investigate potential non-compliance activity when events are referred to the team
- Devise corrective measures and issue notices, warnings, suspensions, or deactivations of stakeholders where warranted
- Review need for changes to the TIRF REMS Access program as a result of deviations or non-compliance

The TIRF REMS Access Non-Compliance Review Team will meet regularly.

Any needed program modifications or stakeholder notifications will be approved by TRIG prior to implementation.

SOURCES OF NON-COMPLIANT EVENTS

There are a variety of ways in which the TIRF REMS Access program can detect non compliance. Those potential sources include:

- TIRF REMS Assessment reports
- REMS database activity
- TRIG Member Company Adverse Event Reporting or Medical Information
- TIRF REMS Access Program Call Center
- Data Requests and Audits

TIRF REMS Access Assessment Reports

TIRF REMS Access program data will be collected from the following main sources: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program performance, d) safety surveillance, e) periodic surveys of stakeholders. The TIRF REMS Access Non-Compliance Review Team will regularly review the assessment reports for evidence of non-compliance or deviation from program procedures.

REMS Database Activity

The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive). Data for all users will be updated in the TIRF REMS Access database including data from the call center manual process, web-based processes and the pharmacy network.

The TIRF REMS Access Non-Compliance Review Team will regularly analyze database reports to detect evidence of non-compliance or deviation from program procedures.

TRIG Member Company Adverse Event Reporting or Medical Information

Each company in the TRIG is responsible for the intake, investigation, review and reporting of adverse events and answering medical information queries for their own product. Each TRIG member will review adverse events or medical information queries received by that company and forward events which contain evidence of TIRF REMS Access non-compliance or deviation to the TIRF REMS Access Non-Compliance Review Team for further evaluation. For privacy or commercial confidentiality reasons, this information may be redacted before forwarding, and individual investigation for these events will be referred back to the company that initially received the event.

TIRF REMS Program Call Center

The TIRF REMS Access program will have a call center available for questions about the program, or to process non website enrollments. Enrollments or queries that contain evidence of non-compliance or deviation from program procedures will be referred to the TIRF REMS Access Non-Compliance Review Team.

Data Requests and Audits

TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

The TIRF REMS Access Non-Compliance Review Team will review information received from data requests and audit reports to detect evidence of non-compliance or deviation from program procedures.

EVALUATION PROCESS

Events of suspected non compliance or deviation from TIRF REMS Access program procedures will be evaluated by the TIRF REMS Access Non-Compliance Review Team. Further corrective actions for stakeholders may occur and are described below.

CORRECTIVE ACTION MEASURES

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action in accordance with the TIRF REMS Access non-compliance plan. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access Non-Compliance Review Team according to the severity of the action. The stakeholders in this non-compliance plan include prescribers, patients, distributors, inpatient pharmacies and outpatient pharmacies. The primary elements for corrective action include; notices, warnings, suspension, and deactivation, based on the incidence and outcomes of misuse, abuse, and overdose, in addition to accidental or intentional exposure. If a prescriber or pharmacy is

suspended or deactivated, information will be made available through the program to assist patients in finding alternative prescribers or pharmacies.

Notices

Notices are defined as minor violations that demonstrate a misunderstanding of the program requirements. Notices of non-compliance reinforce the program requirements and are intended to re-educate stakeholders. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

Warnings

Warnings are serious violations that result in an improper patient receiving a TIRF medicine. Warnings may be accompanied by other corrective actions (e.g. retraining) that may be required in order to avoid suspension.

Suspension

Suspension is a temporary deactivation from the program pending the completion of a Corrective Action Plan. Multiple warnings received by a stakeholder within a sixty day time-period will result in a Suspension. Multiple warnings received by a stakeholder over longer periods will accumulate, be logged in reports and may result in a suspension at the discretion of the TIRF REMS Access Non-Compliance Review Team.

A suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension, but may not purchase or acquire additional TIRF medicines until the suspension is removed. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension, and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity (e.g. a Chain Pharmacy or a multi-site distributor), the parent entity will be notified of the non-compliant activity and resultant suspension.

Deactivation

Deactivation is defined as an indefinite deactivation from the program. Deactivation may result from the failure of the stakeholder to implement corrective actions, multiple failures to comply with material program elements, and/or non-compliances where there is no feasible corrective action. Deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

A deactivated stakeholder may request reinstatement in the TIRF REMS Access program. Requests for reinstatement must be in writing (e.g. letter, fax, etc.) and contain sufficient details on corrective actions taken to prevent any future non-compliance with program elements. Patients that have been deactivated will only be reinstated by a request made by the patient's prescriber. Requests for reinstatement will be evaluated by the TIRF REMS Access Non-

Compliance Review Team which will make a recommendation to TRIG. TRIG will make the final determination on reinstatement.

TIRF REMS ACCESS PROGRAM AUDITS

As part of non-compliance monitoring, TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

C. Internal Quality and Compliance

The TIRF medicines REMS program team will be supported by written procedures to define process and will be audited against these for compliance.

6. OTHER RELEVANT INFORMATION

A. The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program, all TIRF medicines in an individual REMS program will be transitioned to the TIRF REMS Access program. The transition for the TIRF REMS Access program will begin upon system availability. From this point onward all *new* stakeholders will be required to enroll in the TIRF REMS Access program.

Upon system availability the individual REMS program websites, call centers, and enrollment forms will be redirected to the TIRF REMS Access program. The TIRF REMS Access program will provide information and direction on why the individual REMS program website is no longer available, in addition to providing an introduction to the new TIRF REMS Access program and resources available to stakeholders. Historical data from all individual REMS programs will be referenced to determine the date of last prescription so that the TIRF REMS can accurately calculate 6 months of no prescription activity.

All pharmacies and prescribers already enrolled in an individual REMS program will be notified (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. They will also be notified in these letters that:

- They must review the Education Program on the TIRF REMS Access program website or request a copy from the call center.
- If the prescriber changes the patient's TIRF medicine at any time the prescriber is required to counsel the patient on the new product and provide the relevant Medication Guide but no new Prescriber-Patient Agreement Form (PPAF) is required.

Prescribers
Enrollment data for each enrolled prescriber will be transferred from the individual REMS program to the TIRF REMS Access program database when it is available. These prescribers will then be able to prescribe any TIRF medicine within the TIRF REMS Access program. Healthcare providers will be guided to review the educational program for the TIRF REMS Access program but will not be tested on these materials. These prescribers will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

Inpatient Pharmacies
Enrollment data for each enrolled inpatient pharmacy will be automatically transferred from the individual REMS program to the TIRF REMS Access program database when it is available. Inpatient pharmacies will then be able to order and dispense any TIRF medicine within the TIRF REMS Access program to inpatients.

Outpatient Pharmacies
All outpatient pharmacies in an individual REMS program will be automatically transitioned to the new TIRF REMS Access program.

However, chain pharmacies will need to execute a TIRF REMS Access program contract with their switch provider before they can order and dispense all TIRF medicines. Chain pharmacies that have not executed a TIRF REMS Access program contract with their switch provider will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If chain pharmacies do not execute a TIRF REMS Access program contract with their switch provider within six months, they will no longer be able to order or dispense any TIRF medicine.

Independent pharmacies will need to agree to the shared program terms and conditions before they can order and dispense all TIRF medicines. Independent pharmacies that have not agreed to the shared program terms and conditions will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If outpatient pharmacies do not sign the new business contracts within six months they will no longer be able to order or dispense any TIRF medicine, and will have to complete an updated contract if they wish to continue to dispense TIRF medicines.

All pharmacies that have been transitioned from an individual REMS program will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their original enrollment in the individual REMS program.

Patients
Enrollment data for patients will be automatically transferred from the individual REMS program to the TIRF REMS Access program database. Patients who have previously been

enrolled in an individual REMS and have completed a PPAF can be prescribed/receive any TIRF medicine within the TIRF REMS Access program. Patients will only be required to complete a new PPAF for the TIRF REMS Access program every 2 years from their last PPAF.

Distributors
Distributors already enrolled in a single product REMS program will be notified of the transition to the TIRF REMS Access program (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. Enrollment data for distributors will be transferred from the individual REMS program to the TIRF REMS Access program database. Distributors will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

B. The TIRF REMS Access Program Steering Committee

A TIRF REMS Access program steering committee will be comprised of representatives from each Sponsor who will provide high level oversight and strategic direction for the TIRF REMS Access program. One voting member from each Sponsor company will be included in the Steering Committee. Significant issues and trends will be reviewed and appropriate recommendations made to the TIRF medicine Operations Team.

C. Abbreviations

The following abbreviations refer to the REMS program descriptors and products.

TIRF Medicines:	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access:	REMS program for TIRF medicines
TIRF Sponsors:	The group of sponsors that are submitting this REMS (please refer to the 'List of TIRF REMS Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.)

7. REFERENCES

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PROPOSED TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for <u>outpatient</u> use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment*).

ii. Complete and sign the *Prescriber Enrollment Form*. In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for <u>all</u> patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with <u>each</u> new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.

2) My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

4) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

5) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

6) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain pharmacy) or authorized pharmacist (outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. There is a different set of enrollment requirements for **outpatient pharmacies,** (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use), **including chain pharmacies,** and **inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Outpatient Pharmacy Enrollment Form* or the *Chain Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Outpatient Pharmacy Enrollment Form or Chain Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

e. ***Inpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form.* In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for <u>all</u> patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

g. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- *The TIRF REMS Access Program Overview (*Outpatient Pharmacy, Chain Pharmacy *or* Inpatient Pharmacy, *as applicable)*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- Pharmacy Enrollment Form (Outpatient, Chain, or Inpatient, as applicable)
- Frequently Asked Questions (FAQs)
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program. For outpatient pharmacies (including chain pharmacies) only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the TIRF REMS Access program. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2, respectively.

c. Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

   ii. The patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are

available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

2. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

3. TIRF Sponsors will develop a TIRF REMS Access system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

4. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF

medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

5. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. This will be accomplished by reconciling the *Patient-Prescriber Agreements* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.
6. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
7. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
8. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
9. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
10. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
11. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1

List of TIRF Medicines Available only through the TIRF REMS Access Program[1]

Product Name	Applicant/Sponsor	Dosage Strength	NDC#
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg	42747-221-32
		200 mcg	42747-222-32
		300 mcg	42747-223-32
		400 mcg	42747-224-32
		600 mcg	42747-226-32
		800 mcg	42747-228-32
ACTIQ® (fentanyl citrate) oral transmucosal lozenge	Cephalon, Inc.	200 mcg	63459-502-30
		400 mcg	63459-504-30
		600 mcg	63459-506-30
		800 mcg	63459-508-30
		1200 mcg	63459-512-30
		1600 mcg	63459-516-30
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg	63459-541-28
		200 mcg	63459-542-28
		400 mcg	63459-544-28
		600 mcg	63459-546-28
		800 mcg	63459-548-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01
ONSOLIS® (fentanyl buccal soluble film)	Meda Pharmaceuticals	200 mcg	0037-5200-30
		400 mcg	0037-5400-30
		600 mcg	0037-5600-30
		800 mcg	0037-5800-30
		1200 mcg	0037-5120-30

Product Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg	00093-5370-65
		400 mcg	00093-5371-65
		600 mcg	00093-5372-65
		800 mcg	00093-5373-65
		1200 mcg	00093-5374-65
		1600 mcg	00093-5375-65
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200mcg	49884-459-55
		400 mcg	49884-460-55
		600 mcg	49884-461-55
		800 mcg	49884-462-55
		1200 mcg	49884-463-55
		1600 mcg	49884-464-55
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Mallinckrodt, Inc.	200 mcg	0406-9202-30
		400 mcg	0406-9204-30
		600 mcg	0406-9206-30
		800 mcg	0406-9208-30
		1200 mcg	0406-9212-30
		1600 mcg	0406-9216-30
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55523-0072-30
		800 mcg	55523-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30

[1]Note: Adopted from FDA Orange Book available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907/S-007 and S-008

SUPPLEMENTAL APPROVAL

Mallinckrodt Inc
Attention: Jasen Wallace
675 McDonnell Boulevard
Hazelwood, MO 63042

Dear Mr. Wallace:

Please refer to your Supplemental Abbreviated New Drug Applications (sANDAs) dated December 5 and December 6, 2011 submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

We also acknowledge receipt of your amendments dated December 22 and 29, 2011.

These "Prior Approval" supplemental new drug applications provide for labeling updates and a proposed risk evaluation and mitigation strategy (REMS).

We have completed our review of these supplemental applications, as amended. They are approved effective on the date of this letter for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this ANDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for the class of transmucosal immediate-release fentanyl (TIRF) products, including OTCF, to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors. The details for the REMS requirements and the need for a single, shared system to implement the REMS for all members of the TIRF products were outlined in our REMS notification letters dated November 12, 2010 and August 19, 2011.

Your proposed REMS, submitted on December 5, 2011, with the agreed revisions and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and implementation system.

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. The individual sponsors who are part of the single shared system are collectively referred to as TIRF sponsors. This single shared system, TIRF REMS Access program, includes the following products:

NDA 021947	Fentora (fentanyl buccal tablets)
NDA 022266	Onsolis (fentanyl buccal soluble film)
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanyl) nasal spray
NDA 020747	Actiq (fentanyl citrate) oral transmucosal lozenge
ANDA 077312	Oral Transmucosal Fentanyl Citrate
ANDA 078907	Oral Transmucosal Fentanyl Citrate

Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy.

Prominently identify any submission containing a REMS proposed modification with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR ANDA 078907

PROPOSED REMS MODIFICATION

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.80 and 314.81).

If you have any questions, call Adolph Vezza, Labeling Reviewer, at 240-276-8987.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosures:
REMS
Medication Guide
Final product Labeling

(b) (4)

IMPORTANT:
Oral Transmucosal Fentanyl Citrate is available only through a restricted distribution program called the TIRF REMS ACCESS program. For more information call 1-866-822-1483 or visit www.TIRFREMSaccess.com.

Mallinckrodt

NDC 0406-9202-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **200 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- **Accidental ingestion of this medicine by a child could be harmful or fatal.**
- **Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.**
- **Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.**
- **Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.**

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **200 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 200 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **200 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
1. **Remove the oral transmucosal fentanyl citrate unit from the person's mouth.**
2. **Call for emergency medical help right away.**

While waiting for emergency help:
3. **If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.**
4. **If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.**
5. **If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.**

Information for Pharmacist
- ☐ **Discuss the oral transmucosal fentanyl citrate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting**
- ☐ **Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode**
- ☐ **Counsel the patient about disposal of partially consumed units**
- ☐ **Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide**
- ☐ **Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com**

Place pharmacy label above

Lot No

Exp

N 3 04069 20230 7

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **200 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1500200 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

(b) (4)

IMPORTANT:
Oral Transmucosal Fentanyl Citrate is available only through a restricted distribution program called the TIRF REMS ACCESS program. For more information call 1-866-822-1483 or visit www.TIRFREMSaccess.com.

Mallinckrodt

NDC 0406-9204-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **400 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- **Accidental ingestion of this medicine by a child could be harmful or fatal.**
- **Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.**
- **Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.**
- **Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.**

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30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **400 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 400 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **400 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
1. Remove the oral transmucosal fentanyl citrate unit from the person's mouth.
2. Call for emergency medical help right away.

While waiting for emergency help:
3. If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.
4. If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.
5. If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.

Information for Pharmacist
- ☐ Discuss the oral transmucosal fentanyl c trate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting
- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Counsel the patient about disposal of partially consumed units
- ☐ Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide
- ☐ Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com

Place pharmacy label above

Lot No

Exp

N 3 04089 20430 1

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30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **400 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1500400 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

(b) (4)

IMPORTANT:
Oral Transmucosal Fentanyl Citrate is available only through a restricted distribution program called the TIRF REMS ACCESS program. For more information call 1-866-822-1483 or visit www.TIRFREMSaccess.com.

Mallinckrodt

NDC 0406-9206-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **600 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- **Accidental ingestion of this medicine by a child could be harmful or fatal.**
- **Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.**
- **Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.**
- **Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.**

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **600 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 600 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **600 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
1. **Remove the oral transmucosal fentanyl citrate unit from the person's mouth.**
2. **Call for emergency medical help right away.**

While waiting for emergency help:
3. **If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.**
4. **If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.**
5. **If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.**

Information for Pharmacist
- ☐ **Discuss the oral transmucosal fentanyl citrate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting**
- ☐ **Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode**
- ☐ **Counsel the patient about disposal of partially consumed units**
- ☐ **Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide**
- ☐ **Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com**

Place pharmacy label above

Lot No

Exp

N 3 04069 20630 5

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **600 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1500600 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

Reference ID: 3066280

FDA_12371

(b) (4)

IMPORTANT:
Oral Transmucosal Fentanyl Citrate is available only through a restricted distribution program called the TIRF REMS ACCESS program. For more information call 1-866-822-1483 or visit www.TIRFREMSaccess.com.

Mallinckrodt

NDC 0406-9208-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **800 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- **Accidental ingestion of this medicine by a child could be harmful or fatal.**
- **Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.**
- **Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.**
- **Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.**

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **800 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 800 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **800 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
1. **Remove the oral transmucosal fentanyl citrate unit from the person's mouth.**
2. **Call for emergency medical help right away.**

While waiting for emergency help:
3. **If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.**
4. **If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.**
5. **If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.**

Information for Pharmacist
- ☐ **Discuss the oral transmucosal fentanyl citrate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting**
- ☐ **Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode**
- ☐ **Counsel the patient about disposal of partially consumed units**
- ☐ **Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide**
- ☐ **Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com**

Place pharmacy label above

Lot No

Exp

N 3 04068 20 30 9

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **800 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1500800 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

(b) (4)

IMPORTANT:
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Mallinckrodt

NDC 0406-9212-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **1200 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- **Accidental ingestion of this medicine by a child could be harmful or fatal.**
- **Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.**
- **Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.**
- **Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.**

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1200 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1200 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1200 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
1. **Remove the oral transmucosal fentanyl citrate unit from the person's mouth.**
2. **Call for emergency medical help right away.**

While waiting for emergency help:
3. **If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.**
4. **If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.**
5. **If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.**

Information for Pharmacist
- ☐ **Discuss the oral transmucosal fentanyl citrate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting**
- ☐ **Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode**
- ☐ **Counsel the patient about disposal of partially consumed units**
- ☐ **Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide**
- ☐ **Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com**

Place pharmacy label above

Lot No

Exp

N 3 04069 21230 6

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1200 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1501200 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

(b) (4)

IMPORTANT:
Oral Transmucosal Fentanyl Citrate is available only through a restricted distribution program called the TIRF REMS ACCESS program. For more information call 1-866-822-1483 or visit www.TIRFREMSaccess.com.

Mallinckrodt

NDC 0406-9216-30

30 Units

Only for patients already taking around-the-clock opioids (narcotics) such as fentanyl or morphine.

Oral Transmucosal Fentanyl Citrate

CII

Rx only

equivalent to **1600 mcg** fentanyl base

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of reach of children.
- Accidental ingestion of this medicine by a child could be harmful or fatal.
- Partially consumed oral transmucosal fentanyl citrate must be disposed of properly.
- Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.
- Call 1-800-223-1499 for a free Child Safety Kit with important additional information about safe use, storage, and disposal of this medicine.

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1600 mcg** fentanyl base

Each drug matrix contains fentanyl citrate equivalent to 1600 mcg fentanyl base, raspberry flavor, citric acid, confectioners sugar, dextrates, magnesium stearate, dibasic sodium phosphate, modified food starch, ethanol, water, purified shellac, propylene glycol, FD&C blue no. 1, ammonium hydroxide.

For oral transmucosal administration. See insert for dosage and administration.

Store at 20° to 25°C (68° to 77°F); excursion permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1600 mcg** fentanyl base

Only for patients already taking around the clock opioids (narcotics) such as fentanyl or morphine.

PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY. DO NOT SUBSTITUTE ORAL TRANSMUCOSAL FENTANYL CITRATE FOR OTHER FENTANYL PRODUCTS

WARNING: Keep out of the reach of children. Accidental ingestion of this medicine by a child could be harmful or fatal. Partially consumed oral transmucosal fentanyl citrate must be disposed of properly. Read enclosed oral transmucosal fentanyl citrate Medication Guide and consult your physician for important warnings and directions.

What to do if a child or an adult accidentally takes oral transmucosal fentanyl citrate
Oral transmucosal fentanyl citrate contains medicine that could be harmful or fatal to a child or an adult who has not been prescribed oral transmucosal fentanyl citrate. In these people, oral transmucosal fentanyl citrate can cause their breathing to slow down or even stop. If you think someone has accidentally taken oral transmucosal fentanyl citrate, follow these steps immediately:
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2. Call for emergency medical help right away.

While waiting for emergency help:
3. If the person has stopped breathing, give mouth-to-mouth resuscitation until emergency help arrives.
4. If the person is asleep wake them up and keep them awake by calling their name and shaking their arm or shoulder.
5. If the person seems to be breathing slowly, every 5 to 10 seconds, tell them to breathe.

Information for Pharmacist
- ☐ Discuss the oral transmucosal fentanyl citrate Child Safety Kit and counsel on need for Child Safety Kit if child at home or visiting
- ☐ Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- ☐ Counsel the patient about disposal of partially consumed units
- ☐ Instruct patients to read the enclosed oral transmucosal fentanyl citrate Medication Guide
- ☐ Oral Transmucosal Fentanyl Citrate must only be supplied through the TIRF REMS ACCESS restricted distribution program For more information call 1 866 822 1483 or visit www T RFREMSaccess com

Place pharmacy label above

Lot No

Exp

N 3 04069 21630 4

30 Units

Oral Transmucosal Fentanyl Citrate CII

equivalent to **1600 mcg** fentanyl base

To order an oral transmucosal fentanyl citrate Child Safety Kit call the oral transmucosal fentanyl citrate welcome kit Information Line: 1-800-223-1499.

Manufactured by:
Mallinckrodt Inc.
Hazelwood, MO
63042 USA

Printed in U.S.A.

1501600 Rev 12/2011

COVIDIEN™

Reference ID: 3066241

Reference ID: 3066280

FDA_12374

920212111
Oral Transmucosal Fentanyl Citrate

HIGHLIGHTS OF PRESCR B NG NFORMATION
These highlights do not include all the nfo mation needed to u e oral tran mucosal fentanyl c trate safely and effectively See full prescr b ng information for oral tran mu osal fentanyl citrate

Oral Transmu o al Fentanyl C trate oral transmu osal CII
In tial U S Approval 1968

WARNING RISK OF RESPIRATORY DEPRESSION MEDICATION ERRORS ABUSE POTENT AL
See full prescr b ng informat on for omplete boxed warning
- **Due to the risk of fatal resp ratory depress on oral transmucosal fentanyl citrate s contraindicated in opioid non tolerant patients 1) and in management of acute or postoperative pain including headache/m g a nes 4)**
- **Keep out of reach of ch ldren 5 3)**
- **U e wi h CYP3A4 inhibitors may cause fatal resp ratory dep es ion (7)**
- **When prescr b ng do not convert pat ents on a mcg per mcg bas s from any other oral transmucosal fentanyl product to oral transmucosal fentanyl cit ate (2 1 5 1)**
- **When d spensing do not substitute w th any other fentanyl products 5 1)**
- **Contains fentanyl a Schedule II controlled ubstance w th abuse liability imilar to other opio d analgesics 9 1)**
- **O al transmucosal fentanyl c trate is available only hrough a est icted program ca led the TIRF REMS ACCESS program Outpat ents hea thcare profess onals who p es ribed to outpatients pharmacies and d stributors are requ red to enroll in the p ogram 5 10)**

RECENT MA OR CHANGES

Ind cat ons and Usage (1)	12/2011
Wa nings and P ecautions T RF REMS ACCESS Program (5 10)	12/2011

INDICAT ONS AND USAGE

Oral transmuco a fentanyl c trate s an opio d agoni t indicated for he management of break hrough cancer pain in pat ents 16 years of age and o der who are al eady rece v ng and who are tolerant to around the clock op oid therapy for the r underly ng pers stent cancer pain (1)
L mitations of U e
Oral t ansmucosal fentanyl c trate may be d spen ed only to patients enrolled n the TIRF REMS ACCESS prog am (1)

DOSAGE AND ADMINISTRAT ON

- Patients must requi e and use around the clo k opio ds when tak ng oral t an mucosal fentanyl c trate (1)
- Init al dose of oral t an mucosal fentanyl c trate 200 mcg Presc ibe an in tial supply of six 200 m g oral t an mucosal fentanyl c trate units (2 1)
- Ind vidua ly titrate to a tole able dose that provides adequate analges a us ng s ngle oral transmu o al fentanyl citrate dosage un t per b eakthrough can er pa n ep sode (2 1)
- No more han two doses can be taken per breakthrough pain episode (2 2)
- Wait at least 4 hours before t eating another epi ode of b eakthrough pain w th oral transmucosal fentanyl it ate (2 3)
- L m t onsumption to four or fewer units per day once succes ful dose s found (2 3)

DOSAGE FORMS AND STRENGTHS

- Solid o al transmuco al lozenge n 200 m g 400 mcg 600 m g 800 mcg 1200 m g and 1600 m g (3)

CONTRAIND CATIONS

- Opio d non tolerant patients 4)
- Management of acute or postope at ve pa n including h ada he/m gra nes and dental pa n 4)
- Intole ance or hype sensitiv ty to fentanyl or components of o al transmuco al fentanyl citrate (4)

WARNINGS AND PRECAUTIONS

- Clin cally s gn ficant espi atory and CNS dep ess on can occur Monitor pat ents accordingly (5 1)
- Fu l and part ally consumed oral t an mucosal fentanyl c trate units ontain med c ne that can be fatal to a chi d En u e p oper sto age and d sposal Inter m afe torage ontainer available ("oral t an mucosal fentanyl c trate Chi d Safety K t") (5 3)
- Use wi h other CNS depres ants and potent cytochrome P450 3A4 nh bito s may increa e dep essant effects including re p rato y depres ion hypotension and profound sedation Consider dosage adju tments if warranted (5 4)
- T trate oral t an mucosal fentanyl citrate autiously in patients w th chron c obst u tive pulmonary d sease or pre ex sting medical ond tions predispos ng them to respi atory dep ession and in patients sus eptible to int a ranial effects of CO_2 retention (5 6 5 7)

ADVERSE REACT ONS

Mo t common frequency ≥5%) nausea dizz ness somnolence vomiting a then a and headache dy pnea const pation anx ety confus on dep ession a h and insomn a (6 1)

To report SUSPECTED ADVERSE REACT ONS contact Mall nckrodt Inc at 1 800 778 7898 or FDA at 1 800 FDA 1088 or *www fda gov/medwatch*

DRUG NTERACT ONS

See Boxed Warn ng and Wa nings and P ecautions (5 4 7)

USE IN SPEC FIC POPULATIONS

- Adm nister oral transmucosal fentanyl it ate wi h caut on to patients w th liver or kidney dysfunct on 8 6)

See 17 for PATIENT COUNSELING INFORMATION and Medicat on Guide

Revi ed December 2011

FULL PRESCRIBING INFORMAT ON CONTENTS*

*Sections or subse tions om tted from the Ful Presc ib ng Informat on a e not listed

FULL PRESCRIB NG NFORMAT ON

WARNING RISK OF RESPIRATORY DEPRESSION MEDICATION ERRORS ABUSE POTENT AL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in pat ents treated w th oral transmucosal fentanyl citrate nclud ng follow ng use n op o d non tolerant patients and improper dos ng The subst tution of oral transmucosal fentanyl citrate for any other fentanyl product may re u t n fatal overdose

Due to the risk of resp ratory dep e sion oral tran mucosal fentanyl citrate is cont a nd cated n the management of acute or postoperative pain including headache/migraine and n op o d non tolerant patients *[see Contraindi at ons (4]*

Death has been reported in ch ldren who have accidenta ly ingested oral transmucosal fentanyl itrate Oral transmucosal fentanyl cit ate must be kept out of reach of ch ldren *[see Pat ent Counseling Informat on (17 3) and How Suppl ed Storage and Handling 16 1)]*

The concomitant use of o al t ansmucosal fentanyl it ate w th CYP3A4 nhibitors may esult in an n rease n fentanyl plasma concentrat ons and may cause potentially fatal resp ratory depress on *[ee Drug Inte actions (7)]*

MED CATION ERRORS

Substantial d fferences exist in the pharmacokinetic profile of o al transmuco al fentanyl cit ate compared to other fentanyl products that result in clinica ly mportant d fferences n the extent of absorption of fentanyl that could resu t in fatal overdose

- **When prescr b ng do not convert patients on a mcg per mcg bas s from any other fentanyl products to oral transmu osal fentanyl c trate *[see Dosage and Administration 2 1]***
- **When d spensing do not substitute an oral transmucosal fentanyl citrate prescript on for other fentanyl products**

ABUSE POTENT AL

O al transmucosal fentanyl citrate contains fentanyl an opioid agon st and a Schedule II controlled substance with an abuse liabil ty s milar to other opioid analgesics Oral t ansmucosal fentanyl citrate can be abused n a manner sim lar to other op oid agonists legal or ll cit This should be considered when p es ribing or dispensing oral t ansmucosal fentanyl citrate in s tuat ons where the phys cian or pharmacist is concerned about an increased risk of misuse abuse or divers on

Becau e of the r sk for misuse abuse addiction and overdose oral transmucosal fentanyl cit ate is available only th ough a rest icted program requ red by he Food and Drug Admin stration called a R sk Evaluation and Mit gation Strategy (REMS) Under the T ansmucosal Immediate Release Fentanyl (T RF) REMS ACCESS program outpat ents healthca e profes ionals who p e cr be to outpatients pharmacies and d str butors must en o l in he program *[see Warnings and Precaut ons 5 10)]* Fu ther nformation s available at www TIRFREMSaccess com or by ca l ng 1 866 822 1483

1 NDICATIONS AND USAGE

Oral transmucosal fentanyl cit ate is indi ated for he management of b eakthrough pain in cancer patients 16 years of age and older who are already eceiv ng and who a e tolerant to a ound he lock op oid he apy for the r underlying pers stent cancer pa n Patients cons dered op o d tolerant are those who a e tak ng around the clock med c ne consi ting of at least 60 mg of oral morph ne daily at least 25 mcg of transdermal fentanyl/hour at lea t 30 mg of oral oxycodone daily at least 8 mg of oral hydromo phone da ly at least 25 mg oral oxymo phone da ly or an equ analgesic dose of another opioid daily for a week or longer Patients must emain on around the clo k opio ds when tak ng oral t an mucosal fentanyl c trate

Th s product **mu t not** be used n opioid non tolerant patients because life hreatening espi atory depres ion and death cou d occur at any dose n pat ents not on a chronic regimen of op oids For th s eason o al transmucosal fentanyl it ate s ontraind cated n the management of acute or po toperat ve pa n

Oral transmucosal fentanyl c trate s ntended to be used only in the ca e of opio d tole ant cancer patients and only by oncolog sts and pa n spec al sts who a e knowledgeable of and sk lled in the u e of Schedule l opioids to treat cancer pain

L m tat ons of Use

As a part of the Transmucosal Immediate Release Fentanyl TIRF) REMS ACCESS program oral t ansmucosal fentanyl cit ate may be d spen ed only to outpatients enrolled in he program *[see Wa nings and P ecautions (5 10]* For inpat ent adm n st ation of oral t ansmucosal fentanyl it ate (e g hospitals hosp ces and long term care fac l ties that presc ibe for inpat ent use) patient and pre criber enro lment is not requi ed

2 DOSAGE AND ADMINISTRAT ON

Heal hcare professionals who pre cribe o al transmucosal fentanyl citrate on an outpatient bas s must enroll n the TIRF REMS ACCESS p og am and comply w th he requ rements of the REMS to ensure safe u e of oral t ansmucosal fentanyl c trate *[see Warnings and Pre autions (5 10]*

As w th a l op oids the afety of pat ents u ing such p oducts s dependent on hea th ca e profes ionals presc ibing them n st ict confo mity w th their approved labeling w th e pe t to pat ent elect on dos ng and proper cond tions for use

2 1 Init al Dose

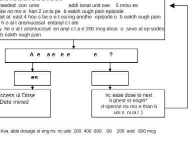
Individua ly tit ate o al transmucosal fentanyl c trate to a dose that p ovides adequate analgesia and minimizes side effects The nit al do e of oral t ansmucosal fentanyl c trate to treat episodes of b eakthrough cancer pain s **always** 200 mcg The oral transmucosal fentanyl c trate unit should be con umed over 15 minutes Pat ents shou d be pres ribed an initial t trat on supply of s x 200 mcg oral t ansmucosal fentanyl c trate units thus limit ng the number of units n the home dur ng t tration Patients should use up all units befo e ncreas ng to a higher dose to prevent confus on and poss ble ove do e

2 2 Dose T tration

F om h s initial dose closely fo low pat ents and change the dosage level unt l the pat ent eaches a do e that provides adequate analges a us ng a ingle oral transmu osal fentanyl citrate do age unit per b eakthrough cancer pain ep sode If signs of excess ve opio d effects appear before the unit s consumed the do age unit should be emoved from the patient's mouth mmed ately d sposed of p ope ly and ubsequent do es shou d be dec ea ed Patients should ecord their use of oral transmucosal fentanyl c t ate over several ep sodes of break h ough cancer pa n and eview the r expe ience wi h the r phys cians to determ ne if a dosage adjustment is war anted

In cases whe e the b eakthrough pain ep sode s not relieved 15 minutes after complet on of the oral t ansmucosal fentanyl c trate unit (30 minutes after the tart of he unit) patients may take **ONLY ONE** add t onal dose of the same trength for hat episode Thus pat ents shou d take a maximum of two doses of o al transmucosal fentanyl cit ate for any breakthrough pa n epi ode

Patients must wa t **at least 4 hours** before treat ng another ep sode of breakth ough pa n w th o al transmuco al fentanyl citrate To reduce he r sk of overdos ng dur ng t trat on patients should have only one st ength of o al transmuco al fentanyl citrate available at any one t me



*Ava able dosage st eng hs nc ude 200 400 600 00 200 and 600 mcg

2 3 Maintenance Dosing

Once titrated to an effe tive dose patients should gene ally use **ONLY ONE** oral t ansmucosal fentanyl c t ate unit of the app opriate strength per breakthrough pa n epi ode

On those o casions when the breakth ough pa n ep sode is not relieved 15 minutes a ter omplet on of the o al transmucosal fentanyl it ate un t patient may take **ONLY ONE** add t onal dose using the same st eng h for that epi ode

Patients MUST wait **at lea t 4 hours** before treat ng another ep sode of breakth ough pa n with oral t an mucosal fentanyl c trate

Once a succes ful dose has been found (i e an average ep sode s t eated with a s ngle un t) pat ents hou d l m t onsumption to four or fewer un ts per day

Dosage adjustment of oral transmu o al fentanyl citrate may be requi ed in some patients in order to ontinue to provide adequate elief of breakth ough pa n

Genera ly he oral t ansmucosal fentanyl c trate dose should be inc ea ed only when a s ngle adm nistrat on of the u rent do e fa ls to adequately treat the breakthrough pain episode for several consecut ve ep sodes

f the pat ent exper ences greater han four b eakthrough pain ep sodes per day he dose of the maintenance (around the clock) opio d used for persi tent pa n should be e evaluated

2 4 Adm n stration of Oral Transmuco al Fentanyl Citrate

Open the bli ter package wi h sc ssors immediately pr or to product use The patient shou d place the oral transmucosal fentanyl c trate unit n his or her mou h between the cheek and lower gum occa ionally mov ng the d ug mat ix from one s de to the o her us ng the handle The oral transmucosal fentanyl c trate unit should be sucked not chewed A unit dose of oral transmucosal fentanyl c t ate if chewed and swallowed might resu t in lower peak oncent at ons and lower bioavailability than when consumed as di ected *[see Cl n cal Pharma ology 12 3)]*

The oral t an mucosal fentanyl c trate unit should be consumed over a 15 minute period Longer or ho ter consumption times may produce less efficacy than epo ted n oral transmucosal fentanyl it ate l n cal tr als If s gns of excess ve op oid effects appear before the unit s onsumed emove he drug matr x from the pat ent's mou h immediately and de rease future do es

2 5 D scont nuation of O al Transmucosal Fentanyl Citrate

For pat ents equ r ng d scont nuation of opio ds a gradual downward tit ation is recommended because it is not known at what dose level the op oid may be discont nued w thout p oduc ng the signs and symptoms of abrupt w thdrawal

3 DOSAGE FORMS AND STRENGTHS

Ea h dosage unit has white to off white color and is a solid d ug mat ix on a handle Ea h st eng h is ma ked on he ind vidual sol d drug matr x and the handle tag *[see How Suppl ed/Sto age and Handl ng (16 3]*

Available St engths	
Dosage Strength fentanyl base)	**Imprint**
200 mcg	FENTANYL 200 MCG
400 mcg	FENTANYL 400 MCG
600 mcg	FENTANYL 600 MCG
800 mcg	FENTANYL 800 MCG
1200 mcg	FENTANYL 1200 MCG
1600 mcg	FENTANYL 1600 MCG

4 CONTRAINDICATIONS

Oral transmuco al fentanyl it ate is cont aindicated n op oid non tole ant patients O al t ansmucosal fentanyl citrate is cont aindicated n the management of acute or postope at ve pain includ ng headache/mig aine Life threaten ng resp ratory depress on and death could occur at any do e n opio d non tole ant pat ents

Patients cons de ed opio d tolerant are those who are tak ng around the clock med c ne consi ting of at least 60 mg of oral mo ph ne da ly at least 25 mcg of transde mal fentanyl hour at least 30 mg of oral oxycodone da ly at lea t 8 mg of oral hydromo phone da ly at least 25 mg o al oxymorphone daily or an equianalges c dose of ano her opio d da ly for a week or longer

Oral transmucosal fentanyl c trate is cont a ndicated n pat ents w th known intolerance or hype sensit vity to any of its components or he drug fentanyl Anaphylaxis and hypersensit vity have been reported n as o iat on w th he use of o al transmucosal fentanyl c trate

5 WARN NGS AND PRECAUTIONS

See Boxed Wa n ng **WARNING RISK OF RESP RATORY DEPRESSION MEDICATION ERRORS ABUSE POTENTIAL**

5 1 Respi atory Depression

Resp ratory depress on s he chief hazard of op oid agon sts ncluding fentanyl he act ve ng edient in o al transmucosal fentanyl c trate Re pirato y depres ion s more likely to occur in patients with unde lying respi atory disorde s and e derly or deb l tated patients usua ly following large in tial doses in opioid non tolerant pat ents or when opio ds a e g ven in conjunct on w th o her drugs that depress re p rat on

Resp ratory depress on f om op oids is manifested by a edu ed urge to brea he and a de reased ate of espiration often assoc ated with the "s gh ng" pa tern of b eathing (deep brea hs separated by abno mally long pauses) Ca bon diox de retention from opio d induced espiratory depres ion can exacerbate the sedat ng effects of op oids Th s makes overdoses involving drugs w th sedat ve p ope ties and opio ds e pe ially dangerous

5 2 Important Information Regard ng Prescr bing and D spensing

When prescribing DO NOT convert a pat ent to oral transmucosal fentanyl citrate f om any other fentanyl product on a mcg per mcg basis as oral t an mucosal fentanyl c trate and other fentanyl p oducts are not equ valent on a m crogram per m crogram basis

Oral transmucosal fentanyl it ate s NOT a generic vers on of Fentora® (fentanyl c trate buccal tablet) **When d spens ng DO NOT substitute an oral transmucosal fentanyl c trate prescr pt on for a Fentora prescr ption under any ircumstances Fentora and o al transmuco al fentanyl citrate are not equivalent** Substant al d fferences ex st n the pharma ok netic profile of oral transmucosal fentanyl c trate compared to o her fentanyl p oducts ncluding Fentora hat re u t in l n cally mportant differences in the ate and extent of abso ption of fentanyl **As a result of these differences the substitut on of oral transmucosal fentanyl c trate for any other fentanyl product may result in a fatal overdose**

There are no safe onversion d rections available for patients on any other fentanyl products (Note This includes oral t ansdermal or parenteral formulations of fentanyl) The efore for opio d tolerant patients he in tial dose of oral transmucosal fentanyl it ate hou d **always be** 200 mcg Each patient should be indiv dually t trated to provide adequate analges a wh le min miz ng s de effects *[see Dosage and Admini tration 2 2)]*

5 3 Pat ent Caregiver Instructions

Patients and the r careg vers must be instructed that oral tran mucosal fentanyl c trate conta ns a medi ine in an amount which can be fatal to a child Death has been eported in children who have accidenta ly ingested oral t ansmucosal fentanyl c trate Pat ents and their caregi e s mu t be nstructed to keep bo h used and unused dosage units out of he reach of chi dren While all units should be disposed of immediately after use part ally consumed un ts epresent a special r sk to ch ldren In the event that a un t s not completely consumed t must be properly disposed as soon as poss ble *[see How Suppl ed/Sto age and Handl ng 16 1 16 2) Pat ent Counseling Info mat on (17 3) and Medi ation Gu de]*

Phys cians and di pens ng pharmac sts must spec fi a ly question patients or caregi e s about the p esence of chi dren n the home (on a full t me or v siting bas s) and counsel them regarding the dangers to h ld en f om nadve tent exposu e

Oral transmucosal fentanyl citrate could be fatal to ind viduals for whom t s not presc ibed and for those who a e not opioid tolerant

5 4 Addit ve CNS Depressant Effects

The concom tant u e of oral transmucosal fentanyl citrate w th other CNS depre sants n luding o her op oids sedat ves or hypnot cs general ane theti s phenothiaz nes tranquil zers skeletal muscle elaxants sedat ng antihi tamines and alcohol c beverages may produce increased dep essant effects (e g resp ratory dep ession hypotension and profound sedat on) Concomitant use with potent nh bito s of cytochrome P450 3A4 soform (e g ery h omyc n ketoconazole and e tain protease inh b tor) may ncrease fentanyl le els esult ng in inc eased depressant effects *[see Drug Interactions (7)]*

Patients on con omitant CNS depre sants must be monitored for a change in opio d effects Cons derat on should be given to adju ting the dose of o al transmucosal fentanyl cit ate if wa ranted

5 5 Effects on Ability to Drive and Use Machines

Op o d analge ics impa r the mental and/or phys cal ability requi ed for he perfo mance of potent ally dangerous tasks (e g driv ng a car or operating machinery) Warn pat ents taking o al transmu o al fentanyl citrate of these dangers and counsel them accord ngly

5 6 Chronic Pulmonary Disease

Because potent opio ds can cause respi atory depress on titrate oral t ansmucosal fentanyl citrate w th aution in patients with chronic obstruct ve pulmona y d sease or p e exi ting medical ond t ons pred sposing them to respi atory depress on In such pat ents even normal he apeutic doses of o al transmu osal fentanyl c trate may fu ther de rease respi atory dri e to the po nt of espi atory failure

5 7 Head Injur es and Increased Intracranial Pressure

Adm nister o al transmu o al fentanyl c trate w th extreme caut on n pat ents who may be pa ti ularly sus eptible to the int a ranial effects of CO_2 etention such as those w th ev dence of inc ea ed ntracran al p essure or impai ed consc ousness Opioids may obscure the clin cal course of a patient w th a head njury and should be used only if clin cally warranted

5 8 Ca d ac Disease

Intravenous fentanyl may p odu e bradycardia Therefo e use oral transmucosal fentanyl citrate with aution n patients wi h bradya rhythmias

5 9 MAO Inhibitors

Oral transmucosal fentanyl citrate is not ecommended for use in patients who have eceived MAO nh bito s wi h n 14 days becau e seve e and unpred ctable potentiation by MAO nh bito s has been reported w th op oid analge ics

5 10 Transmucosal Immediate Release Fentanyl (TIRF) R sk Evaluation and Mit gat on Strategy (REMS) Program

Because of the isk for m suse abuse addiction and overdose *[See Drug Abuse and Dependen e 9)]* oral t an mucosal fentanyl c trate s ava lable only hrough a e tr cted prog am ca l the T RF REMS ACCESS p og am Under the TIRF REMS ACCESS program outpat ents heal hcare professionals who pres ribed for outpat ent use pharmacies and d str butors mu t enro l n the program For inpat ent adm nistrat on (e g hosp tals ho p ces and long te m are facilities that p escr be for npatient use) of o al transmucosal fentanyl citrate pat ent and prescr ber en ollment s not requ red

Requi ed components of the T RF REMS ACCESS program are

- Hea thcare p ofess onals who presc ibe o al transmu o al fentanyl c trate for outpat ent use must review he presc iber educational mater als for the TIRF REMS ACCESS program en oll n the p ogram and comply with the REMS requ rements
- To rece ve oral transmuco al fentanyl c trate outpat ents mu t understand the isks and benefits and sign a Patient Pre criber Agreement
- Pharmacies that di pense o al transmucosal fentanyl citrate mu t enroll n the program and agree to omply with he REMS equ rements
- Wholesale s and d str butors that dist ibute oral transmucosal fentanyl it ate must enro l n the p ogram and distribute only to au ho ized pharmacies

Fu ther nformation includ ng a l st of qual fied pha macies dist ibutors s ava lable at www TIRFREMSacce s com or by all ng 1 866 822 1483

6 ADVERSE REACTIONS

6 1 Clinical Stud es Experience

The safety of oral t an mucosal fentanyl c trate has been evaluated in 257 opioid tolerant chron c cancer pain patients The durat on of oral transmucosal fentanyl cit ate u e var ed dur ng the open label study Some patients were followed for over 21 months The average duration of therapy in the open label study was 129 days

he adverse react ons seen w th oral transmucosal fentanyl cit ate a e typ cal opio d s de effects F equently these adverse react ons wi l ease or decrease n ntensity w th ontinued use of oral t ansmucosal fentanyl c trate as the patient is titrated to the p oper dose Expect opio d s de effects and manage hem acco d ngly

The most ser ous adve se ea tions assoc ated with all op o ds nclud ng oral t an mucosal fentanyl c trate are resp ratory depress on (potentia ly leading to apnea or espi atory a rest) ir ulatory dep ession hypotension and shock Follow all patients for symptoms of espiratory depres ion

Because the cl nical t ials of ora transmucosal fentanyl citrate were des gned to evaluate safety and efficacy n t eating b eakthrough cancer pain all patients we e al o taking on omitant opioids such as susta ned release morphine or transde mal fentanyl for their per istent cancer pain The adver e event data presented here eflect the actual percentage of pat ents expe iencing ea h adverse effect among pat ents who received o al t ansmucosal fentanyl cit ate for breakthrough cancer pa n along w th a concom tant op oid for per istent cancer pain There has been no attempt to correct for concom tant u e of other op oids duration of oral t an mucosal fentanyl c trate the apy or cancer related symptoms Adverse react ons are included regardless of causality or sever ty

Because cl nical t ials a e conducted under widely vary ng conditions adverse react on rates observed in he clini al trials of a drug cannot be di ectly compared to rates in the clin cal tr als of ano her drug and may not eflect the rates observed in p acti e

Th ee short term cl nical t ials w th im lar t trat on schemes we e conducted n 257 pat ents with mal gnancy and b eakthrough cancer pain Data are available for 254 of these pat ents The goal of tit ation in hese tr als was to find the dose of o al transmucosal fentanyl cit ate hat p ov ded adequate analge ia wi h acceptable s de effects (suc e sful dose) Pat ents were t trated from a low dose to a successful do e n a manner s m lar to current t tration dos ng guidel nes **Table 1** l sts by do e groups adverse reactions wi h an ove all frequency of 1% or g eater that occu red dur ng titrat on and are ommonly a sociated w th opio d admin st ation or are of part cular clin cal inte e t The ability to assign a dose response relationship to these adverse eact ons is l m ted by he t trat on schemes used n hese stud es Adve se eactions are l sted n descend ng order of frequency with n each body system

Table 1
Percent of Patients w th Spec fic Adverse Events Commonly Assoc ated with Op o d Adm n stration or of Part cular Clinical Interest Which Occu red During Tit at on (Events in 1% or More of Pat ents)

Dose Group	Percentage of Pat ents Reporting Event				
	200 600 mcg (n=230)	**800 1400 mcg (n=138)**	**1600 mcg (n=54)**	**>1600 m g (n=41)**	**Any Dose* (n=254)**
Body As A Whole					
Asthenia	6	4	0	7	9
Headache	3	4	6	5	6
Accidental Injury	1	1	4	0	2
Digest ve					
Nausea	14	15	11	22	23
Vomit ng	7	6	6	15	12
Con tipation	1	4	2	0	4
Nervous					
Dizziness	10	16	6	15	17
Somnolence	9	9	11	20	17
Confus on	1	6	2	0	4
Anx ety	3	0	2	0	3
Abnormal Ga t	0	1	4	0	2
Dry Mouth	1	1	2	0	2
Ne vousne s	1	1	0	0	2
Vasod latation	2	0	2	0	2
Ha lucinations	0	1	2	2	1
Insomnia	0	1	2	0	1
Thinking Abnormal	0	1	2	0	1
Vertigo	1	0	0	0	1
Respiratory					
Dyspnea	2	3	6	5	4
Sk n					
Pruritus	1	0	0	5	2
Rash	1	1	0	2	2
Sweating	1	1	2	2	2
Special Senses					
Abnormal Vision	1	0	2	0	2

* Any Dose = A pat ent who experienced the ame adverse event at mu t ple doses was only counted once

The fo low ng adverse react ons not reflected in **Table 1** occu red dur ng t tration wi h an ove a l f equency of 1% or greater and a e listed n descending o der of f equency w thin each body sy tem

Body as a Whole Pain fever abdominal pain ch lls back pa n chest pa n nfect on
Cardiovascular Mig aine
Digestive Diar hea dyspeps a flatulence
Metabolic and Nutr tional Pe ipheral edema dehydrat on
Nervous Hypesthesia
Respiratory Pha yng tis cough inc ea ed

The follow ng react ons occur ed during tit ation wi h an overa l frequency of less than 1% and a e listed in descend ng order of frequen y w thin each body ystem

Body as a Whole Flu syndrome absce s bone pain
Cardiovascular Deep thrombophlebitis hyperten ion hypoten ion
Digestive Ano exia eructation esophageal tenosis fecal impaction gum hemo rhage mouth ul erat on o al mon l asis
Hemic and Lymphatic Anemia leukopenia
Metabolic and Nutr tional dema hype calcem a we ght loss
Musculoskeletal Myalgia patholog cal fracture myas hen a
Nervous Abnormal dreams urinary etent on agitation amnes a emotional lab l ty euphor a ncoordinat on l bido decreased neuropathy pare thesia speech disorder
Respiratory Hemoptysis pleu al effus on rhin tis a thma hiccup pneumonia e p rato y nsufficiency sputum n reased
Skin and Appendages Alopecia exfol ative dermat t s
Special Senses Taste perver ion
Urogenital Vag nal hemo rhage dysuria hematu ia ur nary ncontinence ur na y t act infection

A long te m extension study was conducted in 156 patients with mal gnancy and b eakthrough cancer pain who were treated for an ave age of 129 days Data are ava lable for 152 of these pat ents **Table 2** li ts by do e g oups adverse reactions w th an ove all frequency of 1% or g eater that occur ed dur ng he long term extens on tudy and are commonly as ociated with opio d adm nistrat on or a e of part cular l n cal ntere t Adverse rea tions are l sted in descend ng order of f equen y with n each body ystem

Table 2
Percent of Patients w th Adverse Events Commonly A soc ated with Opio d Adm n stration or of Particular Clinical Interest Whi h Occur ed During Long Term T eatment (Events in 1% or More of Patients)

Dose Group	Percentage of Patients Reporting Event				
	200 600 mcg (n=98)	**800 1400 mcg (n=83)**	**1600 mcg (n=53)**	**>1600 mcg (n=27)**	**Any Dose* (n=152)**
Body As A Whole					
Asthen a	25	30	17	15	38
Headache	12	17	13	4	20
Accidental In u y	4	6	4	7	9
Hypertonia	2	2	2	0	3
D gest ve					
Nausea	31	36	25	26	45
Vomit ng	21	28	15	7	31
Constipation	14	11	13	4	20
Intest nal Obstruct on	0	2	4	0	3
Card ovascular					
Hypertension	1	1	0	0	1
Nervous					
Dizziness	12	10	9	0	16
Anx ety	9	8	8	7	15
Somnolence	8	13	8	7	15
Confus on	2	5	13	7	10
Depress on	9	4	2	7	9
Insomnia	5	1	8	4	7
Abnormal Ga t	5	1	0	0	4
Dry Mouth	3	1	2	4	4
Nervousness	2	2	0	4	3
Stupor	4	1	0	0	3
Vasod latation	1	1	4	0	3
Thinking Abnormal	2	1	0	0	2
Abnormal Dreams	1	1	0	0	1
Convul ion	0	1	2	0	1
Myoclonus	0	0	4	0	1
Tremor	0	1	2	0	1
Vertigo	0	0	4	0	1
Respiratory					
Dyspnea	15	16	8	7	22
Sk n					
Rash	3	5	8	4	8
Sweating	3	2	2	0	4
Pruritus	2	0	2	0	2
Special Sen es					
Abnormal Vision	2	2	0	0	3
Urogen tal					
Urinary Retent on	1	2	0	0	2

* Any Dose = A pat ent who experienced the ame adverse event at mu t ple doses was only counted once

The fo low ng ea tions not efle ted n **Table 2** occur ed w th an overa l frequency of 1% or greater n the long te m exten ion tudy and a e listed in descending o der of f equency w thin each body sy tem

Body as a Whole Pa n fever ba k pain abdominal pa n he t pain flu syndrome chi ls nfect on abdomen enla ged bone pain as ites ep is neck pain vi al infection fungal infection cachexia ce lulit s malaise pelvic pa n
Cardiovascular Deep thrombophlebitis migra ne palpitation vascular di order
Digestive Diar hea ano exia dyspeps a dysphag a oral mon lia is mou h ulcerat on rectal d sorder tomat t s flatulence gastrointe tinal hemor hage ging vit s jaund ce pe iodontal abscess e uctat on glossitis ectal hemorrhage
Hemic and Lymphatic Anem a leukopen a thrombocytopen a ecchymos s lymphadenopa hy lymphedema pancytopen a
Metabolic and Nutrit onal Pe ipheral edema edema dehydrat on we ght loss hyperglycem a hypokalem a hypercal emia hypomagnesem a
Musculoskeletal Myalgia patholog cal fracture jo nt d sorder leg c amps arthralgia bone d sorder
Nervous Hypesthesia pare thesia hypokines a neu opa hy speech d sorder
Respiratory Cough increa ed pharyngitis pneumonia h nit s s nu it s bronchitis ep staxis asthma hemoptys s sputum increa ed
Skin and Appendages Skin ulcer alopecia
Special Senses Tinn tus conjunct vit s ear diso der taste perver ion
Urogenital Ur nary tract infection ur nary ncontinence breast pain dysu ia hematur a scrotal edema hyd onephros s k dney fa lure ur nary u gency u inat on impa red breast neoplasm vag nal hemorrhage vaginitis

The follow ng react ons occur ed w th a frequency of less than 1% in he long te m exten ion study and are listed in de cend ng o der of f equency w thin ea h body sy tem

Body as a Whole Allergic react on cyst fa e edema flank pain granuloma bacterial nfect on nject on s te pa n mucous membrane d sorder neck rig dity
Cardiovascular Ang na pector s hemorrhage hypotension per phe al vascular di o der postural hypotens on tachycardia
Digestive Che l t s esophag tis fecal incont nence gast oenteritis gast ointestinal disorder gum hemorrhage hemorrhage of colon hepatorenal syndrome liver tenderness tooth ca ies too h di order
Hemic and Lymphatic Bleeding time n reased
Metabolic and Nutritional A idosis generalized edema hypocalcem a hypogly emia hyponat emia hypoproteinem a thirst
Musculoskeletal Arthr t s muscle at ophy myopathy synovitis tendon d sorder
Nervous A ute b ain syndrome ag tat on cereb al is hemia facial pa aly is foot d op hallucinat ons hem pleg a m o is ubdu al hematoma
Respiratory H ccup hyperventilat on lung diso der pneumo ho ax resp ratory fa lure vo ce a terat on
Skin and Appendages He pes zo ter ma ulopapular rash skin discolorat on u tica ia ves culobullous ra h
Special Senses Ear pain eye hemo rhage lacr mat on diso der part al pe manent deafne s partial transitory deafness
Urogenital K dney pain noctur a ol gu ia polyur a pyelonephritis

6 2 Postmarket ng Experience

Adver e reactions a e reported voluntar ly from a populat on of unce tain size and therefo e t is not always poss ble to reliably estimate the r frequency or establ sh a causal relationsh p to d ug exposure Decis ons to include these react ons n labeling a e typ cally based on one or mo e of the fo lowing fa tors (1) ser ousness of the eaction (2) frequency of the report ng or (3) strength of causal connect on to oral t an mucosal fentanyl c trate

The fo low ng adverse react ons have been identified du ing postapproval use of o al transmuco al fentanyl citrate (wh ch conta ns approx mately 2 g ams of ugar per unit)

Digestive Dental decay of vary ng sever ty includ ng dental car es tooth loss and gum line e osion
General Di o ders and Adm n strat on S te Cond tions Appli ation site eactions n luding ir itation pain and ulcer

7 DRUG INTERACTIONS

Fentanyl s metabol zed ma nly v a he human cytoch ome P450 3A4 soenzyme sy tem (CYP3A4) the efore potential nteract ons may occur when oral t an mucosal fentanyl c trate is g ven concurren ly with agents hat affect CYP3A4 activ ty The concomitant use of oral transmucosal fentanyl citrate wi h trong CYP3A4 nh bito s (e g ritona ir ketoconazole traconazole t oleandomycin clar thromyc n nelfinavir and nefazodone) or moderate CYP3A4 inhib tors (e g amprenav r ap ep tant diltiazem eryth omycin fluconazole fo amprenavir and verapami) may re u t in ncreased fentanyl plasma con entrat ons potentia ly au ing se ious adve se drug effects ncluding fatal resp ratory depress on Patients rece ving o al transmucosal fentanyl c trate concom tantly w th mode ate or strong CYP3A4 inh b tors should be carefully mon tored for an extended per od of t me Dosage inc ea e should be done conser atively

G apefruit and grapefruit ju ce dec ease CYP3A4 act vity increa ing blood concentrat ons of fentanyl thus shou d be avoided

D ugs that induce cytochrome P450 3A4 act vity may have the oppos te effects

Concomitant use of o al t an mucosal fentanyl c trate wi h an MAO inh b tor or w thin 14 days of d scontinuat on is not ecommended *[ee Wa nings and Precaut ons (5 9)]*

8 USE N SPECIFIC POPULATIONS

8 1 Pregnancy

P egnancy Category C

The e are no adequate and we l ontrolled stud es n pregnant women Oral t an mucosal fentanyl citrate shou d be used dur ng pregnancy only if the potent al benefit just fies the potential r sk to the fetus No ep demiolog cal tudies of congenital anomal es n nfants born to women treated w th fentanyl du ing p egnancy have been epo ted

Ch on c maternal treatment wi h fentanyl during p egnancy has been as o iated wi h t an ient respi atory dep e sion behavioral changes or sei u es n newborn infants cha acter st c of neonatal abstinence syndrome

In women treated acutely wi h int avenous or ep du al fentanyl dur ng labor symptoms of neonatal espiratory or neu ological depres ion were no more f equent than wou d be expe ted n nfants of unt eated mo he s

Transient neonatal muscular igid ty has been observed in infants whose mothers we e t eated with int avenous fentanyl

Fentanyl s embryocidal in rats as ev denced by ncreased esorpt ons in pregnant rats at doses of 30 mcg/kg V or 160 mcg/kg SC Convers on to human equivalent doses nd cates h s is wi h n the ange of he human recommended dosing for oral transmucosal fentanyl c trate

Fentanyl cit ate was not teratogenic when admini tered to p egnant animals Publ shed stud es demonstrated that admin stration of fentanyl (10 100 or 500 mcg/kg/day) to p egnant rats from day 7 to 21 of he r 21 day ge tat on v a mplanted m croosmot c min pumps was not teratogenic (the high dose was approx mately 3 t mes the human dose of 1600 mcg per pa n episode on a mg/m^2 bas s) Intravenous adm nistrat on of fentanyl (10 or 30 mcg/kg) to pregnant female rats f om gestation day 6 to 18 was embryo or fetal toxic and cau ed a sl gh ly increased mean delivery t me n the 30 mcg kg day group but was not te atogen c

8 2 Labor and Del very

Fentanyl ead ly passes ac oss he placenta to he fetus therefore do not use oral t ansmucosal fentanyl citrate du ing labor and delivery (n luding ae arean section) since it may cause respi atory dep ession in the fetus or in the newbo n nfant

8 3 Nurs ng Mothers

Fentanyl s exc eted in human mi k he efore do not use o al t ansmucosal fentanyl cit ate n nursing women because of the poss bility of sedation and/or espiratory depre sion in he r infants Symptoms of opioid w thdrawal may occur in infants at the cessat on of nurs ng by women us ng oral t ansmucosal fentanyl c trate

8 4 Pediat ic Use

Safety and effectiveness in ped atr c patients below 16 yea s of age have not been establ shed

In a clinical tudy 15 opio d tole ant pediatric pat ents wi h breakth ough pa n ranging in age from 5 to 15 years were treated w th o al transmucosal fentanyl it ate The study was too sma l to allow conclusions on safety and efficacy in this pat ent populat on Twelve of the fifteen op oid tolerant chi d en and adole cents aged 5 to 15 yea s n h s study eceived o al transmu o al fentanyl citrate at do es ang ng f om 200 mcg to 600 mcg The mean CV% range) dose normali ed (to 200 mcg) C_{max} and $AUC_{0\ 8}$ values were 0 87 ng/mL (51% 0 42 1 30) and 4 54 ng h/mL 42% 2 37 6 0) espect vely for ch ldren ages 5 to <11 years old (N = 3) and 0 68 ng/mL (72% 0 15 1 44) and 8 38 (192% 0 84 50 78) respectively for chi d en ages ≥11 to <16 y (N = 9)

8 5 Ger atric U e

Of the 257 patients in cl nical stud es of oral t ansmucosal fentanyl c trate in breakthrough cancer pain 61 (24%) were 65 yea s of age and older while 15 (6%) we e 75 yea s of age and older Tho e pat ents over he age of 65 years were t trated to a mean do e that was about 200 mcg less than the mean dose tit ated to by younger pat ents No difference was noted in the safety profile of the group over 65 years of age as ompared to younger pat ents in o al transmucosal fentanyl citrate cl nical t ials

Elderly pat ents have been shown to be mo e sens tive to the effects of fentanyl when adm n ste ed int avenou ly compared w th he younger populat on Therefore exerc se caut on when ndiv dua ly titrat ng oral transmucosal fentanyl it ate n elderly pat ents to p ov de adequate efficacy while m nim zing risk

8 6 Patients w th Renal or Hepat c Impai ment

Insuffic ent nformat on exi ts to make recommendat ons regard ng the use of oral transmucosal fentanyl c trate in patients w th mpai ed renal or hepat c funct on Fentanyl s metabolized p ima ily via human cytochrome P450 3A4 isoenzyme ystem and mostly elim nated n urine f he drug is used n these pat ents t should be used w th caution because of the hepat c metaboli m and renal ex ret on of fentanyl

8 7 Gender

Both male and female opioid tolerant cancer pat ents were studied for the treatment of b eakthrough cancer pa n No clin cally elevant gender differences we e noted e ther in do age requi ement or n observed ad e se eact ons

9 DRUG ABUSE AND DEPENDENCE

9 1 Contro led Substance

Fentanyl s a Schedule II contro led sub tance hat can p odu e drug dependen e of the mo ph ne type Oral t ansmucosal fentanyl c t ate may be ubject to misuse abuse and add ct on

9 2 Abuse and Add ction

Manage the handling of oral transmu o al fentanyl c trate to minimize the r sk of d vers on ncluding estr ct on of acce s and ac ount ng procedures as app opriate to the lin cal setting and as requ red by law *[ee How Suppli d Storage and Handling (16 1 16 2]*

Conce ns about abuse addiction and diver ion should not prevent the p oper management of pain However a l patients t eated with op oids equ re careful monito ing for s gns of abuse and add ction because use of opioid analgesic produ ts ca ries the r sk of addi tion even under appropr ate medical use

Add ction s a primary ch on c neurob ologic d sease wi h genet c psy hosoc al and env ronmental factors influen ing its development and man festations It s characteri ed by behavio s that include one or more of he follow ng mpai ed control over drug use ompulsi e use cont nued use desp te ha m and c aving Drug addi tion is a treatable di ea e utiliz ng a mult dis ipl nary approach but relap e s common "Drug seeking" behavior is very common n addi ts and drug abusers

Abuse and add ct on are separate and dist nct from physical dependence and tolerance Physic ans should be awa e that addict on may not be accompanied by concurrent tolerance and ymptoms of phys cal dependence in a l add cts In addit on abuse of op oids can oc ur n the absence of add ct on and is characteri ed by m suse for nonmed cal pu po es often in comb nat on w th other psychoact ve substan es S n e o al t an mucosal fentanyl c trate may be d verted for non med cal use careful record keep ng of p escr b ng nformation includ ng quantity frequency and enewal requests is strongly adv sed

P oper as essment of patients p oper p escr b ng practices pe iodic re evaluation of therapy and proper di pens ng and torage a e appropr ate measures that help to lim t abuse of op oid drugs

Hea thcare professionals should contact their State Professional Licens ng Boa d or State Contro led Substances Author ty for nformation on how to prevent and detect abuse or d version of this product

9 3 Dependence

Gu de the adm nistrat on of o al transmucosal fentanyl c trate by the response of the pat ent Phy ical dependence per se is not o d narily a concern when one is t eating a patient w th ch on c cancer pain and fear of tole ance and phys cal dependence should not deter us ng doses that adequately elieve the pa n

Op o d analges cs may cause physical dependence Phys cal dependence esults n w thdrawal symptoms n pat ents who abruptly d scontinue he drug Withdrawal also may be prec p tated through the adm n st ation of drugs with op oid antagoni t act vity e g naloxone nalmefene or mixed agon st/antagoni t analge ics (pentazoc ne buto phanol bup eno ph ne na buph ne)

Phys cal dependence usua ly does not occur to a cl nica ly ignificant deg ee until after everal weeks of cont nued op oid usage Tolerance in which increa ingly larger doses a e requi ed in order to produce he same deg ee of analgesia s n t ally manifested by a shortened durat on of analgesic effect and subsequently by decreases n the intens ty of analges a

10 OVERDOSAGE

10 1 Clinical Presentat on

The manifestat ons of oral transmucosal fentanyl it ate ove do age are expected to be im lar n nature to intravenous fentanyl and other opio ds and are an extension of ts pharmacolog cal act ons with the most ser ous s gnificant effect be ng resp ratory depress on *[ee Clin cal Pha macology (12 2]*

10 2 Immediate Management

Immed ate management of opio d overdose n ludes removal of he oral transmuco al fentanyl c trate un t f ti l n the mouth ensur ng a patent ai way phys cal and ve bal timulat on of the patient and asse sment of level of consc ousness vent latory and ci culatory tatus

10 3 Treatment of Overdosage (Acc dental Ingest on) in the Opio d NON Tolerant Person

P ovide entilatory upport obtain ntravenous a cess and employ naloxone or o her opio d antagonists as clinica ly ind cated The duration of espirato y depres ion following overdose may be longer han the effects of the opioid antagonist's act on (e g the half l fe of naloxone ranges from 30 to 81 minute) and repeated admini trat on may be nece sary Consult the package nsert of the ndividual opio d antagoni t for details about such use

10 4 Treatment of Overdose in Opioid Tolerant Patients

P ovide ventilatory support and obta n ntravenous access as cl nica ly ind cated Jud cious use of naloxone or another op oid antagonist may be war anted n some nstances but t s assoc ated wi h the r sk of p ecip tat ng an a ute wi hd awal syndrome

10 5 General Considerations for Ove dose

Management of seve e oral transmuco al fentanyl c trate o e dose includes secu ing a patent a rway as ist ng or cont oll ng vent lation establ shing ntravenous acce s and GI decontam nation by lavage and/or a tivated charcoal once he patient's airway is se u e In the presence of resp ratory dep ess on or apnea ass st or control vent lat on and admin ster oxygen as indicated

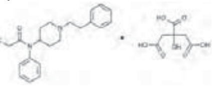
A though muscle r gid ty nterfe ing with resp rat on has not been seen following the use of o al transmucosal fentanyl cit ate this s pos ible w th fentanyl and other op oids f it occurs manage it by us ng ass sted or ontrolled vent lat on by an op oid antagon st and as a final a ternat ve by a neu omuscular block ng agent

11 DESCR PT ON

O al transmucosal fentanyl cit ate is a olid formulat on of fentanyl c trate a potent op oid analgesic ntended for oral transmucosal adm nistrat on Oral transmu osal fentanyl it ate s fo mulated as a white to off wh te olid d ug matr x on a handle that is fractu e esistant ABS plast c) under normal ond tions when used as d rected

O al transmucosal fentanyl citrate is des gned to be d ssolved lowly in the mouth to facilitate transmu o al absorpt on The handle a lows he oral transmucosal fentanyl c trate unit to be emoved from the mouth if s gns of exce sive opio d effects appear du ing admini tration

Act ve Ingred ent Fentanyl citrate USP is N (1 Phene hyl 4 p peridy) prop onan l de c trate (1 1) Fentanyl s a highly l poph l c compound (octanol water part tion coefficient at pH 7 4 s 816 1) hat s freely soluble n organic solvents and pa ingly soluble in water 1 40) The molecular we ght of he f ee base s 336 5 (the c trate sa t s 528 6) The pKa of he tert ary n trogens a e 7 3 and 8 4 The compound has the follow ng structural formula



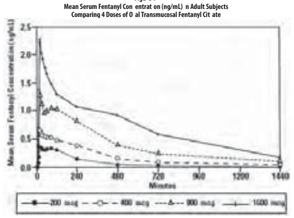
$C_{\ 2}H_{28}N_2O \cdot C_6H_8O_7$ MW = 528 59

Inact ve Ingred ents Raspberry flavor c tr c a id confectioners sugar dextrates magnesium stea ate dibas c od um phosphate mod fied food tarch ethanol water pur fied she lac propylene glycol FD&C blue no 1 ammon um hydrox de

12 CL NICAL PHARMACOLOGY

12 1 Mechani m of Act on

12 2 Pharmacodynamics



The pharmacok netic paramete s of the four strengths of o al transmucosal fentanyl citrate tested in he dose proport onal ty study a e shown in **Table 3** The mean C_{max} anged from 0 39 to 2 51 ng/mL The med an t me of max mum plasma concentration T_{max}) across he e four doses of oral t an mucosal fentanyl c trate var ed from 20 to 40 minutes (range of 20 to 480 m nutes) as measured a ter the start of adm n st ation

Table 3
Pharmacokinetic Parameters* in Adu t Subjects Receiving 200 400 800 and 1600 mcg Units of Oral Transmucosal Fentanyl C trate

Pharmacok net c Parameter	200 mcg	400 mcg	800 mcg	1600 mcg
T_{max} m nute med an (range)	40 (20 120)	25 (20 240)	25 (20 120)	20 (20 480)
C_{max} ng/mL mean (%CV)	0 39 (23)	0 75 33)	1 55 30)	2 51 (23)
AUC $_{-1440}$ ng/mL minute mean (%CV)	102 (65)	243 (67)	573 (64)	1026 67)
$t_{1/2}$ m nute mean (%CV)	193 (48)	386 (115)	381 (55)	358 (45)

* Ba ed on arterial blood samples

D str bution

Fentanyl is highly l poph l c An mal data showed hat fo lowing abso ption fentanyl s ap dly distributed to he bra n hea t lungs k dneys and spleen fo lowed by a slower redistribut on to muscles and fat The plasma p otein binding of fentanyl s 80 to 85% The ma n b nd ng prote n s alpha 1 a id glycoprote n but bo h album n and lipoprote ns cont ibute to some extent The free fract on of fentanyl ncreases w th ac dosis The mean volume of d str bution at teady state V s) was 4 L/kg

Metabol sm

Fentanyl s metabol zed n the liver and n the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform Norfentanyl was not found to be pharma ologica ly act ve n animal tudies *[see Drug Interactions (7)]*

Eliminat on

13 NONCLINICAL TOX COLOGY

14 CL NICAL STUD ES

In two dose titrat on studies 95 of 127 patients (75%) who were on stable do es of either long acting oral opio ds or transdermal fentanyl for their per istent cancer pain t trated to a succe sful dose of oral transmucosal fentanyl cit ate to treat their breakth ough cancer pa n with n the dose range offered (200 400 600 800 1200 and 1600 mcg) A "successful" dose was defined as a dose where one un t of o al transmucosal fentanyl it ate cou d be used con isten ly for at least two con ecutive days to t eat break h ough cancer pa n w thout unacceptable s de effects In he e stud es 11% of patients w thdrew due to adverse react ons and 14% w thdrew due to other reasons

The succe sful dose of oral transmucosal fentanyl c t ate for b eak hrough cancer pain was not pred cted from the daily maintenance dose of op oid used to manage the pers stent cancer pa n and s thus best determined by dose t t ation

A double bl nd pla ebo contro led crossover study was perfo med n ancer pat ents to evaluate the effect veness of o al transmu o al fentanyl it ate for the treatment of breakth ough cancer pain Of 130 pat ents who entered the study 92 patients (71%) ach eved a successful dose du ing he t tration phase The dist ibut on of successful do es s hown n **Table 4**

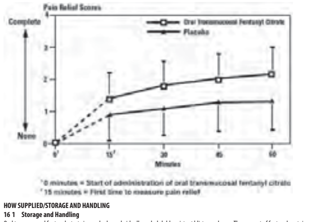
Table 4
Suc es ful Dose of Oral Transmucosal Fentanyl C trate Following Init al T tration

Oral Transmucosal Fentanyl C trate Dose	Total No %) (N=92)
200 m g	13 (14)
400 m g	19 (21)
600 m g	14 (15)
800 m g	18 (20)
1200 mcg	13 (14)
1600 mcg	15 (16)
Mean +/ SD	789 +/ 468 mcg

On average patients over 65 yea s of age tit ated to a mean dose that was about 200 m g le s han the mean dose to wh ch younger adu t patients we e t trated

O al transmucosal fentanyl c trate was admini tered beginn ng at T me 0 minutes and p oduced more pa n rel ef ompared w th placebo at 15 30 45 and 60 m nutes as measured after he start of adm nistrat on (*see* **F gure 2**) The d ffe en es we e statistica ly significant

Figure 2
Pain Rel ef (PR) Scores (Mean±SD) Du ing the Double Blind Phase
A l Pat ents w th Evaluable Ep sodes on Both Oral Transmucosal Fentanyl C trate and Placebo (N=86)



16 HOW SUPPLIED/STORAGE AND HANDLING

16 1 Storage and Handling

16 2 Disposal of O al Transmucosal Fentanyl Cit ate

Information (17 4)] Th s conta ner s to be u ed by patients or he r caregivers in the event hat a part ally consumed unit cannot be d sposed of promp ly In truct ons for usage of his container are included in the *Medicat on Guide*

Patients and membe s of the r household must be advised to d spose of any un ts emain ng f om a p escr ption as soon as they are no longer needed In truct ons a e included in *Patient Counseling Information (17 6)* and n the *Medi ation Gu de* If additional assi tance s required ca l Mallinck odt Inc at 1 800 778 7898

16 3 How Suppl ed

O al transmuco al fentanyl citrate is suppl ed n s x dosage trengths Each un t is ind vidually wrapped in a h ld esistant protective blister package These bl ster packages a e packed 30 per he f carton for use when patients have been titrated to he appropr ate dose

Each dosage un t has a white to off white color Each nd vidual solid d ug mat ix is marked w th "FENTANYL" and he st eng h of the un t ("200 MCG" "400 MCG" "600 MCG" "800 MCG" "1200 MCG" or "1600 MCG") The do age st eng h s also marked on the handle tag the blister package and the carton See blister package and carton for product nformation

Dosage Strength (fentanyl base)	Carton/Blister Package Color	NDC Number	Impr nt
200 mcg	Gray	NDC 0406 9202 30	FENTANYL 200 MCG
400 mcg	Blue	NDC 0406 9204 30	FENTANYL 400 MCG
600 mcg	Orange	NDC 0406 9206 30	FENTANYL 600 MCG
800 mcg	Purple	NDC 0406 9208 30	FENTANYL 800 MCG
1200 mcg	Green	NDC 0406 9212 30	FENTANYL 1200 MCG
1600 mcg	Bu gundy	NDC 0406 9216 30	FENTANYL 1600 MCG

Note Colors are a secondary aid in product identif cation Please be sure to confirm he printed dosage before d spensing

17 PAT ENT COUNSELING INFORMAT ON

See FDA approved pat ent label ng *(Med cat on Guide)*

17 1 Patien /Ca egiver Instructions

- Before nit ating treatment w th oral transmu o al fentanyl c trate explain the tatements below to pat ents and/or ca egivers Inst uct pat ents to read the Med cation Gu de each t me o al transmucosal fentanyl c trate s di pensed be au e new nformation may be available
  - Outpatients must be en olled in the T RF REMS ACCESS program before they can rece ve o al transmucosal fentanyl citrate
  - Allow pat ents the opportunity to ask quest ons and d scuss any concerns regarding o al transmucosal fentanyl it ate or the TIRF REMS ACCESS p ogram

17 2 Dental Care

17 3 Diabet c Patients

17 4 Oral Transmucosal Fentanyl C trate Child Safety Kit

17 5 Disposal of U ed Oral Transmu osal Fentanyl Citrate Units

17 6 Disposal of Unopened Oral Transmucosal Fentanyl C trate Un ts When No Longer Needed

MED CATION GU DE

Oral Tran mucosal Fentanyl Citrate CII

These are medical emergencies that an cause death

Read this Medicat on Guide completely before you start taking o al t ansmucosal fentanyl cit ate

What is the most impo tant information I shou d know about o al transmucosal fentanyl itrate?

Figure 1

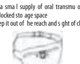


Figure 2

Figure 3

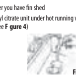


Figure 4

Figure 5

Figure 6

Figure 7

Figure 8A

Figure 8B

Figure 9A

Figure 9B

Figure 10

Figure 11

Figure 12

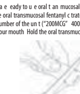


Figure 13A

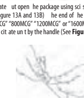


Figure 13B

Figure 14

Figure 15

Figure 16

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COVIDIEN™

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12/28/11

92021211M
Ora Transmucosa
Fentany Ctra e

SPECIMEN

MED CAT ON GU DE
Ora Transmucosa
Fentany C rate C
(or ə • ranzmu kō s • ĕn tə nĭ •sĭt r t
200 mcg, 400 mcg, 600 mcg,
800 m g, 1200 mcg, 1600 mcg

MPORTANT
Do not use ora t ansmucosa en any c tra e un ess you are regu ar y us ng another op o d pa n med c ne around-the c o k orat east one week or onger or your ancer pa n and your body s used o these med c nes (th s means that you a e op o d to erant) You can ask your hea thcare prov der f you are op o d o erant
Keep ora transmucosa fen any c rate n a safe p ace away f om ch dren
Get eme gency he p r ght away f
• a ch d takes ora ransmuco a fen any c tra e O a transmuco a en any c t ate can cause an overdose and dea h n any ch d who uses t
• an adu t who has not been pre cr bed ora ransmuco a en any c tra e uses t
• an adu t who s not a ready tak ng op o ds around- he c ock uses o a t ansmuco a fentany c trate
These are med ca eme genc es that can cau e death f poss b e, emove o a t ansmuco a entany c rate from the mou h

Read th s Med cat on Gu de ompe e y before you s art ak ng o a ransmucosa fentany c rate and ach t me you get a new p escr pt on The e may be new nf rm t n Th s M dcat on Gu de does not t ke the p ace of ta k ng o your doctor about your med a cond t on r your t eatment hare th s mpo tant nformat on w th memb rs of your hou eho d and other areg ve s

What s the most mpo tant nformat on shou d know about ora ransmu o a fen any c t ate?
Ora ransmucosa fentany c trate can cause fe threaten ng breath ng prob ems wh ch an ead to death
1 **Do not use ora t an mucosa en any c t ate f you a e not op o d to erant**
2 f you s op tak ng your around-the c ock op o d pa n med c ne for your ancer pa n ou must stop us ng o a ransmucosa fent ny c rate You may no onger be op o d to era t Ta k to your hea thc re p ov der about how o reat your pa n
3 **Use ora transmucosa fentany c t ate exact y as p escr bed by your hea thcare prov der**
   - You must not use more than 1 un t of ora ransmuco a fen any c ra e at a t me and no mo e th n 2 un ts of ora tr nsmu osa fentany c t ate dur ng each ep sode of b eakth ough can er pa n
   - You must wa t at ea t 4 hours before tr at ng a new ep sode of b eak hrough pa n **See the Med at on Gu de sect on "How hou d use o a transmucosa fentany c tra e" and the Pat ent nstruct ons for U e at the end of h s Med cat on Gu de about how o use ora ransmu o a fentany c tra e the r ght way**
4 **Do not sw t h f om o a ransmu o a entany c trate o o her med c nes hat conta n fentany w thout a k ng o your hea th are prov der** he amount of fentany n a d se of ora ran muco a fentany c t ate s not the ame as he amount f fentany n o her med c nes that onta n fen any Your h a hcare p ov d r w p escr be a s art ng d se of ora ran muc sa fen any c tr te hat may be d fferent t an oth r fentany onta n ng med c nes you may have been ak ng
5 **Do not** use ora tran muc sa fentany c ra e f r hort-te m pa n that you wou d expect to go away n a few days su h as
   - pa n after su gery
   - headache or m g a ne
   - denta pa n
6 **Never g ve ora t an mucosa en any c t ate o anyone e se,** even f hey have he same symp oms you have t may ha m hem or ev n cause death

Ora tr nsmu osa fentany c tra e s a fede a y con ro d su stan e (C becau e t s a s rong op o d (nar ot c pa n med c ne that an be m su ed by peop e who abuse p escr pt on med c nes or tre t drugs
- **Prevent theft, m suse or abuse Keep o a transmucosa entany c rate n a sa e pace** to pote t t f om be ng to en Ora t ansmucosa fen any c rate an be a ta get for peop e who abuse op o d (nar ot c med c nes or s reet drugs
- **Se ng or g v ng away h s med c ne s aga nst the aw**

O a tr n muc sa fen any c tra e s ava ab e on y th ough a p ogram a ed the **T**ansmuco a mmed ate **R**e ase **F**entany (**T**RF **R** sk **E**va at n and **M** t gat on **S** ra egy (**REMS** ACCESS p ogram To ece ve ra t ansmucosa fentany c rate you must
- ta k o your hea thca e prov der
- under tand the benef s and r ks of ora tr nsmu osa fentany c tr te
- agree to a of the nstruct ons
- s gn the Pat ent Pres r ber Ag eement fo m

What s ora t ansmu osa fentany c rate?
- O a ransmucosa fen any c rate s a p escr pt on med c ne hat con a ns the med c ne fentany
- O a tr nsmu osa f ntany c t ate s used o m nage brea through pa n n adu s (16 yea s of age nd o der w th can er who a e a eady rout ne y ak ng o her op o d pa n med c nes around- he-c ock for cancer pa n
- O a t ansmucosa fen any c t ate s ta ted on y af er you have been ak ng o her op o d pa n med c es and your body has go ten u ed o hem (you are op o d to era t DO NOT USE ra t ansmucosa fen any c tr te f you are not op o d to e ant
- O a ransmucosa fen any c rate s a ozenge (a tach d to a h nd e that you p ace between your cheek and ower gum nds ck on o d sso ve
- You must s ay under your hea th are p ov ders are wh e ak ng o a ran muc sa fentany c ra e
- O a t ansmucosa fen any c t ate s on y
   - ava ab e through he T RF REMS ACCESS prog am
   - g v n o peop e who a e op o d o e ant

t s not known f ora t ansmucosa fentany c t ate s safe and ffect ve n h dren nder 16 yea s of age

Who hou d not use ora transmu osa fen any c t ate?
Do not use ora ransmuco a fen any c t ate
- **f you are not op o d to erant Op o d o erant means that your are a ready ak ng other op o d pa n med c nes a ound the-c ock for at east one week or onger or your cancer pa n, and your body s u ed to these med c nes**
- for sho t- erm pa n hat you e pect to go away n a few days such as
   - pa n after su gery
   - headache or m g a ne
   - denta pa n
- f you a ea erg c to any of the ngred en s n o a t ansmucosa fent ny c ra e See the nd of h s Med at on Gu de for a comp te t of ngr d en s n o a ransmucosa fent ny c tr te

What shou d te my hea thca e prov der befo e us ng o a ransmuco a en any c tra e?
Before us ng ra ransmuco a fen any c rate te your hea hca e p ov der f you
- have t oub e brea h ng or ung p ob ems such s a thma whe z ng or hortn ss of b eath
- have h d a head n ury or b a n prob em
- have ver or k dney prob ems
- have e zures
- have a s ow hea t r te or o her hea t p ob ms
- have ow b ood pressure
- have men a pr b ems nc ud ng ma or d press on ch zophren a or ha uc nat ons (see ng or hear ng h ngs hat a e not here
- have a pa t or pre ent r nk ng p ob m (a oho sm or a f m y h tory of dr nk ng p ob ms
- have a past or pres nt drug abu e or dd ct on prob em or a f m y h tory of a drug abuse prob em or add ct on prob em
- have d abe es Ea h ra ransmucosa fentany c t ate un t onta ns about 1/2 easpo n (2 g ams of sugar
- have ny o her m d ca cond t ons
- re p egnant or p n to become p egnant O a ransmucosa fen any c rate may ause ser ous ha m to your unbo n b by
- A e bre stfeed ng or p an to reas fe d O a ran mu osa fen any c ra e pas es nto your br ast m k t c n cau e erous h rm to your baby You shou d not use o a ran muco a fentany c t ate wh e b eas feed ng

Te your hea th are p ov der about a he med c nes you take, nc ud ng p escr pt on nd non-p escr pt on med c nes v tam ns nd he ba supp ements Some med c nes may cause ser ous or fe th eaten ng med a p ob ems wh n ta en w h ora ran muco a fentany c tr te Somet m s the do es of erta n med c nes nd ora tran muc sa fent ny c rate need o be changed f used ogeth r
- Do not t ke any m d c ne wh e us ng o a tr nsmu osa fent ny c t ate unt you have ta ked to your hea hcare prov der Your hea thca e p ov der w e you f t s afe to take o her med c nes wh e you a e us ng ora ran muc sa fentany c ra e
- Be v ry carefu about o her med c nes that may ma e you s epy such as o her pa n med c nes ant dep essa ts s eep ng p s ant -anx ety m d c nes ant h s am nes or tr nqu ers

Know he med c nes you ake Keep a st of hem to show your hea th are p ov der and ph rmac t wh n you get a new med c ne

How shou d use ora transmucosa entany c trate?
Be ore you can beg n to use o a rans-mucosa fen any c t ate
- Your h a hcare prov der w expa n the T RF REMS ACCESS prog am to you
- You w s gn the T RF REMS ACC SS P tent-Pre cr ber Agre ment form
- Ora t ansmucosa fentany c t ate s on y ava ab e at pharmac es hat a e part of the T RF REMS ACCESS program Your hea thca e p ov d r w et you know the pharmacy cosest o your home whe e you can ha e your ora ran muco a fen any c tra e pres r pt on f d

Us ng o a transmu osa fentany c t ate
- **U e ora ransmu o a fentany c trate exact y as prescr bed Do not use ora transmu osa fentany c rate more often than p e cr bed**
- Your h a hcare prov der w ch nge the dose unt you and your hea thc re prov der f nd he r ght d se for you
- **See the deta ed Pat ent nstru t ons for U e at he end of th s Med cat on Gu de for nfo mat on about how to use o a ransmu osa fentany c trate the r ght way**
- F n sh the ora t ansmuco a fen any c rate un t comp e e y n 15 m nutes to g t he mo t e ef f you f n sh o a tran muco a fen any c tra e oo qu ck y you w swa ow more of the med c ne and get ess re ef
- **Do not b te or hew o a transmucosa fentany c tra e You w get ess re ef for your breakthrough cancer pa n**
- You may dr nk ome wa er before us ng ora tran mucosa fen any c t ate but you shou d not dr nk or eat nyth ng wh e us ng o a ransmucosa fen any c ra e
- You must not use more than 2 un ts of o a tr nsmu osa f ntany c t ate dur ng each ep ode of break hrough can er pa n
   - Use 1 un t for an ep ode of b eak-th ough cancer pa n F n h the un t over 15 m nutes
   - f your b eak hrough can er pa n s not re eved 15 m nut s af er you f n shed the o a ran mu osa f ntany c t ate un t use **on y 1** more un t of o a t ansmuco a f ntany c tr te at th s t me
   - f your b eak hrough pa n does not get bet er af er the second un t of o a t ansmucosa fent ny c tra e ca your hea thca e prov der for n tru t ons **Do not use another un t of ora tran mucosa entany c trate at th s t me**
- Wa t at e st **4** hou s befo e reat ng a new ep ode of b eakth ough ancer pa n w th ora ran muc sa fentany c ra e
- t s mpo tant for you to keep tak ng your a ound the-c ock op o d pa n med c ne wh e us ng ora t ansmu osa fentany c t ate
- Ta k o your hea thca e prov der f your dose of ra t ansmucosa fentany c rate does not re e e your b eakth ough ancer pa n Your hea thca e p ov der w dec de f your dose of o a tr nsmu osa fentany c t ate needs to be changed
- Ta k o yo r ea hca e p ov d r f you have mo e than 4 ep sodes of brea through cancer pa n per day The dose of your around the c o k op o d pa n med c ne may need to be d us ed
- f you beg n to fee d zzy s ck o your stomach or very s eepy befo e o a tr nsmu osa fentany c ra e s comp e e y d s o ved emove ora tr nsmuc sa fen any c t ate f om your mouth
- f you use t o much o a ran muco a fen any c tra e or over ose you or your ca eg er shou d ca for eme gency med a he p or have someone take you o the nea est hosp ta me gency r om r ght away

What shou d avo d wh e us ng ora ransmu osa fentany c tra e?
- **Do not dr ve, operate heavy mach nery, or do o her dangerous act v t es** unt you k ow how ora ransmuco a fen any c ra e afe ts you Ora tran muc sa fen any c tr te an make you s eepy Ask your hea thc re prov der wh n t s okay to do hese act v t es
- **Do not dr nk a coho wh e us ng ora transmucosa entany c tra e** t can n rea e your ch nce of ge t ng dang rous s de e fe ts

What a e the poss b e s de e fects of ora ransmu osa fentany c tra e?
O a transmucosa entany c trate an ause er ous s de ef ects, nc ud ng
1 **Breath ng p ob ems that can become fe- h eaten ng,** See **"What s the most mpo tant nformat on hou d know about ora transmucosa fentany c rate?"**
   Ca your hea h are prov der or get emergency med ca he p r ght away f you
   - have t oub e b eath ng
   - have drows ness w th s owed bre th g
   - have s ow ha ow b eath ng (t e hest moveme t w th brea h ng
   - f e fa nt very d zzy confused or have unusua symptoms

   These symptoms can be a s gn t at you used too much ora ransmuco a fen any c tra e or he dose s oo h gh for you **These symptoms may ead to er ous prob ems or death f not trea ed r ght away f you have any of these symp oms, do not use any more ora transmu osa fentany c t ate unt you ha e ta ked to your hea thcare prov der**
2 **De reased b ood pressu e** Th s can make you fee d zzy or ghtheaded f you get up oo fast from s t ng or y ng down
3 **Phys ca dependence Do not s op tak ng ora transmucosa fentany c rate or any other op o d w thout ta k ng to your hea hcare prov der** You ou d become s k w h un omfor ab e w thd awa symp oms beca se your body has become used to the e med c nes Phys ca dependency s not he same as drug add ct on
4 **A chance of abuse or add ct on** The chance s h gher f you a e r have ever been add ted o or abused other m d c t ns st eet drugs or a coho or f you have a h tory of menta prob ems

he most common s de e fec s of o a ran muc sa fentany c ra e a e
- nausea
- vom t ng
- d z ne s
- s eep n ss
- we kness
- headache
- anx ety
- confus on
- depre s on
- ra h
- troub e s eep ng

C nst pat on (not oft n enough or hard bowe mov men s s a very common s de ff ct of pa n med c nes (op o ds nc ud ng o a ransmucosa fen any c t ate and s un ke y to go away w hout rea ment a k o your hea thc re prov der about d e ary hanges and the u e of a at ves (m d c nes o t eat const pat on and s oo sof enes to p event or t eat con t pat on wh e tak ng o a ran muc sa fentany c ra e

O a ransmuco a fentany c tra e conta ns sugar Cav t es a d too h decay can happen n peop e t k ng o a ran mu osa fen any c ra e When t k ng o a t ansmucosa fen any c ra e you shou d a k to your dent st about p oper ca e of your te th

e your hea th are p ov der f you have any s de effect hat b thers you or that do not go away

hese a e not a he po s b e s de effects of o a tr nsmu osa fen any c tra e For more nf rm t n a k your hea thca e prov der or ph rmac t

a your do tor for med a adv ce a out s de ff cts You may r port s de e fe ts to FDA at 1 800- DA 1088

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/s/

KEITH O WEBBER
01/04/2012

Dear Sir or Madam,

The transmucosal immediate-release fentanyl (TIRF) risk evaluation and mitigation (REMS) single-shared system was approved on December 28, 2011. As you know, the go-live date for the REMS is March 12, 2012; however, FDA has recently learned that the implementation of the REMS has not proceeded as anticipated. To ensure that patients continue to have access to TIRF medicines until the TIRF REMS Access program is fully operational, **FDA advises that it will not be necessary to recall product as of March 12, 2012.**

In addition, to accommodate enrollment of integrated healthcare systems whose pharmacy management systems do not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program, the TIRF REMS Access contractor has informed us that they are developing a telephone Call Center that should be operational by mid-April. FDA does not intend to object if integrated healthcare systems are not enrolled until the Call Center is operational. In the interim, those systems will continue to have access to TIRF medications.

FDA is preparing a new enforcement discretion letter, which we will issue soon, stating our expectations for actions to be taken during the transition period until the program is fully operational.

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research

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/s/

KRISTEN MILLER
03/06/2012

LESLIE K BALL
03/06/2012

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 078907
Communication Type:	Correspondence
Communication Group:	NDA Information Request/Advice
Communication Name:	General Advice Letter
Communication ID:	COR-NDAIR-10
Drafted by:	Leslie Ball 3/6/12, 3/7/12 Karena Cooper 3/5/12, 3/6/12, 3/7/12 Kathleen Davies 3/6/12 Nancy Clark 3/11/12 Jane Axelrad 3/4/12
Reviewed by and dates	Leslie Ball 3/6/12, 3/7/12, 3/8/12 Jane Axelrad 3/2/12, 3/4/12, 3/6/12, 3/7/12, 3/8/12 Karena Cooper 3/6/12, 3/7/12 Kathleen Davies 3/5/12, 3/6/12, 3/7/12 Claudia Karwoski 3/5/12, 3/6/12, 3/7/12 Gita Toyserkani 3/5/12, 3/7/12 Megan Moncur 3/5/12, 3/6/12, 3/7/12 Marcia Williams 3/5/12, 3/6/12, 3/7/12, 3/14/12 Tamika White 3/5/12, 3/6/12, 3/7/12 Kevin Prohaska 3/5/12, 3/6/12, 3/7/12, 3/13/12, 3/14/12 Adam Kroetsch 3/5/12, 3/6/12, 3/7/12
Clearance History:	
Finalized:	
Filename:	
Use Statement:	Use to send general advice to the applicant that is not necessarily related to a pending application.
Notes:	Transmucosal immediate release fentanyl (TIRF) drug products are a class of opioid analgesics indicated only for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. FDA notified the TIRF sponsors that a single shared system (SSS) REMS must be implemented to assure safe use of these products. This SSS REMS was approved December 28, 2011. At that time, some sponsors already had an individual REMS in place, while some did not have any REMS. All TIRF products except for Subsys (NDA 202788) were already marketed products. The purpose of this second enforcement discretion letter is to notify the sponsors that the Food and Drug Administration (FDA) will not take enforcement action on with specific required elements of REMS during the transition to full operation of the SSS REMS.

	FDA issued an initial enforcement discretion letter to the TIRF REMS sponsors on January 31, 2012. The letter detailed conditions and timelines (March 12, 2012 launch date) that were to be met during the transition to full operation of the TIRF REMS. However, in early March, FDA learned there were problems with implementation issues that would prevent full implementation of the SSS REMS on the proposed March 12, 2012 'go live' date. This created concern that patients would not have access to these drugs after March 12, 2012. The current TIRF REMS enforcement discretion is needed to clarify FDA expectations regarding implementation issues, including when full implementation is expected (September 12, 2012). This new enforcement discretion letter will supersede the previous January 31, 2012 enforcement discretion letter and any individual TIRF REMS enforcement discretion letter (e.g., Cephalon's July 20, 2011 letter). Significant meetings for the current TIRF REMS enforcement letter were held: 3/05/12 3/09/12 3/13/12
CC:	Leslie Ball Jane Axelrad Karena Cooper Kathleen Davies Claudia Karwoski Megan Moncur Gita Toyserkani Marcia Williams Tamika White Kevin Prohaska Kevin Kroetsch Nancy Clark Dickinson Kristen Everett Kristen Miller Kimberly Compton Sharon Hertz Judith Racoosin Mathew Sullivan Carla Cartwright

Version: DARRTS 3/28/11

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907

ENFORCEMENT DISCRETION

Mallinckrodt Inc
Attention: Jasen Wallace
675 McDonnell Boulevard
Hazelwood, MO 63042

Dear Mr. Wallace:

This letter is in reference to your new drug application (NDA) or abbreviated new drug application (ANDA) and the approved risk evaluation and mitigation strategy (REMS) for drug products that comprise the Transmucosal Immediate-Release Fentanyl (TIRF) REMS, a single-shared system. This single shared system includes the following products:

NDA 020747	Actiq (fentanyl citrate) oral transmucosal lozenge
NDA 021947	Fentora (fentanyl citrate) buccal tablet opioid analgesics
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanly) nasal spray
NDA 022266	Onsolis (fentanyl buccal soluble film)
NDA 202788	Subsys (fentanyl sublingual spray)
ANDA 077312	Oral transmucosal fentanyl citrate
ANDA 078907	Fentanyl citrate

The TIRF REMS was approved December 28, 2011, under section 505-1(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) as a requirement to ensure that the benefits of the drug outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication error. Failure to comply with the requirements of an approved REMS, or with other requirements under section 505-1 of the FDCA, may result in enforcement action (see sections 303(f)(4)(A), 502(y), and 505(p) of the FDCA).

This letter supersedes our previous enforcement discretion letters issued for individual TIRF REMS programs and for the class TIRF REMS Access program.

On January 31, 2012, FDA sent a letter to the sponsors of the TIRF REMS indicating its intention to exercise enforcement discretion during the time it was expected to take to implement the REMS program. The letter stated that after the go-live date for the REMS on March 12, 2012, any TIRF product remaining in pharmacies not enrolled in the REMS was to be recalled.

FDA has recently learned that implementation of the REMS has not proceeded as anticipated. For example, several large integrated healthcare systems or “closed systems” have identified difficulties in accessing the TIRF REMS Access Program through the Relay Health electronic switch. These health systems will need to either modify their systems to work through the switch, or participate in the REMS through a separate mechanism that is to be established by the TIRF REMS Access program.

To minimize disruptions in patient access to TIRF medicines, FDA has determined that it will not be necessary to recall product. In addition, FDA intends to exercise enforcement discretion regarding your compliance with the implementation of the TIRF REMS during the transition to full operation of the TIRF REMS if the following conditions are met:

- FDA has been notified, by April 30, 2012, that a system to allow enrollment of pharmacies and verification of safe use conditions (i.e., prescriber and patient enrollment), is operational for pharmacies (including integrated health systems) who are unable to enroll in the TIRF REMS Access Program. This can be done through a telephone system and/or Web portal.
- After June 30, 2012, all Integrated Health Care Systems are enrolled in the TIRF REMS Access Program.
- After September 12, 2012, no TIRF product is dispensed unless the prescriber, pharmacy, and patient are enrolled in the TIRF REMS Access program.

With regard to the previously requested periodic status reports about the transition to full operational status of the TIRF REMS Access program, we have determined that periodic status reports for individual applications are not necessary, although you should submit a single bridging report showing the activities during the period between your last REMS assessment for your individual REMS and the March 12, 2012 "go-live" date for the TIRF REMS Access program. The first formal assessment of the TIRF REMS Access program is due June 28, 2012.

As an NDA [or ANDA] sponsor subject to the terms of the TIRF REMS approval letter of December 28, 2011, we remind you it is your responsibility to comply with the terms of the approved TIRF REMS. FDA expects you to be in full compliance with all of the requirements of the approved TIRF REMS no later than September 12, 2012. Please note that you may be inspected to ensure compliance with the TIRF REMS. Non-compliance with any part of the TIRF REMS may result in enforcement action, including civil monetary penalties.

If you have any questions, call Marcia Williams, Ph.D., Acting Team Leader, at (301) 796-0160.

Sincerely yours,

{See appended electronic signature page}

Leslie K. Ball, M.D.
Acting Director
Office of Scientific Investigation
Office of Compliance
Center for Drug Evaluation and Research

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/s/

LESLIE K BALL
03/20/2012

Mallinckrodt

COVIDIEN

GENERAL CORRESPONDENCE: REMS KAB SURVEY METHODOLOGY

May 18, 2012

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

RE: ANDA 078907
Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg

Dear Sir or Madam:

Reference is made to the "Prior Approval" supplement (S-007) approved January 4, 2012 that provided for a single, shared REMS system developed for the transmucosal immediate-release fentanyl (TIRF) class of products.

Mallinckrodt, Inc., the Pharmaceuticals business of Covidien, hereby submits this **General Correspondence: REMS KAB Survey Methodology** that will document the level of knowledge and assess the attitudes and behaviors of the patient-caregiver, pharmacist, and prescriber in regards to key information and risk messages communicated through the shared REMS system. The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

This application, which has been organized according to the June 2008 Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, is approximately 3 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0040. It has been checked and found free from virus infection using McAfee VirusScan Enterprise 8.7i Antivirus Software. For technical assistance, please contact Jeremy Grise, Manager, Regulatory Operations at 314-654-8259.

MALLINCKRODT INC.
675 MCDONNELL BLVD.
HAZELWOOD, MO
63042

314-654-2000 (T)

WWW.COVIDIEN.COM

Mallinckrodt

COVIDIEN

Correspondence related to this submission should be addressed to Jasen Wallace, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-3157, or Rebecca Welton, Associate Director, Regulatory Affairs, at 314-654-5607.

Sincerely,

Jasen Wallace
Senior Regulatory Affairs Specialist
Email: jasen.wallace@covidien.com
Fax: 314-654-3157

ALLI C R T I C.

COVIDIEN

AMENDMENT TO PAS (S-007): REMS MODIFICATION 2

September 28, 2012

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

RE: ANDA 078907: OTFC 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg
Amendment to PAS (S-007): REMS Modification 2

Dear Sir or Madam:

Reference is made to the Prior Approval Supplement (S-007) approved January 4, 2012 providing for a single shared REMS system developed for the transmucosal immediate-release fentanyl (TIRF) products. Further reference is made to the REMS Modification amendment submitted February 7, 2012. Further reference is also made to e-mail dated June 28, 2012 from Mr. Mark Liberatore in which he provided an overview of the additional changes needed to incorporate closed system pharmacies into the TIRF REMS Access Program for pre-submission review by Wednesday, July 25, 2012. The following files were transmitted to Mr. Mark Liberatore via email on July 24, 2012, but FDA requested that this information be formally submitted in the ANDA. In response to this request, the following revised files are provided in this sequence:

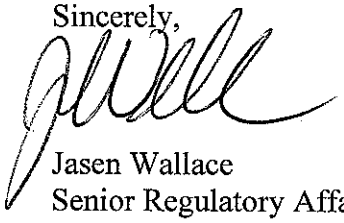
- Chain Pharmacy Enrollment Form
- Closed System Pharmacy Overview
- Education Program (submitted as a PDF file rather than a PowerPoint file)
- FAQ
- Outpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Letter
- REMS (please note there is one difference from the previous submission made in July 2012; in section III a reference to “ANDA” Sponsors was added.)
- TIRF Supporting Document

Please note FDA requested that TIRF sponsors submit redlined documents at this time. Final documents will be submitted after discussions are complete.

This amendment, which has been organized according to the June 2008 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications,* is approximately 2 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0042. It has been checked and found free from virus infection using McAfee VirusScan Enterprise 8.7*i* Antivirus Software. For technical assistance, please contact Jeremy Grise, Manager, Regulatory Operations at 314-654-8259.

Correspondence related to this application should be addressed to Jasen Wallace, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-3157, or Rebecca Welton, Associate Director, Regulatory Affairs, at 314-654-5607.

Sincerely,



Jasen Wallace
Senior Regulatory Affairs Specialist
jasen.wallace@covidien.com
Fax: 314-654-3157

Transmucosal Immediate Release Fentanyl (TIRF)

Sponsors:

TIRF REMS Industry Group (TRIG) of Companies

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) SUPPORTING DOCUMENT

1. TABLE OF CONTENTS

2. BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended release and immediate release products. Extended release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic [Biedrzycki et al, 2009]. Secondary effects of fentanyl on central nervous system, respiratory and gastro-intestinal functions are typical of opioid analgesics and are considered to be an effect [Simpson et al, 2007].

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TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, BTP). All the TIRF medicines as such, are short acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and on occasion fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

In order to mitigate these risks, TIRF Sponsors will implement a Risk Evaluation and Mitigation Strategy (REMS) for the transmucosal immediate release fentanyl products (or "TIRF medicines"), intended for use in breakthrough pain (BTP) in patients with cancer, while ensuring treatment access for patients who would benefit from this therapy.

The TIRF medicines which are the subject of this proposed TIRF REMS are shown in Table 1 below. Table 1 shows the products and dosage forms. These products are currently used for the treatment of BTP in adult patients with cancer who are already receiving, and are tolerant to, around-the-clock (ATC) routine opioid therapy. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

Table 1: TIRF Medicines

Product Name (active ingredient)/formulation	Applicant/Sponsor	Availability	Initial Dose
ABSTRAL® (fentanyl) sublingual tablets	ProStrakan, Inc.	100 mcg 200 mcg 300 mcg 400 mcg 600 mcg 800 mcg	100 mcg
ACTIQ® (fentanyl citrate) oral transmucosal lozenge*	Cephalon, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
FENTORA® (fentanyl citrate) buccal tablet	Cephalon, Inc.	100 mcg 200 mcg 400 mcg 600 mcg 800 mcg	100 mcg**
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg 400 mcg	100 mcg
ONSOLIS® (fentanyl), buccal soluble film	Meda Pharmaceuticals	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Barr Laboratories, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg

Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Par Pharmaceutical, Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge* (generic equivalent of ACTIQ®)	Mallinckrodt Inc.	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	200 mcg
SUBSYS™ (fentanyl sublingual spray)	Insys Therapeutics Inc.	100 mcg 200 mcg 400 mcg 600 mcg 800 mcg 1200 mcg 1600 mcg	100 mcg

*Can be used in patients aged 16 and older
**Unless substituting from an Actiq dose of 600 mcg or greater. Please see full prescribing information.

The TIRF REMS Access proposal presented here addresses the current requirements set forth by the FDA provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

A. Clinical Features of BTP

BTP is a transient exacerbation of pain of moderate to severe intensity that occurs on a background of otherwise stable pain in a patient receiving regular, continuous opioids. It is characterized by rapid onset, with pain reaching maximal intensity within 3 minutes and lasting approximately 30 minutes [Laverty, 2007]. Often classified by its relationship to specific events or spontaneous onset, BTP arises as a consequence of the cancer, the anticancer treatment or a concomitant illness. BTP can affect up to two-thirds of patients with cancer, and can have a significant impact on patient quality of life [Breivik et al., 2009]. Moreover, a number of patients remain inadequately treated for their BTP or feel dissatisfied with their pain control

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[Fishbain, 2008]. There is therefore a need for effective pharmacologic treatments that will help relieve and control the symptoms of BTP. An ideal treatment for BTP is an analgesic with good efficacy, rapid onset and short duration of action, with minimal adverse effects in appropriately selected patients, and is easy and quick for a patient or caregiver to administer.

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B. Assessment of Key Risks of TIRF Medicines

The TIRF REMS Access program will address the primary risks of overdose, misuse, abuse, addiction and serious complications due to medication errors. These are broad risks relating to the distribution, sale, use and misuse of opioids in the US and are not unique to TIRF medicines. However, TIRF medicines are absorbed transmucosally and partially bypass gastrointestinal absorption and first-pass metabolism, resulting in rapid onset of analgesic effect, and potentially, adverse effects. The key acute risk for any individual exposed to TIRF medicines is excessive respiratory depression which can be fatal if untreated. This risk is highest in opioid non-tolerant patients. Therefore, TIRF medicines must not be used by opioid non-tolerant patients. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

By restricting the use of TIRF medicines to opioid tolerant patients the risk of serious outcomes such as severe respiratory depression should be minimized. Opioid addiction arising in palliative care patients is rare [Hojsted et al, 2007]**.**

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3. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

4. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors will execute the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program including patients, prescribers, pharmacists and distributors will be enrolled in the TIRF program, educated on the requirements of the program and required to document that they understand and will abide by the "elements to assure safe use."

Program materials will be provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program will contain both TIRF medicine class and product-specific components. Enrollment forms, the Patient-Prescriber Agreement Form (PPAF), stakeholder letters and overview documents containing program information will be provided to stakeholders as TIRF medicine materials. In addition, the Medication Guides will be provided to stakeholders in product-specific material format unique to the respective TIRF medicine being prescribed / dispensed.

The program procedures will be monitored for adherence and will be modified as necessary to ensure optimal effectiveness. The TIRF Sponsors will conduct ongoing and retrospective analysis as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

A. Additional Potential Elements

a. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF medicine prescription. Every TIRF medicine will have a unique Medication Guide. There will be sufficient copies distributed by each Sponsor to ensure that every patient receives a copy with each prescription. Medication Guides will be available through individual TIRF Sponsors, the TIRF REMS Access website, and the TIRF REMS Access call center.

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The Medication Guide contains FDA approved language including an explanation of the risks associated with the use or misuse of TIRF medicines, augmented with information on precautions for safe use of the product, a brief explanation of essential elements of the TIRF REMS Access program, and contact information for customer assistance (i.e., call center with toll-free number and website). The TIRF medicine Medication Guides are developed to enhance patient awareness and understanding of the potential serious risks associated with the use of TIRF medicines with the intent of increasing the patients' appropriate use of TIRF medicines. The Medication Guides include critical information that every patient and caregiver should know about TIRF medicines including, but not limited to:

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- Patients should not use a TIRF medicine unless they are regularly using another opioid pain medicine around-the-clock for their constant cancer pain and their body is used to these medicines (opioid tolerant).
- TIRF medicines must be kept in a safe place away from children.
- If a child, or an adult who is not already taking opioids regularly, takes a TIRF medicine, this is a medical emergency and can cause death. Get emergency help right away.

A copy of each product specific Medication Guide is distributed with every TIRF medicine.

TIRF Sponsors will supply all enrolled prescribers and pharmacies with sufficient copies of the Medication Guides to ensure that every patient who is prescribed and dispensed a prescription will have access to the specific TIRF medicine Medication Guide each time it is prescribed or dispensed.

The Medication Guide will be available through the TIRF REMS Access website, www.TIRFREMSaccess.com. Copies can also be obtained by calling the TIRF REMS Access program at **1-866-822-1483**.

b. Other Information Materials for Patients

The prescriber will discuss the benefits and risks of TIRF medicines as outlined in the Medication Guide with the patient, including proper dosing and administration, appropriate use and handling and storage of TIRF medicines.

The prescriber will discuss enrollment in the TIRF REMS Access program. The prescriber and the patient will review and sign the TIRF REMS Access program Patient-Prescriber Agreement Form (not required for inpatients) and a copy will be provided to the patient or caregiver. The prescriber will also provide the patient or caregiver with a copy of the Medication Guide.

The patient or caregiver will be offered counseling on the specific TIRF medicine by the dispensing pharmacist on appropriate use, storage and disposal, and receive an additional copy of the Medication Guide each time a TIRF medicine is dispensed.

The prescriber will have access to the TIRF REMS Access Program: An Overview for Patients and Caregivers to utilize with patients during discussions regarding the use of TIRF medicines. In patient-friendly language, the materials will focus on a description of the TIRF REMS Access program, including enrollment details and contact information (call center with toll-free telephone number and website address). This overview will also be available for download on www.TIRFREMSaccess.com.

c. Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS is not required. However, TIRF Sponsors will send Dear Healthcare Professional letters to targeted stakeholders to support implementation of the TIRF REMS Access program. These communications will include Dear Healthcare Provider and Dear Pharmacy letters, and will inform prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means of reporting adverse events.

TIRF Sponsors will send letters to healthcare professionals approximately 2 weeks prior to first availability of TIRF REMS Access program.

The target audience for the *Dear Healthcare Provider* letter will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies

that may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

Additional materials will be available via the TIRF REMS Access program website or through the TIRF REMS Access program toll-free number.

B. Elements to Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This can be achieved by prescriber's enrollment through a review of the TIRF REMS Access Education Program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the enrollment form.

TIRF medicines will only be available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies will be enrolled into the TIRF REMS Access program. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use.) ~~and~~ **inpatient pharmacies** (e.g. hospitals that dispense for inpatient use only) and **closed system pharmacies** (e.g. integrated healthcare systems that dispense for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required.) For Long-Term Care (LTC) and Hospice patients whose prescriptions are obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access program.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to undergo enrollment through review of the *TIRF REMS Access Education Program* and successful completion of the *Knowledge Assessment* on behalf of the pharmacy. The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transactions to validate the system enhancements and submit a completed and signed TIRF REMS Access enrollment form. The authorized pharmacist will be responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training must be documented and is subject to audit. At a minimum this documentation should include the store name, the store number, the pharmacist/pharmacy staff member's name, and the date training was completed.

For inpatient pharmacy enrollment, the authorized pharmacist must undergo the *TIRF REMS Access Education Program*, successfully complete the *Knowledge Assessment*, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient

pharmacist must also acknowledge that they understand that outpatient pharmacies within their facility must be separately enrolled.

For chain pharmacies, an authorized chain pharmacy representative must complete enrollment. The authorized chain pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form. Pharmacy sites that have been trained may be updated by the authorized chain pharmacy representative using an online dashboard.

For closed system pharmacies, an authorized closed system pharmacy representative must complete enrollment. The authorized closed system pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized closed system pharmacy representative, on behalf of the closed system, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form. A list of closed system pharmacy sites that have been trained must be provided to the program via a standard electronic file format for processing.

Pharmacies will not be able to successfully order TIRF medicines from distributors unless they are enrolled in the TIRF REMS Access program.

All patients (excluding inpatients) must complete and sign a Patient-Prescriber Agreement Form (PPAF) with their healthcare provider, documenting safe-use conditions. Their healthcare provider will submit a copy of the PPAF to the TIRF REMS Access program via the website at www.TIRFREMSaccess.com, fax at 1-866-822-1487, or regular mail at (Address: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038). Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program. A completed *Patient-Prescriber Agreement Form* needs to be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

a. Prescriber Education and Enrollment

The TIRF REMS Access program education materials are the primary tool for educating prescribers about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The *Education Program* also includes information for prescribers on the requirement to complete a *Patient-Prescriber Agreement Form* before writing the first prescription for a TIRF medicine (not required for inpatients). For inpatient administration of TIRF medicines prescriber enrollment in the TIRF REMS Access program is not required.

The *TIRF REMS Access Educational Program* for prescribers comprises the Education Program and *Knowledge Assessment* that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available on the TIRF REMS Access website (www.TIRFREMSaccess.com):

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Pharmacies

If the prescriber does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded on the TIRF REMS Access website, or requested as a hardcopy from the TIRF REMS Access program call center.

Review of the Knowledge Assessment

Following review of the TIRF REMS Access Education Program, the program Knowledge Assessment must be successfully completed. A description of the process followed in reviewing the Knowledge Assessments is presented below, and this description applies equally to prescribers and pharmacists.

Manual Knowledge Assessment Review (i.e. on receipt of printed materials)

The prescriber should review the *TIRF REMS Access Education Program*, complete the paper *Knowledge Assessment* and return it by fax to the TIRF REMS Access program.

Upon receipt of a manual program *Knowledge Assessment*, a TIRF REMS specialist will review the assessment and determine the stakeholder type.

The TIRF REMS specialist will enter each answer to the assessment question in the validated TIRF REMS Access database.

If the answers are correct (the user has passed the assessment with a score of 100%) and all other enrollment criteria have been met, the user will be enrolled in the program by notice through email or fax.

If answers are incorrect a *Knowledge Assessment* feedback fax will be generated and sent to the enrolling user that only addresses the incorrect questions received. If answers are missing an "Incomplete" fax is generated and sent to the user advising them to resend a completed *Knowledge Assessment* to allow for successful processing of the assessment.

Website Knowledge Assessment Review (web-based materials)

Upon completion of the review of the *Education Program*, the user is required to successfully complete the *Knowledge Assessment* prior to enrolling in the program.

The user is presented with one question at a time and required to provide an answer.

Upon completion of all program assessment questions, the system calculates a score. The score is presented to the user.

If the score is 100%, then the user has passed the program assessment.

If the user's score is less than 100%, they will be presented with the incorrectly answered question that they will be required to retake, in addition to further feedback on the incorrect answer.

The Knowledge Assessment (manual or website) may be attempted up to three times. If a score of 100% is not achieved after three attempts, the TIRF REMS Access Education Program must be reviewed again before retaking the *Knowledge Assessment*. Having performed the training again, a further three unsuccessful attempts at the *Knowledge Assessment* are permitted before enrollment is denied.

Successful completion of the *Knowledge Assessment* is required in order for the prescriber to enroll in the TIRF REMS Access program. Prescribers may enroll online or by paper by completing the TIRF REMS Access Prescriber Enrollment Form.

Verification of prescribers having successfully enrolled will be recorded in the TIRF REMS Access program and will allow them to access the full TIRF REMS Access program and to prescribe TIRF medicines. Prescribers will receive a user ID and password as part of the enrollment process. In addition, these forms will also be available as printed materials and can be downloaded from the website for stakeholders that prefer not to enroll electronically. These forms along with the *Knowledge Assessment* may be completed on paper and faxed to the TIRF REMS Access call center at 1-866-822-1487.

Manual Enrollment

Upon receipt of a paper enrollment form, a TIRF REMS specialist will review the form for completeness and determine the enrolling stakeholder type (i.e., prescriber or pharmacy). The TIRF REMS specialist will enter all data on the form into the TIRF REMS Access database.

Required for successful enrollment form:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation
4. The program Knowledge Assessment has been passed successfully.
5. All enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation is sent to the stakeholder via the preferred method of communication (fax or email) that is indicated on the enrollment form.

An enrollment form is considered incomplete where:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

If the enrollment form is incomplete, a fax is generated clearly listing all incomplete fields and a description of the action required to resolve the issue. The fax is sent to the fax number provided by the enrolling user on the enrollment form (email or phone can be used to send/discuss the incomplete form if the fax number is not available). The enrolling user must provide the incomplete information and return it to the TIRF REMS Access program for reprocessing. The enrollment is not considered complete until all required fields have been received and validated.

Web-based Enrollment

The enrolling user will be required to review the TIRF REMS Access Education Program, complete the *Knowledge Assessment* with a score of 100%, and complete the appropriate enrollment form.

Required for successful enrollment:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation.
4. The enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation and completed enrollment form are sent via the indicated preferred method of communication (fax or email) provided by the enrolling user on the enrollment form. In the case that email is not available, a fax confirmation will be sent. Enrollment confirmation is also provided via the website.

An enrollment form is considered incomplete when:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

Unsuccessful Enrollment: The field edit messages are displayed back to the enrolling user. The enrolling user cannot progress further with the enrollment process until errors are corrected. Only the user's initial registration information will be retained; no enrollment data are saved to the TIRF REMS Access database.

TIRF Sponsors will maintain a database containing a list of all enrolled prescribers and their status (i.e. active or inactive). Upon initial activation, prescribers remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate prescribers for non-compliance reasons.

If a previously active prescriber becomes inactive, the prescriber will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment form in its entirety.

While a prescriber is inactive, prescriptions from that prescriber can no longer be filled under the TIRF REMS Access program. If the prescriber is providing care for patients using TIRF medicines at the time of prescriber inactivation, it is the prescriber's responsibility to ensure that the patients continue to receive appropriate pain medication via referral to another prescriber in the TIRF REMS Access program.

Prescribers are re-educated and re-enrolled in the TIRF REMS Access program every two years. TIRF Sponsors will notify prescribers of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify prescribers of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of TIRF medicines.

All communication methods utilized by the TIRF REMS Access program will provide information on how to report any suspected adverse events, including reports of misuse and abuse to TIRF Sponsors.

b. Outpatient Pharmacies~~y~~: Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating pharmacists about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines.

The TIRF REMS Access education for pharmacists comprises the *TIRF REMS Access Education Program* and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Pharmacies

If the pharmacy does not want to perform the *Education Prog*ram and *Knowledge Assessment* online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested from the TIRF REMS Access program call center.

The *Education Program* will cover information regarding how to validate prescriptions via the TIRF REMS Access program before they are filled as well as information on appropriate dispensing and use of TIRF medicines. Following review of the *Education Program*, the authorized pharmacist may enroll the pharmacy by successful completion of the *Knowledge Assessment* and the appropriate TIRF REMS Access program pharmacy enrollment form. On

receipt of a valid enrollment form, the outpatient and chain pharmacies~~y~~ will be sent by fax or email the instruction guide on the test transactions they will be required to run to verify that their pharmacy management system has been configured. If the test transactions have been completed successfully, the pharmacy will be enrolled and confirmation will be sent to the pharmacy. If the test transactions are not completed successfully, the pharmacy will not be enrolled and a message will be sent to contact the call center in order to further explain the need to configure the pharmacy management system.

The authorized pharmacist will be responsible for educating all pharmacy staff that participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training should be documented and is subject to audit.

An authorized chain and closed system pharmacy representative may complete the TIRF REMS Access training, *Knowledge Assessment* and enrollment on behalf of all their pharmacies within the chain or closed system and then document and manage training of all pharmacy staff according to their ~~by the chains'~~ internal processes. The authorized chain pharmacy representative would ~~also~~ ensure completion of system testing to verify ~~that~~ their pharmacy management system has been configured. The authorized chain representative may update trained stores on their chain pharmacy dashboards or submit a list to the TIRF REMS Access program for uploading into the database. The authorized closed system pharmacy representative would ensure their trained closed system dispensing locations were placed into their closed system enrollment file according to the standard file format and submitted to the TIRF REMS Access program for uploading into the database. ~~Upon completion of enrollment, the authorized chain representative would update trained stores on their chain pharmacy dashboards or would submit a list to the TIRF REMS Access program for uploading into the database.~~

Enrolled p~~P~~harmacies will be recorded in the system which will allow them access to the TIRF REMS Access program to dispense TIRF medicines. Following ~~web based~~ enrollment and successful completion of the test transactions (for chain pharmacies,) the authorized pharmacist will receive a username and enrollment ID, where the user can then create a password for the TIRF REMS Access website.

In addition, outpatient and chain pharmacy enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the Knowledge Assessment and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled p~~P~~harmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, the pharmacy will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines or dispense TIRF medicines under the TIRF REMS Access program.

Pharmacies are re-educated and re-enrolled every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies, of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program

b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any TIRF medicine.

The pharmacist will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

c. Inpatient Pharmacies: Education and Enrollment

The TIRF REMS Access Education Program is the primary tool for educating inpatient pharmacies about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The Education Program also includes information about the requirements of the TIRF REMS Access program in the inpatient setting.

The TIRF REMS Access education materials for inpatient pharmacies comprise the Educational Program and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Pharmacies

An authorized pharmacist of the inpatient pharmacy is required to undergo the TIRF REMS Access Pharmacy Education Program. If the pharmacist does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested as a hardcopy enrollment from the TIRF REMS Access program call center.

The Education Program will cover information about the requirements of the TIRF REMS

Access program. Following review of the Education Program, the authorized pharmacist may enroll the pharmacy by successfully completing of the Knowledge Assessment and the TIRF REMS Access Inpatient Pharmacy Enrollment Form.

Inpatient pharmacy enrollment will be recorded in the system. Upon successful enrollment the inpatient pharmacy will have the ability to order TIRF medicines for inpatient dispensing. Pharmacies will receive a user ID and password as part of the enrollment process.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the *Knowledge Assessment* and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled inpatient pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled inpatient pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, it will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines.

Inpatient pharmacies are re-educated and re-certified every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program.

b. Changes to the Prescribing Information and Medication Guides that affect the benefit-risk profile of any TIRF medicine.

The inpatient pharmacy will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

d. Patient Enrollment and Counseling

Patient enrollment is not required for inpatient use of TIRF medicines.

- Prescribers for outpatients will be provided with copies of a TIRF medicine Medication Guide and materials to use in counseling patients. Medication Guides are product specific and can be accessed from the specific TIRF Sponsor, the TIRF REMS Access website, or the TIRF REMS Access call center. Patients will be counseled on the TIRF

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REMS product by enrolled prescribers, supported by review of the Medication Guide and the overview of the TIRF REMS Access program for Patients and Caregivers. Patients will also have the opportunity to discuss any questions or concerns they have with their prescriber. Together the prescriber and patient will review and sign the Patient-Prescriber Agreement Form.

- The patient will be counseled by the prescriber and personally sign the *Patient-Prescriber Agreement Form* unless they are unable to act on their own behalf. For incapacitated patients, the patient counseling can be provided to and signed by the patient's legally authorized representative or medical guardian.
- Both the prescriber and patient must complete the *Patient-Prescriber Agreement Form* and the prescriber must provide a completed copy by fax or through the TIRF REMS Access website to the TIRF REMS Access program within 10 working days. Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program.
- The TIRF REMS Access Program: An Overview for Patients and Caregivers will be available for distribution to the patient by the prescriber or through the program website. This overview details the steps the patient must follow. Further information will be available on the TIRF REMS Access program website or at the TIRF REMS Access call center.
- Patients will be offered counseling by the dispensing pharmacist on the responsible use, handling and disposal of TIRF medicines. A copy of a specific TIRF medicine's Medication Guide will be provided by the pharmacist when their prescriptions are dispensed by the pharmacy.
- A database will be maintained containing a list of all enrolled patients and their status (i.e. active or inactive). Upon initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include: a prescription has not been filled for more than 6 months or the patient receives prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, overdose, or addiction.
- If a previously active patient becomes inactive, the patient can become active again by completing the standard patient counseling and re-evaluation by their prescriber (i.e. a complete review of the current TIRF medicine's Medication Guide) and completing a new Patient-Prescriber Agreement Form.
- If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot authorize the prescription for the

TIRF medicines to be filled until the new prescriber is active in the TIRF REMS Access program.

- Patients will be re-counseled and required to complete a new *Patient-Prescriber Agreement Form* every 2 years. TIRF Sponsors will notify the patient's prescriber of forthcoming enrollment expiration and the need to complete a new *Patient-Prescriber Agreement Form*.
- If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify the patient's prescriber of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program
    b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any and all TIRF medicines.

e. Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies must verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

TIRF Sponsors will use a model that uses a pharmacy billing claim and engages a switch provider in the validation process for outpatient and chain pharmacies. The switch provider provides information to pharmacists at point-of-dispensing via their pharmacy terminals. Their secure connectivity network provides a single point of access between pharmacies and payers so that transactions are routed quickly and reliably, instantly transmitting claims to the appropriate processor and returning the adjudicated response to the pharmacy within seconds.

Patients must complete a Patient-Prescriber Agreement Form (PPAF) prior to being given a prescription for a TIRF medicine. This may be done in two ways – online at www.TIRFREMSaccess.com or paper based. If conducted online, the PPAF will be recognized immediately. Paper based PPAFs must be faxed to the program within 10 working days to complete enrolment.

Outpatient and Chain Pharmacies: Prescription Verification

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On receipt of a prescription for a TIRF medicine at an enrolled outpatient or chain pharmacy, the pharmacist will enter the prescription details in their pharmacy management systems and send the transaction to the TIRF REMS Access program via the Switch Provider. The TIRF REMS Access program will use this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the REMS database will then be interrogated, via the Switch Provider, in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, a billing request will be sent to the payer by the Switch. Once the payer authorizes payment the switch provider will then authorize the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will reject the claim (prior to the claim being forwarded to the payer) and the pharmacy will receive a rejection notice from the Switch Provider. This automated feedback will indicate the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notify the pharmacist to contact the TIRF REMS Access call center for further information. The current switch authorization process typically takes 3-5 seconds to complete. Interrogation of the TIRF REMS Access program enrollment database should add not more than 1 second to the overall process. This method of verification is designed to integrate into normal pharmacy workflow patterns and therefore minimize burden to the pharmacy while providing a robust control on ability to dispense TIRF medicines outside of the TIRF REMS Access program.

The TIRF REMS Access system communicates an authorization number when the submitted prescription billing request passes all qualification rules and the processor approves the billing request. The switch provider appends the authorization to a message field before delivering the response to the pharmacy practice management system.

If the pharmacy is enrolled and the electronic prescription verification process fails, prescription verification can be facilitated through the call center. The call center representative can enter the required fields necessary to provide prescription verification.

The 'back-up' process/system is not the primary method for verification, and will only be available to enrolled, active pharmacies. All instances where the back-up process is used will be adequately documented, including the specific reason it is being used. A report on back-up system use will be included in the REMS Assessment.

Back-up system utilization will be incorporated into compliance monitoring; if excessive use is observed corrective action will be implemented.

Closed System Pharmacies: Prescription Verification

On receipt of a prescription for a TIRF medicine at an enrolled closed system pharmacy, the pharmacist will contact the TIRF REMS Access program via phone or fax to provide prescription details for verification. The TIRF REMS Access program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the closed system pharmacist will continue to contact the TIRF REMS Access program via phone or fax with prescription information in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, the closed system pharmacy will be provided an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will not provide an authorization number and the closed system pharmacy will receive a rejection notice. This feedback will be provided to the closed system pharmacy via phone or fax and will include the reason for rejection, information on how the rejection may be resolved and instructions on not dispensing the TIRF prescription until resolution is reached.

f. The TIRF REMS Access Program Website

- The TIRF REMS Access program website (www.TIRFREMSaccess.com) contains information about the TIRF REMS Access program and serves as one method by which prescribers can receive education and enroll themselves in the TIRF REMS Access program. The prescriber will also be able to complete and submit a Patient-Prescriber Agreement Form via the website.
- Outpatient and inpatient ~~P~~pharmacies can use the website for education and enrollment, including a dashboard functionality to allow chain pharmacies to manage their stores
- Closed system pharmacies can use the website for education.
- The website includes the TIRF REMS Access Education Program, Knowledge Assessment and enrollment forms that must be reviewed and completed before enrolling. The website is referenced in all TIRF REMS Access program and TIRF medicine related materials.
- Prescribers can use the website to inform patients of enrolled pharmacies that can dispense TIRF medicines.

The TIRF REMS Access program Website also serves as a resource for:

- Description of the TIRF REMS Access program
- Ordering TIRF REMS Access Medication Guides
- Full Prescribing Information for all TIRF medicines
- Medication Guides for all TIRF medicines
- Patient/Caregiver, Prescriber, Outpatient~~Pharmacy and~~ Inpatient and Closed System Pharmacies TIRF REMS Access program overviews in on-screen and printer friendly format
- TIRF REMS Access program contact information
- Frequently Asked Questions

g. The Key Elements of this REMS that Mitigate the Risks Associated with the Use of TIRF medicines are:

i. A certified prescriber who has acknowledged and agreed to adhere to the conditions that must be met for the appropriate outpatient use of each TIRF medicines.

- Prescribers will be educated and certified on the risks of inappropriate patient selection, including non-opioid tolerant patients. In order to become enrolled, outpatient prescribers will be required to complete the TIRF REMS Access Education Program and Knowledge Assessment. Enrollment is contingent upon prescribers documenting that they understand the risks of TIRF medicines and agree to the appropriate use of TIRF medicines (See appended Prescriber Enrollment Form).
- Without this enrollment, patients, with prescriptions from outpatient prescribers will be unable to have TIRF medicine prescriptions filled by an enrolled pharmacy.
- The TIRF REMS Access program will maintain a database of all enrolled prescribers.

ii. The certified outpatient or chain pharmacy has agreed to send all claims through the system to verify eligibility. The certified closed system pharmacy has agreed to contact the TIRF REMS Access program to verify eligibility and receive authorization prior to dispense.

- All pharmacies that intend to purchase and dispense TIRF medicines must be enrolled in the TIRF REMS Access program in order to receive product from distributors. Pharmacies will be enrolled only after an authorized pharmacist undergoes *TIRF REMS Access Education Program*, completes a *Knowledge Assessment* and submits an enrollment form.
- Pharmacies that are not enrolled will be unable to obtain supplies of TIRF medicines.
- The TIRF REMS Access program will maintain a database of all certified pharmacies.

Outpatient Pharmacies

- The outpatient or chain pharmacy will ensure that the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- The closed system pharmacy will have processes in place to ensure the TIRF REMS Access program is contacted and authorization has been received prior to the dispensing of a TIRF prescription.
- The authorized pharmacist will ensure that all pharmacy staff involved in dispensing TIRF medicines at their pharmacy have been educated on the risks associated with TIRF medicines, maintain auditable training records for pharmacy staff, and adhere to the requirements of the TIRF REMS Access program.
- The pharmacist must ensure that TIRF medicines have been dispensed under the following safe use conditions:

- The pharmacist has dispensed TIRF medicines only to enrolled patients, based on a valid Schedule II prescription from an enrolled prescriber and receipt of an authorization message from the TIRF REMS Access program.
- The pharmacist has offered counseling to patients on appropriate TIRF medicine use.
- The pharmacist has provided each patient with a product specific Medication Guide for every TIRF prescription dispensed, instructed the patient to read it and has answered any questions the patient may have.

- Additionally, all TIRF medicine prescriptions will be tracked based on the following:
  - Prescription validation and dispensing steps performed by enrolled pharmacists;
  - Generation of a prescription authorization number from the TIRF REMS Access database upon confirming enrollment status. This tracking will enable identification of prescriptions, as well as provide utilization information used in the evaluation of the TIRF REMS Access program.

Inpatient Pharmacies

- The authorized pharmacist for an inpatient pharmacy will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program. The authorized inpatient pharmacist acknowledges that Pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
- An inpatient pharmacy is not to dispense TIRF medicines for outpatient use.
- A prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.

iii. An informed outpatient and/or caregiver should understand the inherent risks in the use of opioids and know how to administer TIRF medicines appropriately at home. Therefore, each patient must:

- Sign a TIRF REMS Access program *Patient-Prescriber Agreement Form* that documents appropriate use conditions and opioid tolerance (See appended Patient-Prescriber Agreement Form).
- Deliver the TIRF medicine prescription to an enrolled pharmacy.
- Understand that they must be regularly using another opioid pain medicine for their constant pain.

- Be counseled on responsible use and handling by the pharmacist at each dispensing when they receive an additional copy of the appropriate Medication Guide.
- These requirements do not apply to inpatient use of a TIRF medicine.

C. Implementation System

The Implementation System includes the following:

a. Wholesaler/Distributor Enrollment and Fulfillment

- TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

- For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors will be contacted and will receive a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies. The distributor's authorized representative reviews the distributor program materials. The distributor's authorized representative will complete and sign the *Distributor Enrollment Form* and fax it to the TIRF REMS Access program. TIRF Sponsors will not ship TIRF medicines to any distributor who has not completed and signed the enrollment form; by checking the status of the distributor prior to shipping the drug (See appended Distributor Enrollment Form).
- As part of the TIRF REMS Access program, distributors will need to enroll in the TIRF REMS Access program. Distributors will need to confirm their understanding of the distributor requirements in the TIRF REMS Access program, which includes verifying that pharmacies are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
- The distribution process for TIRF medicines as it relates to drug distributors will consist of:
    - Only those TIRF medicine Sponsor contracted distributors will be eligible for TIRF REMS Access program enrollment.
    - TIRF medicine distributors will be contacted and will receive a communication describing the TIRF REMS Access program.
    - TIRF medicine distributors must acknowledge receipt and understanding of the TIRF REMS communication, by completing the TIRF REMS Access Distributor Enrollment Form, in order to become a customer eligible to receive and/or distribute TIRF medicines from TIRF Sponsors. In addition to the TIRF REMS Access *Distributor Enrollment Form*, the distributor's authorized contact will receive communication on how to verify pharmacies that are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.

- The procedures for the TIRF REMS Access program will include the method for timely communications of newly enrolled as well as inactive pharmacies in the TIRF REMS Access program.
- The procedures for the TIRF REMS Access program will also include the procedure for reporting and management of non-compliance with the TIRF REMS Access distribution program.
- Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.
- Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years. TIRF medicine Sponsors will notify distributors (based on contractual relationships in place between Sponsor and distributors) of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.
- If there are substantive changes to the TIRF REMS Access program, impacted TIRF Sponsor or TIRF Sponsor team will update all affected materials and notify distributors of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    i. Significant changes to the operation of the TIRF REMS Access program.
    ii. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of impacted TIRF medicine.

b. The TIRF REMS Access Program Database

- The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive).
- Management of the TIRF REMS Access database will be contracted to an appropriately qualified third party vendor and overseen by the TIRF Sponsors. Data for all users will be updated in the TIRF REMS Access database. This includes data received from both the call center manual process and web-based processes. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing their TIRF medicine. Additionally, TIRF Sponsors will monitor to ensure their TIRF medicine is only being dispensed for outpatient use to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by the TIRF Sponsors if noncompliance is found.
- TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a Patient-Prescriber Agreement Form with each TIRF medicine patient, and to submit it to the REMS program within ten (10) working days. A maximum of three prescriptions are

allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This will be accomplished by reconciling the *Patient-Prescriber Agreement Forms* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.

- TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
- TIRF Sponsors will monitor the prescribing and dispensing of TIRF medicines to enrolled patients. If non-compliance is found, TIRF Sponsors will institute corrective actions. Please refer to Section 5(B) for further details.
- TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

Based on monitoring and evaluation of these elements to ensure safe use, TIRF Sponsors will work to improve implementation of these elements and to ensure compliance with the TIRF REMS Access program requirements, as applicable.

c. TIRF REMS Access Program Call Center

The TIRF REMS Access program includes a call center component. The call center will be staffed by qualified and trained specialists, who will provide TIRF REMS Access program support to patients, prescribers, pharmacies and distributors.

The call center specialists' responsibilities will include, but are not limited to, the following:

- Provide TIRF REMS Access program enrollment assistance to prescribers, pharmacies, distributors and patients
- Processing of prescriber, pharmacy and distributor enrollments and Knowledge Assessment forms
- Provide stakeholder enrollment verification in the TIRF REMS Access database
- Processing of Patient- Prescriber Agreements Forms
- Assist prescribers or patients in locating enrolled pharmacies
- Collect prescription information for enrolled closed system pharmacies and provide authorization numbers for each dispensing
- Identify and transfer product complaints and potential adverse event information to TIRF Sponsors

- Provide general program information and technical assistance to stakeholders interacting with the TIRF REMS Access website

The TIRF REMS Access program call center hours of operation are Monday – Friday, 8:00am to 8:00pm EST. Callers outside of these hours are instructed to leave a message that will be addressed at the beginning of the next business day. TIRF medicine Medication Guides may include the TIRF Sponsor phone number and may be contacted. TIRF Sponsors may refer caller to Emergency Room.

The TIRF REMS Access program call center flow is show below in Figure 6.

Figure 6 TIRF REMS Access Program Call Center Flow

(b) (4)

D. Timetable for Submission of Assessments of the REMS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. The knowledge, attitude, and behavior (KAB) surveys will be submitted at 12 and 24 months from the date of the REMS approval, and as needed thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

5. REMS ASSESSMENT PLAN

The aim of the TIRF REMS Access program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations will be used in an effort to improve the processes, over time, as needed.

A Data Sources

Data will be collected from the following main sources as described in detail below: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program infrastructure and performance, d) safety surveillance, e) periodic surveys of patients, healthcare providers, and inpatient and outpatient pharmacies. For the purposes of reporting "outpatient" includes chain pharmacy corporate headquarters, chain pharmacy retail stores, independent pharmacies, and closed system pharmacy headquarters and stores.

a. The TIRF REMS Access Program Outreach

The following metrics will be tabulated for every reporting period to assess program outreach efforts:

1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

b. The TIRF REMS Access Product and Program Utilization Statistics

The TIRF REMS Access program data flow is show in Figure 7 below.

Figure 7 TIRF REMS Access Program data flow

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following data will be tabulated for each reporting period and cumulatively:

5. Number of new patients enrolled by state
6. Number of patients inactivated

7. Number of attempts needed for prescribers to successfully complete Knowledge Assessments
    - Method of completion
8. Number of new prescribers enrolled by state
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
9. Number of prescribers who are inactivated
10. Number of new pharmacies enrolled by type (inpatient or outpatient), by state
    - Method of enrollment
    - Number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
11. Number of pharmacies that are inactivated by type (inpatient or outpatient)
12. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments
13. Dispensing activity for enrolled outpatient pharmacies
    - Total number of prescriptions authorized
    - Total number of prescriptions rejected for safety (description of safety issues and any interventions or corrective actions taken)
14. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome)
15. Number of wholesalers/distributors inactivated, total
16. Number of new wholesalers/distributors enrolled
    - Method of enrollment
    - Number of incomplete forms
17. Number of days between passive enrollment and receipt of a Patient-Prescriber Agreement Form
    - Method of PPA submission
18. Number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment with and without a PPAF in place.

c. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be tabulated for each reporting period and cumulatively:

19. Assessment of process for pharmacies to upgrade their pharmacy management systems (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems)

20. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem)
21. Call center report
    - Summary of frequently asked questions
    - Problems reported
22. Description of corrective actions taken to address program/system problems.
23. Number of reports of lack of enrolled prescribers and/or pharmacies in a patient's area
24. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays

The following reports for unintended system interruptions will be provided for each reporting period:

25. Reports identified of inadvertent enrollment deactivations
26. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code)
27. Reports of failure of re-enrollment notifications to reach stakeholders
28. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection.

d. Safety Surveillance

- TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures.
- Surveillance data from the following sources will be included in the REMS Assessment Reports:
    - FDA AERS database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion
    - Other external databases.

e. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Survey results will be reported at 12 months and 24 months after the TIRF REMS Access program approval. TRIG will discuss with the FDA if additional surveys are needed after 24 months. The results from the surveys will be analyzed together with other REMS assessment data, and a report on any corrective actions taken and the outcome of those actions will be provided.

B. TIRF REMS Access Non-Compliance Plan

GOALS & OBJECTIVES

The TIRF REMS Access program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the non-compliance plan is to ensure that TRIG monitors the functioning of TIRF REMS Access and identifies and investigates deviations and non compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program.

TIRF REMS ACCESS NON-COMPLIANCE REVIEW TEAM

A TIRF REMS Access Non-Compliance Review Team will be created. The team will have membership from the companies of the TRIG. A detailed plan for the TIRF REMS Access program will be created and implemented by the team.

The TIRF REMS Access Non-Compliance Review Team's responsibility will be to:

- Evaluate the compliance of patients, healthcare providers, distributors and pharmacies (stakeholders) with the TIRF REMS Access program
- Investigate potential non-compliance activity when events are referred to the team
- Devise corrective measures and issue notices, warnings, suspensions, or deactivations of stakeholders where warranted
- Review need for changes to the TIRF REMS Access program as a result of deviations or non-compliance

The TIRF REMS Access Non-Compliance Review Team will meet regularly.

Any needed program modifications or stakeholder notifications will be approved by TRIG prior to implementation.

SOURCES OF NON-COMPLIANT EVENTS

There are a variety of ways in which the TIRF REMS Access program can detect non compliance. Those potential sources include:

- TIRF REMS Assessment reports
- REMS database activity
- TRIG Member Company Adverse Event Reporting or Medical Information
- TIRF REMS Access Program Call Center
- Data Requests and Audits

TIRF REMS Access Assessment Reports

TIRF REMS Access program data will be collected from the following main sources: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program performance, d) safety surveillance, e) periodic surveys of stakeholders.

The TIRF REMS Access Non-Compliance Review Team will regularly review the assessment reports for evidence of non-compliance or deviation from program procedures.

REMS Database Activity

The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive). Data for all users will be updated in the TIRF REMS Access database including data from the call center manual process, web-based processes, ~~and the~~ pharmacy network and prescription authorizations for closed systems.

The TIRF REMS Access Non-Compliance Review Team will regularly analyze database reports to detect evidence of non-compliance or deviation from program procedures.

TRIG Member Company Adverse Event Reporting or Medical Information

Each company in the TRIG is responsible for the intake, investigation, review and reporting of adverse events and answering medical information queries for their own product. Each TRIG member will review adverse events or medical information queries received by that company and forward events which contain evidence of TIRF REMS Access non-compliance or deviation to the TIRF REMS Access Non-Compliance Review Team for further evaluation. For privacy or commercial confidentiality reasons, this information may be redacted before forwarding, and individual investigation for these events will be referred back to the company that initially received the event.

TIRF REMS Program Call Center

The TIRF REMS Access program will have a call center available for questions about the program, or to process non website enrollments. Enrollments or queries that contain evidence of non-compliance or deviation from program procedures will be referred to the TIRF REMS Access Non-Compliance Review Team.

Data Requests and Audits

TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

The TIRF REMS Access Non-Compliance Review Team will review information received from data requests and audit reports to detect evidence of non-compliance or deviation from program procedures.

EVALUATION PROCESS

Events of suspected non compliance or deviation from TIRF REMS Access program procedures will be evaluated by the TIRF REMS Access Non-Compliance Review Team. Further corrective actions for stakeholders may occur and are described below.

CORRECTIVE ACTION MEASURES

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action in accordance with the TIRF REMS Access non-compliance plan. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access Non-Compliance Review Team according to the severity of the action. The stakeholders in this non-compliance plan include prescribers, patients, distributors, inpatient pharmacies, chain pharmacies, ~~and~~ outpatient pharmacies and closed system pharmacies. The primary elements for corrective action include; notices, warnings, suspension, and deactivation, based on the incidence and outcomes of misuse, abuse, and overdose, in addition to accidental or intentional exposure. If a prescriber or pharmacy is suspended or deactivated, information will be made available through the program to assist patients in finding alternative prescribers or pharmacies.

Notices

Notices are defined as minor violations that demonstrate a misunderstanding of the program requirements. Notices of non-compliance reinforce the program requirements and are intended to re-educate stakeholders. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

Warnings

Warnings are serious violations that result in an improper patient receiving a TIRF medicine. Warnings may be accompanied by other corrective actions (e.g. retraining) that may be required in order to avoid suspension.

Suspension

Suspension is a temporary deactivation from the program pending the completion of a Corrective Action Plan. Multiple warnings received by a stakeholder within a sixty day time-period will result in a Suspension. Multiple warnings received by a stakeholder over longer periods will accumulate, be logged in reports and may result in a suspension at the discretion of the TIRF REMS Access Non-Compliance Review Team.

A suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension, but may not purchase or acquire additional TIRF medicines until the suspension is removed. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension, and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy, closed system pharmacy or distributor is part of a larger entity (e.g. a Chain Pharmacy or a multi-site distributor), the parent entity will be notified of the non-compliant activity and resultant suspension.

Deactivation

Deactivation is defined as an indefinite deactivation from the program. Deactivation may result from the failure of the stakeholder to implement corrective actions, multiple failures to comply

with material program elements, and/or non-compliances where there is no feasible corrective action. Deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

A deactivated stakeholder may request reinstatement in the TIRF REMS Access program. Requests for reinstatement must be in writing (e.g. letter, fax, etc.) and contain sufficient details on corrective actions taken to prevent any future non-compliance with program elements. Patients that have been deactivated will only be reinstated by a request made by the patient's prescriber. Requests for reinstatement will be evaluated by the TIRF REMS Access Non-Compliance Review Team which will make a recommendation to TRIG. TRIG will make the final determination on reinstatement.

TIRF REMS ACCESS PROGRAM AUDITS

As part of non-compliance monitoring, TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

C. Internal Quality and Compliance

The TIRF medicines REMS program team will be supported by written procedures to define process and will be audited against these for compliance.

6. OTHER RELEVANT INFORMATION

A. The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program, all TIRF medicines in an individual REMS program will be transitioned to the TIRF REMS Access program. The transition for the TIRF REMS Access program will begin upon system availability. From this point onward all *new* stakeholders will be required to enroll in the TIRF REMS Access program.

Upon system availability the individual REMS program websites, call centers, and enrollment forms will be redirected to the TIRF REMS Access program. The TIRF REMS Access program will provide information and direction on why the individual REMS program website is no longer available, in addition to providing an introduction to the new TIRF REMS Access program and resources available to stakeholders. Historical data from all individual REMS programs will be referenced to determine the date of last prescription so that the TIRF REMS can accurately calculate 6 months of no prescription activity.

All pharmacies and prescribers already enrolled in an individual REMS program will be notified (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. They will also be notified in these letters that:

- They must review the Education Program on the TIRF REMS Access program website or request a copy from the call center.
- If the prescriber changes the patient's TIRF medicine at any time the prescriber is required to counsel the patient on the new product and provide the relevant Medication Guide but no new Prescriber-Patient Agreement Form (PPAF) is required.

Prescribers
Enrollment data for each enrolled prescriber will be transferred from the individual REMS program to the TIRF REMS Access program database when it is available. These prescribers will then be able to prescribe any TIRF medicine within the TIRF REMS Access program. Healthcare providers will be guided to review the educational program for the TIRF REMS Access program but will not be tested on these materials. These prescribers will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

Inpatient Pharmacies
Enrollment data for each enrolled inpatient pharmacy will be automatically transferred from the individual REMS program to the TIRF REMS Access program database when it is available. Inpatient pharmacies will then be able to order and dispense any TIRF medicine within the TIRF REMS Access program to inpatients.

Outpatient Pharmacies
All outpatient pharmacies in an individual REMS program will be automatically transitioned to the new TIRF REMS Access program.

However, chain pharmacies will need to execute a TIRF REMS Access program contract with their switch provider before they can order and dispense all TIRF medicines. Chain pharmacies that have not executed a TIRF REMS Access program contract with their switch provider will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If chain pharmacies do not execute a TIRF REMS Access program contract with their switch provider within six months, they will no longer be able to order or dispense any TIRF medicine.

Independent pharmacies will need to agree to the shared program terms and conditions before they can order and dispense all TIRF medicines. Independent pharmacies that have not agreed to the shared program terms and conditions will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If outpatient pharmacies do not sign the new business

contracts within six months they will no longer be able to order or dispense any TIRF medicine, and will have to complete an updated contract if they wish to continue to dispense TIRF medicines.

All pharmacies that have been transitioned from an individual REMS program will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their original enrollment in the individual REMS program.

Patients
Enrollment data for patients will be automatically transferred from the individual REMS program to the TIRF REMS Access program database. Patients who have previously been enrolled in an individual REMS and have completed a PPAF can be prescribed/receive any TIRF medicine within the TIRF REMS Access program. Patients will only be required to complete a new PPAF for the TIRF REMS Access program every 2 years from their last PPAF.

Distributors
Distributors already enrolled in a single product REMS program will be notified of the transition to the TIRF REMS Access program (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. Enrollment data for distributors will be transferred from the individual REMS program to the TIRF REMS Access program database. Distributors will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

B. The TIRF REMS Access Program Steering Committee

A TIRF REMS Access program steering committee will be comprised of representatives from each Sponsor who will provide high level oversight and strategic direction for the TIRF REMS Access program. One voting member from each Sponsor company will be included in the Steering Committee. Significant issues and trends will be reviewed and appropriate recommendations made to the TIRF medicine Operations Team.

C. Abbreviations

The following abbreviations refer to the REMS program descriptors and products.

TIRF Medicines:	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access:	REMS program for TIRF medicines
TIRF Sponsors:	The group of sponsors that are submitting this REMS (please refer to the 'List of TIRF REMS Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.)

7. REFERENCES

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TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) My patient is currently using around-the-clock opioid medication and has been for at least one (1) week.

2) My patient is opioid-tolerant. Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

4) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

5) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

6) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that before I can take any TIRF medicine, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* is part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain pharmacy) or authorized pharmacist (outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. There are different enrollment requirements for :

- **outpatient pharmacies** (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use), including chain pharmacies, but excluding closed system pharmacies (see definition below).
- **closed system pharmacies** For the purposes of this REMS, a closed system pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system pharmacies.
- **inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Outpatient Pharmacies:***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment.*

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Outpatient Pharmacy Enrollment Form* or the *Chain Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Outpatient Pharmacy Enrollment Form or Chain Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

e. *Closed System Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Pharmacy Enrollment Form*. In signing the *Closed System Pharmacy Enrollment Form*, the authorized closed system pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and

pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the 'List of TIRF Medicines available only through the

TIRF REMS Access Program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Outpatient Pharmacy, Chain Pharmacy, Closed System Pharmacy* or *Inpatient Pharmacy*, as applicable)

- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Outpatient, Chain, Closed System, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **outpatient pharmacies** (including chain pharmacies) only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system pharmacy, the pharmacy meets the requirements of being deemed a 'closed system' pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in

section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system pharmacies:** prior to dispensing TIRF medicines, enrolled closed system pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

   ii. The patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each

wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

2. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

3. For **outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

4. For **closed system pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax.

TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

5. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the *Patient-Prescriber Agreements* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **outpatient pharmacies** or through the call center **for closed system pharmacies**.
6. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
7. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
8. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
9. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
10. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
11. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA and ANDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA and ANDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

MALLINCKRODT INC.

COVIDIEN

GENERAL CORRESPONDENCE: REMS ASSESSMENT REPORT (12 MONTHS) AND KAB SURVEY REPORTS

December 20, 2012

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

RE: ANDA 078907: Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg

Dear Sir or Madam:

Reference is made to the Transmuscosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) access program approved by the Food and Drug Administration (FDA) on December 28, 2011. Further reference is made to the General Correspondence letter dated May 18, 2012 for the KAB Survey Methodology and to the General Correspondence letter dated June 28, 2012 for the first REMS Assessment Report (6 months) for the reporting period of 12/28/2011 – 04/27/2012.

Mallinckrodt, Inc. the Pharmaceuticals business of Covidien, hereby submits this General Correspondence letter containing the second REMS Assessment Report required 12 months after initial approval of the REMS access program. For this reporting period (4/28/2012 – 10/28/2012), the cut-off date was 10/28/2012, thereby allowing 60 days to prepare the assessment report for FDA submission. Mallinckrodt is also submitting three KAB survey reports documenting the level of knowledge, attitudes, and behaviors of the (1) patient-caregiver, (2) pharmacist, and (3) prescriber regarding key information and risk messages communicated through the shared REMS system. The survey results also collected data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements. The report includes ETASU data (FDA AERS and AAPCC reports).

FDA should refer to our most recent annual report for information on post-approval studies and/or clinical trials.

This general correspondence letter, which has been organized according to the June 2008 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, is approximately 5 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0045. It has been checked and found free from virus infection using McAfee VirusScan Enterprise 8.7*i* Antivirus Software. For technical assistance, please contact Jeremy Grise, Manager, Regulatory Operations at 314-654-8259.

Correspondence related to this application should be addressed to Jasen Wallace, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-3157, or Rebecca Welton, Associate Director, Regulatory Affairs, at 314-654-5607.

Sincerely,

Jasen Wallace

Digitally signed by Jasen Wallace
DN: cn=Jasen Wallace, o=Covidien, ou=Regulatory Affairs, email=jasen.wallace@covidien.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2012.12.19 07:53:42 -06'00'

Jasen Wallace
Senior Regulatory Affairs Specialist
jasen.wallace@covidien.com
Fax: 314-654-3157

1.16 Risk Management Plans

The second REMS Assessment Report is provided herein. This report includes ETASU data (FDA AERS and AAPCC reports), and all three KAB reports (patient, prescriber, and pharmacy).

12-MONTH REPORT PRODUCED AS FDA_81 TO FDA_669

Lemley, Carrie

From: Lemley, Carrie
Sent: Monday, April 15, 2013 9:29 AM
To: Wallace, Jasen C
Subject: Information request for ANDA 078907

Dear Jasen ,

We are reviewing the 12-month assessment report for the TIRF REMS and have the following information request. This IR is being sent to all NDA and ANDA holders under the TIRF REMS. Please submit the requested information to your individual application by **Wednesday, May 15, 2013**.

As part of the TIRF REMS Assessment Report, public FAERS postmarketing reports of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental pediatric exposures/ingestion were submitted. Provision of line listings or individual PTs is insufficient for a thorough analysis of safety data as it relates to the effectiveness of the REMS. The nearly 6 month gap in these data also does not allow a timely analysis of safety data. In order to better assess safety, and to determine whether the REMS is meeting its goals, an analysis of individual Sponsor's internal adverse event data is needed.

REQUEST FOR INFORMATION
For the time period between December 28, 2011 and October 20, 2012:

- Provide an overall summary analysis describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, overdose.)
- In tabular form, for each US case reported from December 28, 2011 to October 20, 2012 that includes one or more of the following events:(death, overdose, misuse, abuse, addiction, inappropriate prescribing*, medication error, accidental pediatric exposures/ingestion), provide at a minimum, the following information if available:
    - Manufacturer control number
    - Patient age
    - Patient gender
    - Event date
    - Report date
    - Description (narrative) of the event
    - Root cause of AE or error, if known
    - Type of pain (cancer, chronic non-cancer, acute)
    - TIRF product name
    - TIRF product Dose
    - TIRF product duration use

- Concurrent extended-release or long-action opioid and dose
- Concurrent CNS depressant medications
- Concurrent illicit drugs or alcohol, if recorded
- Pertinent patient medical history
- Outcome of event

o For clarity in the final report, provide a total number of unique cases . Also note within each table which cases contain more than one event, (e.g. inappropriate prescribing and overdose), with a notation such as an asterisk, so that there is no duplication in case count.

o Include the working definitions for the event term by which each case was classified.

o Append MedWatch forms for the events listed in the table.

*includes inappropriate conversion between TIRFs, inappropriate patient selection

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CARRIE L LEMLEY
04/15/2013

MALLINCKRODT INC.

COVIDIEN

INFORMATION REQUEST:
REMS ASSESSMENT REPORT (12 MONTHS)

May 15, 2013

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

RE: ANDA 078907
Oral Transmucosal Fentanyl Citrate 200, 400, 600, 800, 1200, and 1600 mcg

Dear Sir or Madam:

Reference is made to the Transmuscosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) access program approved by FDA on December 28, 2011. Further reference is made to the REMS 12-month assessment report dated December 20, 2012 for the reporting period of 12/28/2011 – 10/20/2012 and to the ensuing **Information Request** received via email from Carrie Lemley, FDA dated April 15, 2013. A copy of the email is provided herein for reviewing convenience.

Mallinckrodt, Inc. the pharmaceutical business of Covidien, hereby submits this response to the Information Request from Carrie Lemley, FDA dated April 15, 2013. This response provides for the following additional information to the 12-month assessment report:

(1) An overall summary analysis describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, overdose.);

(2) A tabulation including one or more of the following events: death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication error, accidental pediatric exposures/ingestion with the available relevant information;

(3) MedWatch forms for the adverse event case reports.

This Information Request response, which has been organized according to the June 2008 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, is approximately 5 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0047. It has been checked and found free from virus infection using McAfee VirusScan Enterprise 8.7*i* Antivirus Software. For technical assistance, please contact Jeremy Grise, Manager, Regulatory Operations at 314-654-8259.

Correspondence related to this application should be addressed to Jasen Wallace, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-3157, or Rebecca Welton, Associate Director, Regulatory Affairs, at 314-654-5607.

Sincerely,

Jasen Wallace
Senior Regulatory Affairs Specialist
jasen.wallace@covidien.com
Fax: 314-654-3157

Wallace, Jasen C

From: Lemley, Carrie <Carrie.Lemley@fda.hhs.gov>
Sent: Monday, April 15, 2013 8:29 AM
To: Wallace, Jasen C
Subject: Information request for ANDA 078907

Dear Jasen ,

We are reviewing the 12-month assessment report for the TIRF REMS and have the following information request. This IR is being sent to all NDA and ANDA holders under the TIRF REMS. Please submit the requested information to your individual application by **Wednesday, May 15, 2013**.

As part of the TIRF REMS Assessment Report, public FAERS postmarketing reports of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental pediatric exposures/ingestion were submitted. Provision of line listings or individual PTs is insufficient for a thorough analysis of safety data as it relates to the effectiveness of the REMS. The nearly 6 month gap in these data also does not allow a timely analysis of safety data. In order to better assess safety, and to determine whether the REMS is meeting its goals, an analysis of individual Sponsor's internal adverse event data is needed.

REQUEST FOR INFORMATION

For the time period between December 28, 2011 and October 20, 2012:

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- In tabular form, for each US case reported from December 28, 2011 to October 20, 2012 that includes one or more of the following events:(death, overdose, misuse, abuse, addiction, inappropriate prescribing*, medication error, accidental pediatric exposures/ingestion), provide at a minimum, the following information if available:

    - Manufacturer control number
    - Patient age
    - Patient gender
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    - Report date
    - Description (narrative) of the event
    - Root cause of AE or error, if known
    - Type of pain (cancer, chronic non-cancer, acute)
    - TIRF product name
    - TIRF product Dose

- TIRF product duration use
- Concurrent extended-release or long-action opioid and dose
- Concurrent CNS depressant medications
- Concurrent illicit drugs or alcohol, if recorded
- Pertinent patient medical history
- Outcome of event

o For clarity in the final report, provide a total number of unique cases . Also note within each table which cases contain more than one event, (e.g. inappropriate prescribing and overdose), with a notation such as an asterisk, so that there is no duplication in case count.

o Include the working definitions for the event term by which each case was classified.

o Append MedWatch forms for the events listed in the table.

*includes inappropriate conversion between TIRFs, inappropriate patient selection

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS): 12-Month Assessment Report (28DEC2011 to 20OCT2012)

Introduction

On 28DEC2011, the Food and Drug Administration (FDA) approved the single, shared Risk Evaluation and Mitigation Strategy (REMS) for the transmucosal immediate release fentanyl (TIRF) products. The shared system strategy, called the TIRF REMS Access Program, was successfully launched on 12MAR2012 and since then, has been used by all sponsors of TIRF products. The TIRF REMS Access Program is expected to ease the burden on the health care system as it allows prescribers, patients and pharmacies to enroll into just one system.

The Industry Group (Pharmaceutical manufacturers involved with the class REMS) contracted a company to assist with the REMS activities for transmucosal intermediate release fentanyl, particularly with submission of assessment reports. The 12-month TIRF REMS Assessment report was submitted to the FDA on 20DEC2012.

Mallinckrodt received a request for information from the FDA on 15APR2013 in connection with the TIRF REMS 12-month Assessment Report. The inclusive period of the request is from 28DEC2011 to 20OCT2012. The FDA stated that the individual Sponsor internal adverse event data is needed in order to completely assess safety and to determine whether the REMS is achieving its goals. Provision of line listings or individual Preferred Terms (PTs) would not be sufficient for intended evaluation.

The purpose of this review is to provide the FDA with 1) an overall summary analysis describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, overdose.); 2) a tabulation including one or more of the following events: death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication error, accidental pediatric exposures/ingestion with the available relevant information; and 3) MedWatch forms for the adverse event case reports.

Methodology

Mallinckrodt performed a search of the global safety database for all cases of transmucosal immediate release fentanyl (TIRF) received during the inclusive period. The search strategy was based on identifying cases with the suspect product having the fentanyl citrate active moiety and Mallinckrodt's oral transmucosal formulation (OTFC). The adverse event (AE) reports were further screened for cases originating from the United States and reporting special interest events of overdose, misuse, abuse, addiction, medication errors and accidental pediatric exposures/ingestion. US reports with the outcome

of death were also reviewed. In addition, these US cases were evaluated for appropriate prescribing of fentanyl. Cases reporting these special interest events but with an unknown formulation of fentanyl or with a non-Mallinckrodt formulation were excluded in the assessment. When the formulation is unknown, adverse event reports are submitted to the company's oldest fentanyl license which is the OTFC.

Table I: Case Definition

Case Classification	Case Definition
Accidental pediatric exposures/ingestion	Any case that has an event coded to MedDRA Preferred Term (PT) of accidental exposure to product by a child
Addiction	Any case in which a MedDRA Lower Level Term (LLT) of addiction or addicted to drugs or specific drugs codes to MedDRA PT of dependence or drug dependence
Drug abuse	Any case in which an event is coded to MedDRA PT of drug abuse
Fatal outcome	Any case in which an event has an outcome of death
Inappropriate prescribing	Any case in which indication for use of fentanyl or narrative described fentanyl usage apart from management of breakthrough pain in opioid-tolerant cancer patients 16 years of age and older
Intentional drug misuse	Any case that has an event coded to MedDRA PT of intentional drug misuse
Medication error	Any case that has an event that codes to MedDRA High Level Group Term (HGLT) of medication error is classified under Medication Error
Overdose	Any case with an event coded to MedDRA PT of accidental overdose, intentional overdose, overdose and prescribed overdose

Results

A total of 90 case reports with fentanyl as the active moiety were received during the inclusive period. MedWatch forms for all cases are attached (Appendix I).

Of the 90 case reports, 71 cases were of United States origin. Out of the US cases, 33 were of REMS special interest. Tables for each event of special interest are attached as Appendices.

A. Cases with Fatal Outcome

Fifteen cases reported an outcome of death of which 14 were received through literature surveillance activity while 1 was reported spontaneously.

1. Abuse

Five cases (T201200240, T201200242, T201200247, T201200248 and T201200251) reported fatal drug abuse. All of these cases came from the annual report of the American Association of Poison Control Centers (AAPCC). Fentanyl formulation and manufacturer was

unknown. Missing data included event onset, product dose and duration of use. Concurrent medication was provided in four of the cases.

2. Overdose

There was one case of fatal overdose (T201200523). The case was reported spontaneously. However, the reporter did not provide product formulation/manufacturer, amount taken, concurrent medications and pertinent medical history.

3. Other Cases with Fatal Outcome

The remaining 9 cases with fatal outcome came from literature articles. Eight cases were included in the annual report of American Association of Poison Control Centers. Cardio-respiratory arrest and completed suicide were the events associated with death. Fentanyl formulation and manufacturer were not reported. Concurrent medications were mentioned in some of the cases but event onset, product dose and duration of use as well as pertinent medical history were not provided. The last case (T201203533) had the same missing data as the other cases but medical history of hepatic steatosis and ongoing Ibogaine treatment for opioid detoxification was included in the report.

B. Cases without Fatal Outcome

Eighteen cases did not report a fatal outcome. Of these cases, 2 were from literature articles and 16 were from spontaneous sources.

1. Abuse

Two cases, T201204618 and T201204623, were reported spontaneously to a poison control centers. No information was provided for fentanyl formulation/manufacturer, product dose and duration of use, event onset, concurrent medication and pertinent medical history.

2. Overdose

Two cases of overdose were received during the inclusive period (T201203037 and T201203042). Both cases were from literature articles. Fentanyl formulation and manufacturer was not reported. Concurrent medications which included opioid and benzodiazepines as well as pertinent medical history of substance abuse and depression were provided.

3. Misuse

One spontaneous case, T20120461, reported on intentional drug misuse through a poison control center. Missing information included fentanyl formulation/manufacturer and pertinent medical history. Event outcome was not provided.

4. Inappropriate Prescribing

Thirteen spontaneous cases were received showing use of OTFC to be outside the approved indication for the product

5. Addiction, Medication Error and Accidental Pediatric Exposure/Ingestion

During the inclusive period, no case involving addiction, medication error and accidental pediatric exposure/ingestion was received.

Analysis

A. Cases with Fatal Outcome

1. Abuse

The five fatal cases of abuse were from the annual report of the AAPCC. In all cases, the associated event of cardio-respiratory arrest was present which led to the demise of the patients. Cardio-respiratory arrest is currently not in the OTFC US prescribing information (USPI). Very minimal information was provided for T201200247 making assessment of causality between drug and event not possible. For the other four cases, a concurrent medication taken together with fentanyl was reported. These included central nervous system (CNS) depressants such as benzodiazepines (alprazolam and diazepam) and a selective serotonin reuptake inhibitor (SSRI- citalopram). Benzodiazepines affect a key neurotransmitter in the brain called gamma-aminobutyric acid (GABA) which has an inhibitory effect on motor neurons. Benzodiazepines enhance the effect of GABA causing CNS depression. In overdose situations this pharmacological effect is extended leading to a more severe CNS depression and potentially coma or cardiac arrest[1]. When combined with other CNS depressants, the potential for toxicity and fatal overdoses of benzodiazepine increases[2]. In T201200240, alprazolam was the concurrent CNS depressant medication while diazepam was involved in cases T201200242 and T201200251. No dose taken by the patients was provided for these medications as well as for fentanyl. On the other hand, SSRIs have increasingly been associated with various arrhythmias[3]. In August 2011, FDA issued a Drug Safety Communication (DSC) stating that citalopram should no longer be used at doses greater than 40 mg per day because it could cause potentially dangerous abnormalities in the electrical activity of the heart. Changes in the electrical activity of the heart (specifically, prolongation of the QT interval as seen in the electrocardiogram) can lead to risk of an abnormal heart rhythm called Torsade de Pointes, which can be fatal. Patients at particular risk for developing QT interval prolongation include those with underlying heart conditions and those who are predisposed to having low levels of potassium and magnesium in the blood[4]. Citalopram was the concurrent CNS depressant taken by patient

in T201200248. No dose was provided for both citalopram and fentanyl. No pertinent medical history was reported. In these4 cases, causality cannot be solely attributed to fentanyl due to the confounding effect of the concurrent CNS depressant medications.

2. Overdose

In the spontaneous case T201200523, fatal outcome was associated with events of drug diversion and overdose. Fatal overdose is not listed in the OTFC USPI. However, per the USPI, the manifestations of OTFC overdosage are expected to be similar in nature to intravenous fentanyl and other opioids and are an extension of its pharmacological actions with the most serious significant effect being respiratory depression. Very minimal information was provided and, being a lay press report, follow-up was not possible. Hence, an accurate determination of causal relationship between drug and events could not be made.

3. Other Cases with Fatal Outcome

For the 8 cases reported from the AAPCC annual report, fatal outcome was associated with events of cardio-respiratory arrest and completed suicide, both of these events currently not listed in the OTFC USPI. There was very limited information for T201200243 and T201200244. Hence, causality assessment between event and drug was not possible.
For the remaining 6 cases, available information on concurrent medication showed the intake of CNS depressants, namely benzodiazepines (alprazolam, diazepam and clonazepam) and a neuroleptic (anti-psychotic agent-quetiapine). In cases T201200241 and T201200246, alprazolam was the concurrent medication. In T201200245, fentanyl was taken together with clonazepam. Diazepam was reported taken with fentanyl in T201200250. With fentanyl, clonazepam and quetiapine were taken by patient in T201200249. In case T201200255, concurrent intake of clonazepam and alprazolam with marijuana was reported. Fentanyl formulation/manufacturer and dose were not provided.
Benzodiazepines have a wide therapeutic index and taken alone in overdose rarely cause severe complications or fatalities[5]. They are, however, not devoid of serious toxicity and cases of severe coma or fatality have been reported. Taken in overdose in combination with alcohol, barbiturates, opioids, tricyclic antidepressants, or sedating antipsychotics, anticonvulsants, or antihistamines, they are particularly dangerous[6]. On neuroleptics, recent regulatory and clinical concerns about atypical anti-psychotics include risks of QTc interval prolongation, torsades de pointe and sudden cardiac death[7]. In the prescribing information for Seroquel, the Reference Listed Drug (RLD) for quetiapine, rare reports of overdose resulting in death or coma were mentioned. With the confounding effect of concurrent medications, causality could not be attributed to fentanyl alone.

T201203533 was also a literature case with fatal outcome in association with toxicity to various agents, namely fentanyl, diazepam and Ibogaine. Each of these drugs could have

contributed to the fatal outcome. Hence, causal relationship could not be established for fentanyl alone.

B. Cases without Fatal Outcome

1. Abuse

For cases T201204618 and T201204623, only the patient age and gender and event of abuse were provided. No contact information was available making follow-up impossible. Causality could not be assessed due the paucity of relevant information.

2. Overdose

The two literature cases, 201203037 and T201203042, reported on several adverse events experienced with overdose. All these events are currently not listed in the OTFC USPI. Outcome was non-fatal. Information regarding concurrent medications showed that the resultant events that the patients experienced could be due to the confounding effects of fentanyl and the opioid (methadone) and CNS depressants (benzodiazepines). With concurrent use of other medications, a definite causal relationship between events and fentanyl alone could not be determined.

3. Misuse

Case T201204616 was reported spontaneously through a poison control center. The only information provided by the reporter was that the female patient intentionally misused "2 fentanyl, 5 oxycodone with acetaminophen tabs/pills/capsules and 1 methadone tabs/pills/capsules". No associated event with misuse was reported. The limited information prevents establishing a causal relationship between misuse and fentanyl.

4. Inappropriate Prescribing

In the 13 cases where patients reportedly took fentanyl lozenges, use was not for the approved indication for OTFC. The indications in these spontaneously reported cases were: chronic pain, migraine, occipital neuralgia, and back and shoulder pain. There were two cases (T201201383 and T201202533) where OTFC was given for breakthrough pain. However, no associated cancer condition was provided. Most of the events resulting from inappropriate use such as vomiting, nausea, diarrhea, somnolence, pruritus, dental caries, palpitations and fatigue were listed per OTFC USPI. The unlisted events included migraine, tooth fracture and blood testosterone decreased. No fatal outcome was reported despite inappropriate prescribing of OTFC. There was concurrent use of other medications such as the extended release or long-acting opioids (morphine, fentanyl patch, oxycodone and methadone) and the CNS depressants (benzodiazepines- diazepam, temazepam and alprazolam; sedative- zolpidem; anti-convulsant- valproic acid and oxcarbazepine; and anti-

depressant- mirtazapine). The concurrent use of other medications precludes a definite attribution of causality to fentanyl alone.

Conclusion

Review of REMS special interest cases that were received within the reporting period revealed insufficient documentation to allow assessment of a causal relationship between drug and event including outcome. Missing information included product manufacturer and formulation, indication of use, product dose, event onset, concurrent medications and pertinent medical history. In those cases reporting concurrent medications, confounding effects of these medications could not be ruled out. Under such circumstance, causality could not be established as related to fentanyl alone.

Based on the evaluation performed, no clinical evidence supports causal association of event and fentanyl alone.

The goals of the TIRF REMS Access program are to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors and inappropriate prescribing. Based on the review of the 33 US case reports of REMS special interest received during the period of 28DEC2011 to 20OCT2012, there is insufficient data reported to allow a definitive assessment as to whether or not these goals are being met.

References:

[1] Berger, R, Green G, Melnick A. (1975). Cardiac Arrest Caused by Oral Diazepam Intoxication. Clinical Pediatrics 14: 842–844. Retrieved 16 December 2012.

[2] Fraser AD. Use and Abuse of Benzodiazepines. Ther Drug Monitor. 1998; 20(5):481-9.

[3] Pacher P, Kecskemeti V. Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, old Concerns?. Curr Pharm Des. 2004; 10(20): 2463–2475.

[4] FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses". Drug Safety and Availability. United States Food and Drug Administration. 2012-05-22.

[5] Wolf BC, Lavezzi WA, Sullivan LM, Middleberg RA, Flannagan LM. "Alprazolam-related Deaths in Palm Beach County". Am J Forensic Med Pathol 2005; 26 (1): 24–7.

[6] Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M. "A Systematic Review of Research Examining Benzodiazepine-related Mortality". Pharmacoepidemiol Drug Saf February 2009; 18 (2): 93–103

[7] Vieweg, WVR. New Generation of Antipsychotic Drugs and QTc Interval Prolongation. Prim Care Companion J Clin Psychiatry. 2003; 5(5): 205–215.

1.16 Risk Management Plans

This response provides the following additional information to the 12-month assessment report:

1. An overall summary analysis describing any clinical evidence of a causal association between the drug and the reported event (abuse, misuse, overdose.);

2. A tabulation including one or more of the following events: death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication error, accidental pediatric exposures/ingestion with the available relevant information;

3. MedWatch forms for the adverse event case reports.

Mallinckrodt Pharmaceuticals

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION 2

September 11, 2013

Food and Drug Administration (FDA)
Office of Generic Drugs (OGD)
Document Control Room
7620 Standish Place Rockville, Maryland 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200, 400, 600, 800, 1200, and 1600 mcg

Dear Sir or Madam:

Reference is made to Mallinckrodt Inc.'s Prior Approval Supplement for a Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2012. Reference is also made to the Prior Approval Supplement submitted on September 28, 2012 for Proposed REMS Modification #2. As instructed by FDA the shared TIRF REMS is being submitted to DMF #027320 rather than each TIRF REMS sponsor's NDA/ANDA. All previous approved REMS submissions will be included in the DMF to provide the full history of the REMS. The REMS submissions to the DMF are scheduled as follows:

Sequence Number	Content	Planned Submission Date
0000	Initial REMS	August 20, 2013 (complete)
0001	Administrative Info	September 4, 2013 (complete)
0002	Modification 1	September 9, 2013 (complete)
0003	Assessment Report 1	September 12, 2013
0004	Draft Modification 2	September 16, 2013
0005	Assessment Report 2	September 18, 2013
0006	Final Modification 2	September 23, 2013

This Amendment provides for the submission of Final Modification #2. A letter of authorization to access DMF #027320 to review the REMS is provided in Section 1.4.1.

A REMS Assessment for the TIRF REMS Access Program was submitted on December 20, 2012.

This amendment, which has been organized according to the June 2008 Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications,* is approximately 1.5 MB in size, and is provided in electronic format via the Electronic Submissions Gateway as eCTD sequence 0048. It has been checked and found free from virus infection using Trend Micro OfficeScan v10.6.2497.

Mallinckrodt
Pharmaceuticals

Correspondence related to this submission should be addressed to Jessica Emerson, Mallinckrodt Inc., 675 McDonnell Blvd., Hazelwood, Missouri 63042. For additional information, please contact me at 314-654-0238.

Sincerely,

Jessica Emerson

Jessica Emerson
Sr. Regulatory Affairs Specialist
jessica.emerson@mallinckrodt.com

Accenture LLP
585 East Swedesford Road
Wayne, PA 19087
Tel: (610) 535-6500
www.accenture.com

Date: August 28, 2013

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

DMF#: 027320
Holder: McKesson Specialty Health (McKesson)
Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Letter of Authorization for: Not applicable because DMF does not cover multiple items.

McKesson hereby authorizes Mallinckrodt to incorporate by reference information regarding the Transmucosal Immediate Release Fentanyl (TIRF) Access Program in DMF Number 027320 into any application filed by Mallinckrodt. We also authorize the FDA to review the aforementioned specific information in DMF Number 027320 when considering any application filed by Mallinckrodt.

The entire DMF can be referenced, which was submitted on August 20, 2013.

McKesson states that DMF Number 027320 is current and McKesson will comply with the statements made within it. McKesson will notify FDA through an amendment to DMF Number 027320 of any addition, change, or deletion of information in the DMF. McKesson will also notify in writing Mallinckrodt that an addition, change, or deletion of information has been made to the DMF.

Sincerely,

Jann A. Kochel, U.S. Agent
Associate Director, Regulatory Affairs
Accenture, LLP
610-535-6500, ext. 5572
610-535-6515 (Fax)
jann.a.kochel@accenture.com

REMS ASSESSMENT REPORT
REFERENCE TO DMF SUBMISSION

December 30, 2013

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for *Mallinckrodt*'s *Oral Transmucosal Fentanyl Citrate*. Reference is also made to the 24 month Assessment Report submitted to DMF #027320 on December 27, 2013. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted to this application on September 11, 2013.

Please refer to DMF #027320 for our 24-month REMS Assessment Report. The Assessment Report was included in eCTD sequence 0007 to DMF #027320

We are also confirming that we will submit an amendment to this Assessment Report no later than January 31, 2014 providing safety information for our product, consisting of CIOMS II line listings (including all of the data elements requested by FDA) along with MedWatch forms for deaths, overdoses and pediatric exposures.

FDA should refer to our most recent annual report for information on post-approval studies and/or clinical trials.

This assessment report, sequence number 0052, is submitted in electronic format via the Electronic Submissions Gateway (approximately 1 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contact by telephone at (314) 654-8259 or by email at jeremy.grise@mallinckrodt.com

Should you have any questions regarding the content of this submission, or need additional information, please contact me by telephone at (314) 654-0238 or by e-mail at jessica.emerson@mallinckrodt.com.

Sincerely,

Jessica Emerson

Digitally signed by Jessica Emerson
DN: cn Jessica Emerson o Mallinckrodt Pharmaceuticals ou Regulatory Affairs email jessica.emerson@mallinckrodt.com c US
Reason: I attest to the accuracy and integrity of this document
Date: 2013.12.19 10:11:25 06'00'

Jessica Emerson
Sr. Regulatory Affairs Product Specialist
Fax: (314) 654-6496

AMENDMENT TO REMS ASSESSMENT REPORT

January 31, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for *Mallinckrodt's Oral Transmucosal Fentanyl Citrate*. Reference is also made to the 24 month Assessment Report submitted to DMF #027320 on December 27, 2013.

In response to the Agency's request during a teleconference held on November 14, 2013, we are providing safety information for our product in eCTD section 5.3.6 "*Reports of Post-Marketing Experience*". The data consist of CIOMS II line listings (including all of the data elements requested by FDA) along with MedWatch forms for deaths, overdoses and pediatric exposures. Please note that all TIRF REMS sponsors provided safety data to their individual applications in May 2013 covering the period 28-DEC-2011 to 20-OCT-2012. Our 24 month assessment report covers the period from 29-OCT-2012 to 28-OCT-2013. In order to cover the "gap", we are submitting reports covering 21-OCT-2012 to 28-OCT-2013 for this assessment report. Future submissions will revert to the 12 month reporting period covered by our assessment reports. The data consist of CIOMS II line listings (including all of the data elements requested by FDA) along with MedWatch forms for deaths, overdoses and pediatric exposures.

This assessment report, sequence number 0053, is submitted in electronic format via the Electronic Submissions Gateway (approximately 2 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contact by telephone at (314) 654-8259 or by email at jeremy.grise@mallinckrodt.com.

Should you have any questions regarding the content of this submission, or need additional information, please contact me by telephone at (314) 654-0238 or by e-mail at jessica.emerson@mallinckrodt.com.

Sincerely,

Jessica Emerson

Digitally signed by Jessica Emerson
DN: cn=Jessica Emerson, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=jessica.emerson@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.01.22 12:54:22 -06'00'

Jessica Emerson
Sr. Regulatory Affairs Product Specialist
Fax: (314) 654-6496

Mallinckrodt Pharmaceuticals

AMENDMENT TO REMS ASSESSMENT REPORT

April 1, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg. Reference is also made to the 24-month Assessment Report submitted to DMF #027320 on December 27, 2013; and, to the Letter of Authorization (LOA) for DMF 027320 submitted to this application on September 11, 2013.

On March 31, 2014, in response to the Agency's request in an email dated December 5, 2013, the sponsors of TIRF products submitted a report providing an analysis of risks drawn from databases capturing abuse, addiction, overdose and death. This analysis covers the period of July 1, 2012 to September 30, 2013. Please refer to DMF 027320, Sequence 0008 for the report.

This amendment to the assessment report, sequence 0054, is submitted in electronic format via the Electronic Submissions Gateway (<2 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contact by telephone at (314) 654-8259 or by email at jeremy.grise@mallinckrodt.com.

Should you have any questions regarding the content of this submission, or need additional information, please contact Jessica Emerson by telephone at (314) 654-0238, by fax at (314) 654-66496 or by e-mail at jessica.emerson@mallinckrodt.com.

Sincerely,

Karla Werre

Digitally signed by Karla Werre
DN: cn=Karla Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.03.31 13:20:57 -05'00'

Karla Werre
Manager, Regulatory Affairs

PRIOR APPROVAL SUPPLEMENT
TIRF REMS MODIFICATION 3

May 21, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt Inc.'s Oral Transmucosal Fentanyl Citrate which is contained in DMF #027320. Additional reference is made to the Letter of Authorization for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt Inc. hereby notifies FDA of its submission of Modification #3 to the TIRF REMS DMF #027320 in sequence 0009 [May 20, 2014]. The modifications are comprised of changes requested by the FDA in an e-mail dated February 5, 2014, and further changes proposed by the TIRF REMS Industry Group ("TRIG") on March 24, 2014 which were subsequently authorized by FDA on April 22, 2014.

This amendment to the assessment report, sequence 0055, is submitted in electronic format via the Electronic Submissions Gateway (~1 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contact by telephone at (314) 654-8259 or by email at jeremy.grise@mallinckrodt.com.

Should you have any questions regarding the content of this submission, or need additional information, you may contact me by telephone at (314) 654-0238, by fax at (314) 654-6496 or by e-mail at jessica.emerson@mallinckrodt.com.

Sincerely,

Jessica Emerson

Digitally signed by Jessica Emerson
DN: cn=Jessica Emerson, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=jessica.emerson@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.05.19 14:11:06 -05'00'

Jessica Emerson
Sr. Regulatory Affairs Specialist

Mallinckrodt Pharmaceuticals

TIRF REMS CORRESPONDENCE

June 2, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt Inc.'s Oral Transmucosal Fentanyl Citrate which is contained in DMF #027320. Additional reference is made to the Letter of Authorization for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt Inc. hereby notifies FDA of the submission to the TIRF REMS DMF #027320 in sequence 0010 [May 30, 2014] of its response to the FDA Information Request dated May 16, 2014 concerning cash transactions. The e-mail correspondence from FDA to the TRIG on May 16, 2014 is provided herein for reference.

This REMS correspondence, sequence 0056, is submitted in electronic format via the Electronic Submissions Gateway (~1 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contact by telephone at (314) 654-8259 or by email at jeremy.grise@mallinckrodt.com.

Mallinckrodt
Pharmaceuticals

Should you have any questions regarding the content of this submission, or need additional information, you may contact me by telephone at (314) 654-0238, by fax at (314) 654-6496 or by e-mail at jessica.emerson@mallinckrodt.com.

Sincerely,

Jessica Emerson

Jessica Emerson
Sr. Regulatory Affairs Specialist

Werre, Karla L

From: Jarral, Vaishali <Vaishali.Jarral@fda.hhs.gov>
Sent: Friday, May 16, 2014 7:28 AM
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: TIRF REMS Modification #3 proposals

Follow Up Flag: Follow up
Flag Status: Flagged

Hello Karla,

Reference is made to your April 15, 2014 response to our inquiry about your proposed "TRIG Recommendations for Programs Enhancements" sent March 24, related to the addition of information in TIRF REMS materials related to Cash Claim FAQs. In your response you clarified that per your 24-month assessment report Table 29 (page 72 of 131), 7 instances of non-compliance occurred where TIRF medicines were dispensed without verifying stakeholder enrollment through the TIRF REMS pharmacy management system and that the pharmacies involved "were either not aware of the requirement to process cash claims through the TIRM REMS Program or were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway." Your response also stated that to address "apparent prescription processing knowledge deficit" the proposed Cash Claim FAQ information would be added to emphasize that "all claims, highlighting cash claims specifically, must be submitted to the TIRF REMS Access Program to verify the enrollment status of the stakeholders before dispensing a TIRF medicine to a patient and to clearly provide the proper BIN number for transmission of cash claims data."

Prior to the information you provided, our understanding of the TIRF REMS Switch system transmission process was that the transaction is adjudicated through the switch automatically, whether the transaction was an insurance or cash claim. It appears that this is not the case and that, in fact, the process involves additional manual steps at the pharmacy level to enter the Cash BIN # into the system in order for the transaction to be adjudicated. We are concerned that the switch system is not a failsafe process for adjudication of TIRF REMS safety verifications prior to dispensing the product.

We have the following information request (IR) for the TRIG, in response to the information you have provided:

1. Provide a proposal to mitigate this failure mode to assure the Switch System cannot be bypassed prior to dispensing of TIRF products. Describe any ways that participating pharmacies' systems can be modified in order to automatically:
    a. adjudicate of cash claims and eliminate the required pharmacist manual entry of a BIN # and/or
    b. prevent the dispensing of a prescription if the cash claim is not transmitted to the TIRF REMS Access program.
    c. To what extent have certified pharmacies implemented such automated systems?

2. Please explain the method used to identify the 7 cases/7 pharmacies reported in your 24-month REMS assessment. Is the method used to identify these cases comprehensive in identifying all such cases?

3. Since the 24-month REMS assessment, have you identified any additional cases?

4. Provide the root cause analysis of how these cases occurred along with the TRIG's proposed plan for future detection/identification of cases such as these.

5. In your proposed modified FAQ, you ask pharmacists to transmit TIRF REMS CASH claims to the TIRF REMS Access Program using the REMS CASH BIN 014780. FDA has heard that pharmacies may be using other processes to transmit their TIRF REMS cash claims. Please confirm that these instructions will work in all

pharmacies that participate in the REMS, and that they will not interfere with those pharmacies standard REMS operating procedures.

Please submit the response to DMF by May 27, 2014.

Thank you

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Tuesday, April 15, 2014 12:34 PM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Dear Vaishali,
Thank you for your inquiry about the TRIG's change proposal regarding the TIRF REMS Cash Claims requirements. TRIG's responses are as follows:

- Are cash transaction prescriptions currently being routed through the TIRF REMS System?
  - Yes.

- What prompted the TRIG to propose this modification?
  - As provided in Table 29 (page 72 of 131) of the 24-month assessment report, during this reporting period the non-compliance review team identified 7 instances where a TIRF medicine was dispensed without verifying stakeholder enrollment through the TIRF REMS pharmacy management system. A total of 7 pharmacies involved in these non-compliant events indicated they were either not aware of the requirement to process cash claims through the TIRF REMS Access Program (3); or, were aware of the cash claim procedure but received a reject, yet dispensed a TIRF product anyway (4).

- Please provide any additional information to help inform our understanding of this proposal.
  - To alleviate this apparent prescription processing knowledge deficit, the TRIG opted to propose a modification to the FAQ for "Chain and Independent Outpatient Pharmacy Cash Claim" to emphasize that all claims, highlighting cash claims specifically, must be submitted to the TIRF REMS Access Program to verify the enrollment status of the stakeholders before dispensing a TIRF medicine to a patient and to clearly provide the proper BIN number for transmission of cash claims data.

Please let us know if you have additional questions.

Best regards,

Kindest regards,
Karla

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs, Specialty Generics
Mallinckrodt Pharmaceuticals
675 McDonnell Boulevard
Hazelwood MO, 63042 USA
T: 314.654.3517
M: 314.229.7895
karla.werre@mallinckrodt.com
www.mallinckrodt.com

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Monday, April 14, 2014 9:55 AM
To: Werre, Karla L
Subject: RE: TIRF REMS Modification #3 proposals

Thank you.

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Monday, April 14, 2014 10:46 AM
To: Jarral, Vaishali
Subject: RE: TIRF REMS Modification #3 proposals

Vaishali,
Yes, definitely before Friday, likely to be tomorrow.

Regards,
Karla

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Monday, April 14, 2014 9:30 AM
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Karla,

In regards to the information request below, kindly let me know if you will able to respond by this Friday.

Thanks,
Vaishali

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Wednesday, April 09, 2014 11:12 AM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: FW: TIRF REMS Modification #3 proposals

Vaishali,
Thank you for your inquiry. I will pose your question to the TRIG and get back to you promptly.

Kindest regards,

Karla
Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs, Specialty Generics
Mallinckrodt Pharmaceuticals
675 McDonnell Boulevard
Hazelwood MO, 63042 USA
T: 314.654.3517
M: 314.229.7895
karla.werre@mallinckrodt.com
www.mallinckrodt.com

From: Jarral, Vaishali [mailto:Vaishali.Jarral@fda.hhs.gov]
Sent: Wednesday, April 09, 2014 9:57 AM
To: Werre, Karla L
Cc: Liberatore, Mark
Subject: RE: TIRF REMS Modification #3 proposals

Karla,

The Division of Risk Management (DRISK) would like to better understand the TRIG proposal included in your March 24, 2014 email (your email below) document titled 'TRIG Recommendations for Program Enhancements' that relates to TIRF REMS Cash claims requirements. Are cash transaction prescriptions currently being routed through the TIRF REMS System? What prompted the TRIG to propose this modification? Please provide any additional information to help inform our understanding of this proposal.

Thank you,

Vaishali Jarral, M.S., M.B.A
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 22, Room 4472
Silver Spring, MD 20993

301.796.4248
Vaishali.Jarral@fda.hhs.gov

From: Werre, Karla L [mailto:Karla.Werre@mallinckrodt.com]
Sent: Monday, March 24, 2014 2:00 PM
To: Jarral, Vaishali
Cc: Liberatore, Mark
Subject: TIRF REMS Modification #3 proposals

Vaishali,

In addition to the previously communicated modifications to the TIRF REMS provided in our e-mail dated February 18th (remove NDC numbers, remove Attachment A, remove reference to individual generics in Education program), the TRIG proposes to further enhance the program per the attachment entitled, "TRIG Recommendations for Program Enhancements."

Additionally to clarify, in our March 13th conversation, you stated that changes to the assessment metrics and the RSD do not necessarily trigger a modification. Should the changes in the attachment to this e-mail be included in Modification 3?

Kindest regards,

Karla
Karla Werre, MBA, RAC(US) | Manager, Regulatory Affairs
Specialty Generics | **Mallinckrodt Pharmaceuticals**
675 McDonnell Boulevard | Hazelwood MO, 63042 | USA
T: 314.654.3517 | M: 314.229.7895
karla.werre@mallinckrodt.com
RA.generics@mallinckrodt.com

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 078907/MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment REMS ASSESSMENT PLAN REVISION
Communication ID:	(COR-SEC901REMS-10) (COR-SEC901REMS-17)
Drafted by:	M.Liberatore 7/25/14, 8/6/14, 8/12/14
Clearance History:	JRacoosin 7/27/14 K. Lehrfeld 8/6/14 P. Jani/8-12-14 SRT
Finalized:	M. Liberatore
Filename:	
Use Statement:	
Notes:	

Version: DARRTS 06/03/2012

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT
REMS ASSESSMENT PLAN REVISION

Mallinckrodt, Inc.
675 McDonnell Boulevard
Hazelwood, MO 63042

Attention: Jessica Emerson
Senior Regulatory Affairs Product Specialist

Dear Ms. Emerson:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg.

We also refer to your December 30, 2013, submission containing the 24-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. In your one-year assessment report, information regarding the number of enrolled pharmacies from government agencies as well as other integrated systems/mail order data were presented. These categories are absent from your 24-month assessment report. In light of the REMS compliance issues experienced by at least two federal closed systems (the VA and DOD), in future assessment reports, report on the number of enrolled pharmacies in federal and other integrated systems.

2. Although the percentage of Patient-Provider Agreement Forms (PPAFs) received in the 10-day window between patient enrollment and receipt by the REMS program improved from the 12-month report figure (46% vs. 37%), continue to employ strategies that will improve the percentage of PPAFs received in the 10-day window.

3. A total of 73 outpatient pharmacies are described as having an "*incomplete configuration*," though no reasons are provided as to why these 73 pharmacies remain in this status. In all subsequent assessment reports, provide complete information regarding why certain pharmacies are not able to configure their systems.

4. In future assessment reports, provide the most recent American Association of Poison Control Centers (AAPCC) case narratives.

5. Regarding RADARS data submissions in the future provide:
    a. information about the protocols used to generate these data
    b. data from the RADARS Drug Diversion Program
    c. the numbers of patients identified to have taken TIRFs for all of the programs for which you present data.

6. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

7. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

8. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

9. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

Our December 28, 2011, REMS approval letter described the REMS assessment plan. During the review of the first and second year TIRF REMS assessment reports, changes to some of the metrics in the assessment plan were discussed both internally as well as with the TIRF REMS Industry Group (TRIG). The revisions provided in this letter serve to further tailor the metrics to those that are most informative regarding the operation and effectiveness of the TIRF REMS program. In brief, the revised REMS assessment plan comprises:

- Scaled back reporting of TIRF utilization data that focuses on the stakeholders enrolled, inactivated, and the numbers of stakeholders affected by enrollment delays

- Refocused dispensing activity data that includes stratification by closed/non-closed systems.
- A plan to assess non-compliance with the REMS that includes annual audits of randomly selected closed systems and inpatient systems.
- Safety surveillance that will consist of one comprehensive report that includes spontaneous adverse event data from all of the drugs under the TIRF REMS and that will focus on four categories of adverse events: addiction, overdose, death, and pediatric exposures.
- Continued use of stakeholder knowledge surveys to help inform whether the goals of the REMS are being met.

The complete revised REMS assessment plan is attached (see Appendix).

If you have any questions, contact Katherine Won, REMS Coordinator, at (301) 796-7568 or Katherine.Won@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

CAPT Jason J.Y. Woo, M.D., M.P.H.
Acting Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
Revised Assessment Plan

APPENDIX: REVISED ASSESSMENT PLAN

Assessment Plan for TIRF REMS

1. The TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively)
    a. Patient Enrollment:
        i. Number of unique patients enrolled
        ii. Number of patients inactivated
    b. Prescriber Enrollment:
        i. Number of prescribers enrolled
        ii. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
        iii. Number of prescribers inactivated
    c. Pharmacy Enrollment:
        i. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities);
        ii. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
        iii. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);
    d. Distributor enrollment:
        i. Number of distributors enrolled
        ii. Number of distributors inactivated

2. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)
    a. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity

b. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)

c. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons

d. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized

e. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF

f. Number of prescriptions dispensed after ten days without a PPAF in place

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described

b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions

c. Call center report with

i. Overall number of contacts

ii. Summary of frequently asked questions

iii. Summary of REMS-related problems reported

d. Description of corrective actions taken to address program/system problems

4. TIRF REMS Access Non-Compliance Plan: The TIRF sponsors should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Numbers of prescription authorizations per closed system

iii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program. Data to include the 12 month

period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).

iv. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

b. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period
These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program

iii. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

c. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:

i. Description of how the NCRT defines a non-compliance event

ii. Description of how non-compliance information is collected and tracked

iii. Criteria and processes the Team uses to make decisions

iv. Summary of decisions the Team has made during the reporting period

v. How the Team determines when the compliance plan should be modified

d. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action

e. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences

f. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified

h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

i. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

5. Safety Surveillance (data collected per reporting period):

a. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures

b. TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:

i. Line listings under each category of adverse events of interest as listed above

ii. Line listings should provide at a minimum the following information (see sample table provided):

1. Identifying case number
2. Age and Gender of the patient
3. Date of the event as well as of the report
4. The Preferred Terms
5. Indication of TIRF use
6. Duration of TIRF therapy
7. Concomitant medications
8. Event Outcome

iii. Other metrics of interest include:

1. Number of event reports in each event category of interest
2. Counts of adverse events related to inappropriate conversions between TIRF products
3. Counts of adverse events related to accidental and unintentional exposures
4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients

iv. Duplicate cases are identified and eliminated

v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events

vii. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs
ii. Surveys conducted at substance abuse treatment programs
iii. College surveys
iv. Poison control center data
v. Impaired health care workers
vii. Drug-related hospital emergency department visits
viii. Drug-related deaths
ix. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

6. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

08/21/2014

Associate Director for Review Quality, for
Jason Woo, M.D., M.P.H.

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT
TIRF REMS MODIFICATION 3

November 26, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: **ANDA 078907** Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in sequence 0012 [November 25, 2014].

The modifications to the TIRF REMS program included in this submission are comprised of changes requested by the FDA in e-mails dated October 20th, November 6th, and November 18th, 2014 and furthermore, consist of changes proposed and accepted by the TIRF REMS Industry Group ("TRIG") and FDA, respectively on November 7th, 2014. All updated TIRF REMS documents are submitted as both red-lined and clean versions in MS Word format. In addition, PDF documents of the RSD with Appendices and REMS with Supporting Materials are provided. Please note that unchanged TIRF REMS documents are not being resubmitted, but are referenced in the Reviewer's Guide and hyperlinked to the current version. All changes to the www.TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a MS Word file with screenprints in the clean versions.

This amendment, sequence 0059, is submitted in electronic format via the Electronic Submission Gateway (<5 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Jasen Wallace, Manager, Regulatory Affairs, by email at jasen.wallace@mallinckrodt.com, by telephone at (314) 654-3157, or by fax at (314) 654-6496.

Thank you for your prompt attention to this request.

Sincerely,

Karla Werre

Digitally signed by Karla Werre
DN: cn=Karla Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.11.21 06:31:03 -06'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT
TIRF REMS MODIFICATION 3

December 11, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: **ANDA 078907** Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of its submission of an amendment to TIRF REMS DMF #027320 in sequence 0013 [December 10, 2014]. Prior amendments to the REMS for Modification #3 were submitted on April 1, 2014, May 21, 2014 and November 25, 2014. (The last REMS Assessment for the TIRF REMS Access Program was submitted on December 27, 2013.)

In conjunction with the correspondence received November 26, 2014 from Vaishali Jarral of your office, provided herein is the complete documentation of the TIRF REMS Access program including the requested "Dear" letters which were previously omitted. Please note that for the ease of review, this submission (DMF Sequence # 0013) contains the updated TIRF REMS documents in both red-lined and clean versions in MS Word format that were previously submitted via Sequence 0012 on November 25, 2014. All documents are referenced in the Reviewer's Guide and hyperlinked to their current version. All changes to the TIRFREMSAccess.com website prototype are listed in an MS Word document in tabular format within the red-lined versions, while the website prototype itself is being provided as a

MS Word file with screenprints in the clean versions. No new changes requiring additional FDA review are proposed at this time.

The current version of Medication Guide is v01/2012 which may be referenced in Section 1.14.2.2 of Sequence 0037 [Submitted 30May2013].

This amendment, sequence 0061, is submitted in electronic format via the Electronic Submission Gateway (~5 MB). The submission is certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Jasen Wallace, Manager, Regulatory Affairs, by email at jasen wallace@mallinckrodt.com, by telephone at (314) 654-3157, or by fax at (314) 654-6496.

Thank you for your prompt attention to this request.

Sincerely,

Karla Werre

Digitally signed by Karla Werre
DN: cn=Karla Werre, o=Mallinckrodt Inc, ou=Mallinckrodt Pharmaceuticals, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.12.05 12:37:28 -06'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 078907/S012
CommunicationType:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	C.Phillips/11-10-14
Clearance History by:	M. Liberatore 11/20/14; C. Miller 12/3/14
Finalized:	
Filename:	
Use Statement:	Use to notify applicant of an approval action for a supplemental application that includes changes to the labels or labeling
Notes:	USE "sNDA Approval [OTC ONLY]" template for Over-the-Counter sNDA Approvals USE COR-SNDAACTION-06 FOR sNDA CMC APPROVALS USE COR-SNDAACTION-09 FOR sNDA TENTATIVE APPROVALS If supplement approval also fulfills a PMR/PMC, this letter will need to be double-coded as PMR-PMC Fulfilled.

Version: DARRTS 04/30/2014

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907/S-012

SUPPLEMENT APPROVAL

Mallinckrodt Pharmaceuticals
Attention: Jessica Emerson
Senior Regulatory Affairs Specialist
675 McDonnell Boulevard
Hazelwood, MO 63042

Dear Ms. Emerson:

Please refer to your Supplemental Abbreviated New Drug Application (ANDA) dated and received May 21, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg.

We acknowledge receipt of your amendments dated June 10, 2014, November 26, 2014, and December 11, 2014. We also refer to the May 20, 2014, November 25, 2014, and December 10, 2014, submissions to DMF 27320, which contain the proposed modifications to your shared risk evaluation and mitigation strategy (REMS) program.

This "Prior Approval" supplemental abbreviated new drug application provides for modifications to the approved REMS for Oral Transmucosal Fentanyl Citrate, which is part of the single shared system REMS, the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Access Program.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for TIRF Products, of which Oral Transmucosal Fentanyl Citrate is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on November 7, 2013. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the TIRF REMS, including appended REMS materials as applicable, consist of the following:

1. Removal of NDC Numbers from the following:
    i. Independent Outpatient Pharmacy Enrollment Form;
    ii. Chain Outpatient Pharmacy Enrollment Form, and;

iii. TIRF REMS Website

2. Removal of reference to generic equivalents of specific products and replacement with a footnote in the following:
   i. Education Program for Prescribers and Pharmacists, and;
   ii. TIRF REMS Website
3. Removal of “Attachment 1: List of TIRF Medicines Available Only through the TIRF REMS Access Program," and replacement with a hyperlink to the new TIRF REMS Webpage in the following:
   i. TIRF REMS Document;
   ii. Overview for Prescribers;
   iii. Prescriber Enrollment Form;
   iv. Overview for Patients and Caregivers;
   v. Independent Outpatient Pharmacy Overview ;
   vi. Chain Outpatient Pharmacy Overview;
   vii. Closed System Outpatient Pharmacy Overview;
   viii. Independent Outpatient Pharmacy Enrollment Form;
   ix. Chain Outpatient Pharmacy Enrollment Form;
   x. Closed System Outpatient Enrollment Form;
   xi. Inpatient Pharmacy Enrollment Form;
   xii. Distributor Enrollment Form, and;
   xiii. TIRF REMS Website and Website Landing Page
4. Revised criteria for inactivation of Patient-Prescriber Agreement Form (PPAF) in the TIRF REMS Document
5. Revisions to enhance knowledge about conversion of TIRF Medicines in the following:
   i. Education Program for Prescribers and Pharmacists, and;
   ii. TIRF REMS Website
6. Information clarifying the process to electronically transmit TIRF REMS Cash Claims in the following:
   i. TIRF REMS Document;
   ii. TIRF REMS Access Program Frequently Asked Questions (FAQ);
   iii. Independent Outpatient Pharmacy Overview;
   iv. Chain Outpatient Pharmacy Overview, and;
   v. Closed System Outpatient Pharmacy Overview

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed modified REMS, submitted on May 21, 2014, and amended on December 11, 2014, and appended to this letter, is approved.

The TIRF REMS Access Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM309784.pdf

Other products may be added in the future to the TIRF REMS Access Program if additional TIRF NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS. There are no changes to the revised REMS assessment plan attached to our August 21, 2014, REMS Assessment Acknowledgment/REMS Assessment Plan Revisions letter.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 078907
REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 078907
PROPOSED REMS MODIFICATION

If you do not submit electronically, please send 5 copies of REMS-related submissions.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.98, 314.80 and 314.81).

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dose form (FDFs) or active pharmaceutical ingredient (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

If you have any questions, call Chantal Phillips, REMS Coordinator, at 301-796-2259.

Sincerely,

John R. Peters -S

Digitally signed by John R. Peters -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=John R. Peters -S, 0.9.2342.19200300.100.1.1=1300383953
Date: 2014.12.24 09:52:59 -05'00'

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures:
REMS

Initial REMS approval: 12/2011

Most recent modification: 12/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**

  i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.

  ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

  iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment.*

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment.*

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Additional Prescriber Information (All Fields Required)

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued* _____
DEA Number* _____

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/ProductList.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

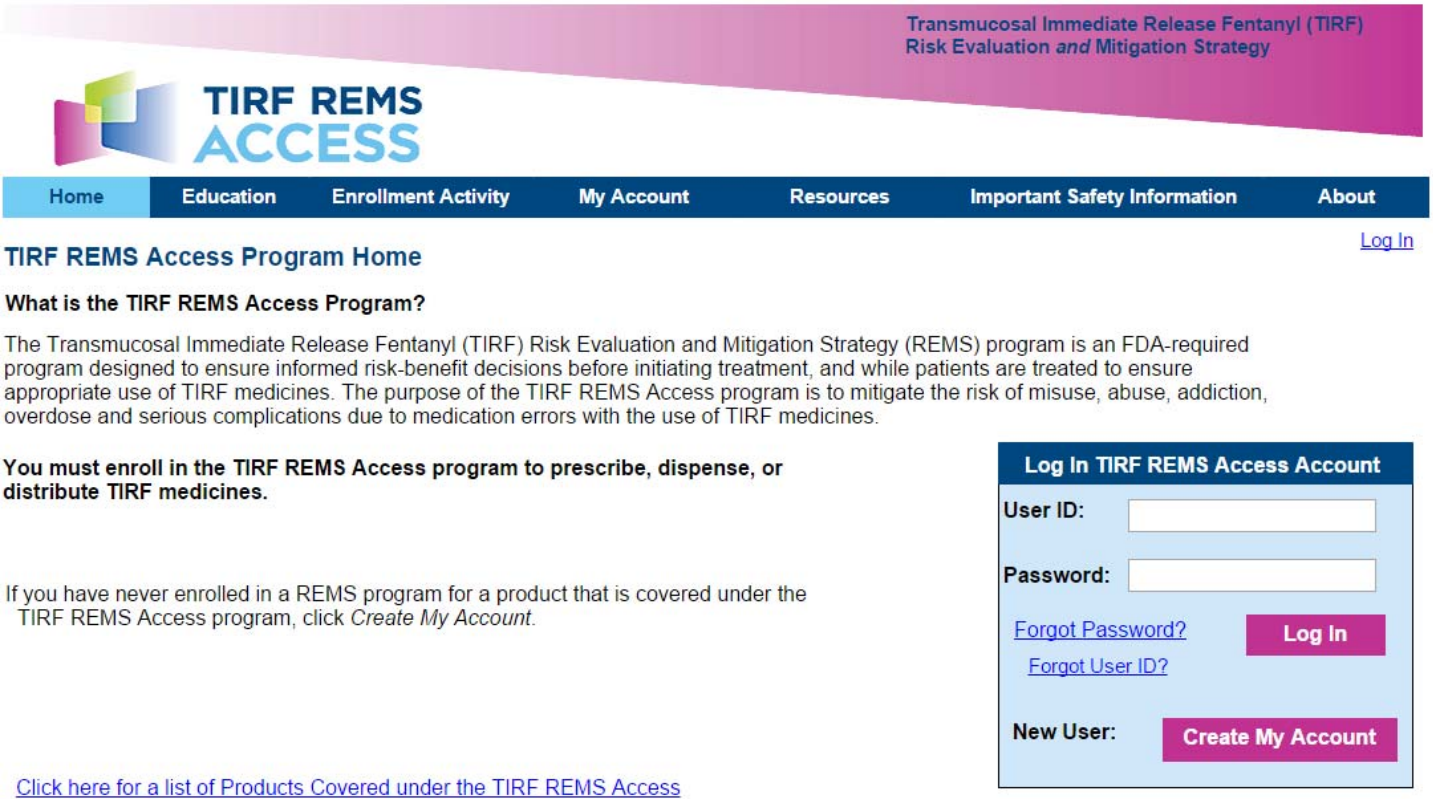
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

  *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

  - Patient First Name,
  - Patient Last Name,
  - Patient Date of Birth,
  - Patient ZIP / Postal Zone,
  - Quantity Dispensed,
  - Days Supply,
  - Prescriber ID,
  - Prescriber Last Name

  *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Chain Outpatient Pharmacies", "An Overview for Independent Outpatient Pharmacies" or "An Overview for Inpatient Pharmacies" for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?
The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?
The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?
For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility
Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

• Patient First Name..... TIRFREMSTEST
• Patient Last Name..... Smithers
• Date of Birth..... 19841105
• Patient ZIP/Postal Zone..... 07921
• Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
• Quantity Dispensed..... 12
• Days Supply..... 4
• Prescriber ID..... BA1111119
• Prescriber Last Name..... REMSTEST

• Test #1 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... “P” (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = “A” (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: *“Invalid test transaction sequence”*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Distributor Responsibilities in the TIRF REMS Access Program:

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

TIRF REMS CORRESPONDENCE
36-MONTH ASSESSMENT REPORT

December 29, 2014

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate,
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of the 36-month REMS Assessment Report to DMF #027320 in eCTD sequence 0014 on December 26, 2014 in advance of the required submission date of December 28, 2014. However, due to the Federal Holiday, the ESG will likely not acknowledge receipt of the assessment until December 29, 2014.

This notification, sequence 0062, is submitted in electronic format via the Electronic Submission Gateway (~5 MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Jasen Wallace, Manager, Regulatory Affairs, by email at jasen.wallace@mallinckrodt.com, by telephone at (314) 654-3157, or by fax at (314) 654-6496.

Thank you for your prompt attention to this submission.

Sincerely,

Karla Werre

Digitally signed by Karla Werre
DN: cn=Karla Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2014.12.18 08:35:20 -06'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

DOCUMENT INFORMATION PAGE

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Application #(s):	ANDA 078907 MF 27320
Communication Type:	Correspondence
Communication Group:	SEC901REMS
Communication Name:	Acknowledge REMS Assessment
Communication ID:	(COR-SEC901REMS-10)
Drafted by:	C.Phillips/7-16-15; J. Sarchet 7-28-2015; C. Phillips 7-28-2015
Clearance History:	Based off NDA clearance
Finalized:	J. Sarchet 8-3-2015
Filename:	
Signatory Authority:	DDS, Division Director, or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	
Notes:	

Version: 10/28/2014

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 078907
MF 27320

REMS ASSESSMENT ACKNOWLEDGMENT

Mallinckrodt, Inc.
675 McDonnell BLVD, BLDG 30-2
Hazelwood, Missouri 63042

Attention: Jasen Wallace
Manager, Regulatory Affairs

Dear Mr. Wallace:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg.

We also refer to your December 29, 2014, submission containing the 36-month assessment of the Transmucosal Immediate-Release Fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) as well as the REMS assessment material submitted to Master File (MF) 27320. This REMS uses a single, shared system for the elements to assure safe use and the REMS assessments.

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete with the following comments:

1. We are not able to assess whether the REMS is meeting its goals. The absence of spontaneous adverse event reports citing either use of a TIRF in opioid non-tolerant individuals or inappropriate conversions between TIRF products is not informative because spontaneous reporting systems are subject to under-reporting of adverse events. In addition, the accidental pediatric exposure data presented in the Assessment Report are difficult to assess due to unequal assessment periods and small numbers of cases. Lastly, the survey results indicate areas of low awareness of some important safe use messages.

2. In order to assess the TIRF REMS goal of prescribing and dispensing TIRF products only to appropriate patients, which includes use only in opioid-tolerant patients, conduct the following analysis: Identify a health care database that includes an adequate number of TIRF product users. Within that database, by year, provide the number of total unique patients dispensed an initial prescription for a TIRF product in the outpatient setting. Determine what proportion of those total unique patients received a prescription for an opioid analgesic product prior to the prescription for the TIRF product. Provide these data separately for patients receiving an opioid analgesic within the 7-days prior and within the 30-days prior to

the initial TIRF prescription. Before embarking on this analysis, provide to FDA your choice of database and the estimated number of TIRF users in the database so that we can determine if the number is adequate.

3. We are not able to establish whether the TIRF REMS is achieving the goal of preventing inappropriate conversion between TIRF medicines. In order to better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF products or just stop them completely. Conduct a persistency analysis based on the data available on the prescriptions processed through the switch system used by retail pharmacies. This analysis should demonstrate the number of patients starting on a TIRF and follow them over weeks and months to summarize their treatment course and change in therapy. The TIRF products can be grouped together, and the specific drug does not need to be disclosed. Following the discontinuation of the TIRF, the persistency analysis should also depict what treatment option the patient uses next. This will be either full discontinuation or switching to another TIRF product. There may be gaps in between prescriptions; propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF and provide a rationale for selection of that gap length.

4. Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues.

5. There has been a notable increase in mean and median prescription processing times during this reporting period versus the previous period. Investigate and identify the causes of these increasing delays in prescription processing and report the results in your next Assessment Report.

6. None of your reported spontaneous adverse events include a root cause analysis as specified in the Assessment Plan. In your subsequent Assessment Reports, include a root cause analysis of adverse events reported to the TRIG Sponsors.

7. The closed system pharmacies continue to struggle with the REMS authorization processes. Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report.

8. Your presentation of the non-compliance data in the submitted report is disorganized. Various events are described in Assessment Report Section 6.1.1 and in the Report's Tables 21 and 22. Events found in one of these areas often sound similar to events reported in other areas, and thus it is unclear whether these different sources are referring to distinct events or are describing the same event. In addition, while your Report's Table 21 indicates seven instances where closed system pharmacies dispensed drugs without obtaining authorization, the audit conducted by the TRIG reports 513 such incidents. Organize and harmonize these

various components into one clear presentation that is comprehensive and eliminates duplication.

9. Provide the criteria as to how compliance decisions are made by the NCRT and include your non-compliance protocol with your next Assessment Report.

10. In subsequent Assessment Report submissions of RADARS data, provide the following:

    a. A more detailed data analysis section that presents the statistical methods used, how calculations were performed, and the assumptions made, at the level of detail as provided in your April 2, 2015, response to the March 19, 2015, FDA Information Request. In addition, include a pre-post REMS means analyses and trend analyses (e.g. segmented regression analyses), statistically comparing event rates for a time-period immediately prior to full implementation of the TIRF REMS with an equivalent period of time after REMS implementation.

    b. Present the data at the dosage unit level as well as population and URDD levels.

    c. The RADARS treatment center data (Opioid Treatment Program and Survey of Key Informants Patients) programs are confounded by the fact that the number of treatment centers participating in each quarter fluctuates (although the overall numbers are generally increasing). In subsequent submissions, limit the presentation of treatment center data to centers that have contributed data in all of the time-periods assessed. In addition, provide the various versions of the survey instruments/pill cards in use throughout the time-periods assessed with dates provided indicating when each instrument was in use.

11. We remind you that the following comments related to the stakeholder surveys were provided in the August 21, 2014, letter to the TRIG. These revisions should be implemented in subsequent surveys along with the new survey revisions described in item 12 below:

    a. In your prescriber survey, only 59% correctly stated that TIRF should not be used to treat "chronic non-cancer pain." It is not clear if this represents a knowledge deficit or a disagreement with how these medicines should be used. In the next survey, include a supplemental question directed at those who respond incorrectly to this question to follow-up as to why they feel that this is an appropriate use of TIRFs.

    b. In future surveys of prescribers, report the proportion of prescriber respondents that work in closed systems.

    c. Given that pharmacists often have the opportunity to see all of the prescriptions that a patient is taking, include a question in the pharmacist survey regarding the CYP3A4 interactions with TIRFs. Also include a question in the pharmacist

survey regarding their understanding that patients are to stop taking their TIRF when they stop taking their around-the-clock opioid.

d. In the pharmacist survey, 81% of those surveyed functioned as the pharmacist in charge for their operations. In future pharmacist surveys, consider ensuring that a higher percentage of non-supervisory dispensing pharmacists are included.

12. Additional comments and recommended revisions to the stakeholder surveys that should be implemented in subsequent surveys follow below:
    a. Patient survey
        i. In subsequent Assessment Reports, provide an analysis of how the demographics of the patient survey respondents compare to the demographics of actual TIRF patients.
        ii. For Question 4, remove Onsolis as a response option because it is no longer available.
        iii. Move Question 13b: *It is okay for patients to take TIRF medicines for headache pain* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.
        iv. Add Question 10a-e: *For which of the following conditions should you use a TIRF medicine?* to Key Risk Message 3: *TIRF medicines should be taken exactly as prescribed by the healthcare provider*.

    b. Pharmacist survey
        i. For Question 26, remove Onsolis as a response option because it is no longer available.
        ii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.
        iii. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.
        iv. Move Question 13c: *TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product* to Key Risk Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

c. Prescriber survey

i. In subsequent Assessment Reports, provide an analysis of how the demographics of the prescriber survey respondents compare to the demographics of actual TIRF prescribers.

ii. For Question 30, remove Onsolis as a response option because it is no longer available.

iii. Move Question 6a: *A cancer patient can be started on a TIRF medicine and an around the clock opioid at the same time* and Question 6b: *A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

iv. Move Question 7b: *Death has occurred* in opioid non-tolerant patients treated with some fentanyl products to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients.*

v. Move Question 10d: *Dosing of TIRF medicines is not equivalent on a microgram to microgram basis* to Key Message 4: *TIRF medicines are not interchangeable with each other, regardless of route of administration*.

vi. Move Question 11a-f: *According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least* to Key Risk Message 1: *TIRF medicines are contraindicated in opioid non-tolerant patients*.

vii. Move Question 18b*: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

viii. Move Question 18c: *Instruct patients that if they stop taking their around the clock opioid medicine, they can continue to take their TIRF medicine* to Key Risk Message 2: *TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain*.

ix. Remove Question 19: *Can patients continue to take their TIRF medicine if they stop taking their around-the-clock opioid medicine?*

If you have any questions, call Wendy Brown, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-9140.

Sincerely,

{See appended electronic signature page}

Trueman W. Sharp, M.D., M.P.H.
Acting Deputy Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRUEMAN W SHARP
08/03/2015

TIRF REMS CORRESPONDENCE
CONSOLIDATED RESPONSES TO INFORMATION REQUESTS
FROM THE 36-MONTH ASSESSMENT REPORT

October 13, 2015

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate,
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of submission of its Consolidated Responses to Information Requests from the 36-month REMS Assessment to DMF #027320 in eCTD sequence 0018 on October 12, 2015.

The current medication guide may be referenced in Section 1.14.2.2 [SN0049, 21OCT2013].

This notification, sequence 0065, is submitted in electronic format via the Electronic Submission Gateway (<3MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Donatus Ako-Arrey, Director, Regulatory Affairs, by email at donatus.ako-arrey@mallinckrodt.com, by telephone at (314) 654-5713, or by fax at (314) 654-6496.

Thank you for your prompt attention to this submission.

Sincerely,

Karla L. Werre

Digitally signed by Karla L. Werre
DN: cn=Karla L. Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2015.10.09 13:30:33 -05'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

TIRF REMS CORRESPONDENCE
48-MONTH ASSESSMENT REPORT

December 28, 2015

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate,
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of submission of the 48-month REMS Assessment Report to DMF #027320 in eCTD sequence 0019 on December 28, 2015.

This notification, sequence 0067, is submitted in electronic format via the Electronic Submission Gateway (~4 MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Donatus Ako-Arrey, Director, Regulatory Affairs, by email at donatus.ako-arrey@mallinckrodt.com, by telephone at (314) 654-5713, or by fax at (314) 654-6496.

Thank you for your prompt attention to this submission.

Sincerely,

Karla L. Werre

Digitally signed by Karla L. Werre
DN: cn=Karla L. Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Date: 2015.12.17 13:32:21 -06'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

TIRF REMS CORRESPONDENCE
SUPPLEMENTAL REPORT TO 48-MONTH ASSESSMENT

May 5, 2016

Kathleen Uhl, M.D., Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate,
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of a submission to DMF #027320 in eCTD SN0023 on May 4, 2016 of a supplemental report to its 48-month REMS Assessment Report. This supplemental report summarizes findings from analyses undertaken in response to an information request on the 36-month assessment in FDA electronic correspondence dated April 15, 2015 and selected comments from the 36-month REMS Assessment acknowledgement letter dated August 3, 2015 (provided herein for reference behind this cover letter).

This notification, sequence 0071, is submitted in electronic format via the Electronic Submission Gateway (~3 MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Juan Baladad, technical point of contact for this electronic submission, may be reached by phone at (314) 654-6107, by fax at (314) 654-6496, or by email at juanito.baladad@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Donatus Ako-Arrey, Director, Regulatory Affairs, by email at donatus.ako-arrey@mallinckrodt.com, by telephone at (314) 654-5713, or by fax at (314) 654-6496.

Thank you for your prompt attention to this submission.

Sincerely,

Karla L. Werre

Digitally signed by Karla L. Werre
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Reason: I attest to the accuracy and integrity of this document
Date: 2016.04.27 08:27:40 -05'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

TIRF REMS CORRESPONDENCE

August 19, 2016

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: **ANDA 078907 Oral Transmucosal Fentanyl Citrate**
(200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg)
DMF Annual Report (Reporting Period: August 21, 2015 – August 20, 2016)

Dear Dr. Uhl:

Reference is made to the Single-Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013 in SN0048.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of submission of the DMF Annual Report for the reporting period August 21, 2015 – August 20, 2016, to DMF #027320 in eCTD sequence 0024 on August 18, 2016.

The current medication guide may be referenced in [SN0037] 30MAY2012.

DMF Annual Report submission notification is submitted as sequence 0072 in electronic format via the Electronic Submissions Gateway (<3.5 MB). The submission is certified to be free from virus infection using McAfee® VirusScan® Enterprise ver. 8.7*i*. Juan Baladad, the technical point of contact for this electronic submission, may be contacted by phone at (314) 654-6107, by fax at (314) 654-6496 or by e-mail at juanito.baladad@mallinckrodt.com.

For questions concerning the content of this submission or for additional information, please contact me, or Kristen Granzow by telephone at (314) 654-6414, by fax at (314) 654-6496 or by e-mail at kristen.granzow@mallinckrodt.com.

Sincerely,

Karla L. Werre

Digitally signed by Karla L. Werre
DN: cn=Karla L. Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2016.08.18 08:48:00 -05'00'

Karla Werre, MBA, RAC(US)
T: 314-654-3517
F: 314-654-6496
karla.werre@mallinckrodt.com

TIRF REMS CORRESPONDENCE
60-MONTH ASSESSMENT REPORT

December 29, 2015

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt hereby notifies FDA of submission of the 60-month REMS Assessment Report to DMF #027320 in eCTD sequence 0027 on December 28, 2016.

This notification, sequence 0075, is submitted in electronic format via the Electronic Submission Gateway (<3 MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Jeremy Grise, technical point of contact for this electronic submission, may be reached by phone at (314) 654-8259, by fax at (314) 654-6496, or by email at jeremy.grise@mallinckrodt.com.

Questions or requests for further information may be addressed to me or to Donatus Ako-Arrey, Director, Regulatory Affairs, by email at donatus.ako-arrey@mallinckrodt.com, by telephone at (314) 654-5713, or by fax at (314) 654-6496.

Thank you for your prompt attention to this submission.

Sincerely,

Karla L. Werre

Digitally signed by Karla L. Werre
DN: cn=Karla L. Werre, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=karla.werre@mallinckrodt.com, c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2016.12.14 13:05:29 -06'00'

Karla Werre, MBA, RAC(US)
Manager, Regulatory Affairs

Mallinckrodt Pharmaceuticals

TIRF REMS CORRESPONDENCE
CONSOLIDATED RESPONSES TO INFORMATION REQUESTS
FROM THE 48-MONTH ASSESSMENT REPORT

January 31, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate Lozenge
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013. Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt Inc. hereby notifies FDA of submission of its Consolidated Responses to Information Requests from the 48-month REMS Assessment to DMF #027320 in eCTD sequence 0026 on January 30, 2017.

The current medication guide can be referenced in section 1.14.2.2.

The notification is provided and submitted in electronic format (sequence 0076) via the Electronic Submissions Gateway (1 MB) and certified to be free from virus infections using Trend Micro OfficeScan v10.6.2497. The technical point of contact for this submission is Jeremy Grise, who may be contacted by telephone at (314) 654-8259.

Questions or request for further information, please contact me by telephone at (314) 654-6141, fax (314) 654-6496, or by email at Kristen.Granzow@mallinckrodt.com.

Sincerely,

Kristen Granzow

Digitally signed by Kristen Granzow
DN: cn=Kristen Granzow, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=kristen.granzow@mallinckrodt.com, c=US
Reason: I am the author of this document
Date: 2017.01.30 16:19:21 -06'00'

Kristen Granzow
Regulatory Affairs Specialist

Mallinckrodt Pharmaceuticals

TIRF REMS CORRESPONDENCE
60-MONTH SUPPLEMENTAL ASSESSMENT REPORT

February 20, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 078907 Oral Transmucosal Fentanyl Citrate
200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Mallinckrodt's Oral Transmucosal Fentanyl Citrate 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, and 1600 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on September 11, 2013.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Mallinckrodt Inc. hereby notifies FDA of submission of the 60-Month Supplemental Assessment Report to DMF #027320 in eCTD sequence 0028 on February 17, 2017.

This notification is submitted in electronic format via the Electronic Submission Gateway (1 MB) and certified to be free from virus infection using Trend Micro OfficeScan v10.6.2497. Jeremy Grise, technical point of contact for this electronic submission, may be reached by phone at (314) 654-8259.

Questions or requests for further information may be addressed to me by telephone at (314) 654-6141, or by fax at (314) 654-6496, or by email at kristen.granzow@mallinckrodt.com

Sincerely,

Kristen Granzow

Digitally signed by Kristen Granzow
DN: cn=Kristen Granzow, o=Mallinckrodt Pharmaceuticals, ou=Regulatory Affairs, email=kristen.granzow@mallinckrodt.com, c=US
Reason: I am the author of this document
Date: 2017.02.16 14:30:52 -06'00'

Kristen Granzow
Regulatory Affairs Specialist

Watson

March 15, 2011

Keith Webber, Ph.D.
Deputy Director, Office of Pharmaceutical Science, FDA
and Acting Director
OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville, MD 20855-2773

Miscellaneous Correspondence – REMS Status
Electronic Submission (eCTD)
via Gateway

RE: Abbreviated New Drug Application 079075
Fentanyl Citrate Buccal Tablets
100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base
Sequence 0037

Dear Dr. Webber:

Watson Laboratories, Inc., ("Watson") is submitting this electronic Miscellaneous Correspondence – REMS Status, Sequence 0037, to its Abbreviated New Drug Application (ANDA) 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base to provide an interim response to the Pre-Approval REMS Notification Letter dated November 12, 2010 (please see attached). Please note that Watson received final approval for all strengths except the 300 mcg strength per the ANDA approval letter dated January 7, 2011; the 300 mcg strength remains tentatively approved as of June 22, 2010.

As a courtesy, Watson is informing FDA that, shortly after receipt of the Pre-Approval REMS Notification Letter, Watson joined the industry working group (TRIG) which was formed at FDA's request, and Watson has been involved in the monthly meetings to develop and implement the single shared REMS for the class of transmucosal immediate-release fentanyl (TIRF) products. Watson will submit a formal, complete response to the Pre-Approval REMS Notification Letter when the final details have been agreed upon by industry and FDA.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. An MS Word file of this cover letter is provided for the reviewer's convenience. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

Watson trusts the interim response is sufficient regarding the status of the REMS. If you have any questions or require additional information, please contact me by telephone at 951-493-4543, by fax at 951-493-4581, or by e-mail at Janie.Gwinn@Watson.com.

Sincerely,

FOR Janie M. Gwinn
Director, Regulatory Affairs
Watson Laboratories, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 079075

PRE-APPROVAL REMS NOTIFICATION

Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880

Attention: Janie M. Gwinn
Director, Regulatory Affairs

Dear Ms. Gwinn:

Please refer to your abbreviated new drug applications (ANDAs) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg.

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Fentanyl Citrate to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.

We further refer to the meeting held on October 28, 2010, at the FDA White Oak Campus, at which we discussed that in the interest of public health and to reduce the burden on the healthcare system of having multiple unique REMS programs, we have determined that a single, shared system should be used to implement the REMS for all members of the class. The necessary REMS elements should be implemented across the class of transmucosal immediate release fentanyl (TIRF) products to address the serious risks described above.

At the October 28, 2010 meeting we informed the sponsors of the TIRF products of our development of standardized REMS materials that could be used in the development of a single shared system to implement the REMS for all TIRF products. At that meeting, we told sponsors that we intend to move rapidly to review and approve REMS for each of the TIRF products that include the standardized program, and we encouraged sponsors to work together to implement a single shared system to reduce the burden on the healthcare system of individual programs. This letter is a follow up to that meeting discussion.

Attachment 1 contains a REMS program that can be implemented as a single shared system across all TIRF products, and we recommend that your proposed REMS conform to this program. The program will include standardized elements and enrollment forms that can be used by all sponsors of TIRF products and can be implemented using existing pharmacy systems.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Fentanyl Citrate poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Fentanyl Citrate. FDA has determined that Fentanyl Citrate is a product for which patient labeling could help prevent serious adverse effects and that has serious risks of which patients should be made aware because information concerning these risks could affect patients' decisions to use, or continue to use Fentanyl Citrate.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fentanyl Citrate.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

- Healthcare providers are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

The Implementation System must include all elements listed in Attachment 1.

In accordance with section 505-1, within 120 days of the date of this letter, you must submit a proposed REMS as a supplement to your NDA.

This submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that includes information that we

believe is pertinent across the class of TIRF products (see Attachment 1). Additionally, all relevant proposed REMS materials including: enrollment forms, educational, and communication materials should be appended to the proposed REMS. These appended documents should also be standardized across the class of TIRF products, with the exception of the product-specific information that will be included in the training program for prescribers. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Attachment 2).

For administrative purposes, designate the proposed REMS submission "**PROPOSED REMS**" and all subsequent submissions related to the proposed REMS "**PROPOSED REMS-AMENDMENT**." To facilitate review of your submission, please provide labeling in Final Printed Labeling (FPL) and Microsoft Word format.

If you have any questions, please contact Melaine Shin, Labeling Reviewer, at melaine.shin@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA #
Drug Name and Dosage Form
Opioid Analgesic
[SPONSOR].
[ADDRESS]
[PHONE]
[FAX]

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the Fentanyl Citrate REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing Fentanyl Citrate only to appropriate patients, which includes use only in opioid-tolerant patients
2. Preventing inappropriate conversion between fentanyl products
3. Preventing accidental exposure to children and others for whom it was not prescribed
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Fentanyl Citrate prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. **Healthcare providers who prescribe Fentanyl Citrate for <u>outpatient</u> use are specially certified.**

   a. Watson will ensure that healthcare providers who prescribe Fentanyl Citrate for **<u>outpatient</u>** use are specially certified.

   b. To become certified to prescribe Fentanyl Citrate, prescribers will be required to enroll in the Fentanyl Citrate REMS program. Prescribers must complete the following requirements to be enrolled:

      i. Review the Fentanyl Citrate REMS prescriber educational materials (*Prescriber Education Program*), including the Full Prescribing Information, and successfully complete the knowledge assessment (*Prescriber Knowledge*

Assessment).

ii. Complete and sign the *Prescriber Enrollment Form*. In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I understand the responsible use conditions for Fentanyl Citrate and the risks and benefits of chronic opioid therapy.

b) I understand that Fentanyl Citrate can be abused, and that this risk should be considered when prescribing or dispensing Fentanyl Citrate in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that Fentanyl Citrate is indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that Fentanyl Citrate must not be used to treat any contraindicated conditions such as acute or postoperative pain, including headache/migraine.

f) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose, and that patients must be titrated individually.

g) I understand that Fentanyl Citrate is not bioequivalent with any other fentanyl product (regardless of route of administration), and that substitution may result in fatal overdose. I understand that patients switching from another fentanyl product to Fentanyl Citrate must not be converted on a microgram-per-microgram basis.

h) I will complete and sign a Fentanyl Citrate REMS *Patient-Prescriber Agreement* with each new patient, before writing the patient's first prescription, and re-new the agreement every two (2) years.

In signing the *Patient-Prescriber Agreement*, the prescriber documents the following:

1) Patient is currently using around-the-clock opioid analgesia and has been for at least one (1) week.

2) Patient is opioid tolerant. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral

oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

3) The Fentanyl Citrate Medication Guide has been provided to and reviewed with the patient or their caregiver

4) The patient or their caregiver has been counseled about the risks, benefits, and appropriate use of Fentanyl Citrate including communication of the following safety messages:

   A. If patients stop taking their around-the-clock opioid medication, they must stop taking Fentanyl Citrate.

   B. NEVER share Fentanyl Citrate

   C. Giving Fentanyl Citrate to someone for whom it has not been prescribed can result in a fatal overdose.

   D. Fentanyl Citrate can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home.

In signing the *Patient-Prescriber Agreement*, the patient and/or their caregiver document the following:

1) My prescriber has given me a copy of the Fentanyl Citrate Medication Guide and has reviewed it with me.

2) I understand that before I can take Fentanyl Citrate, I must be regularly using another opioid pain medicine, around-the-clock, for my constant pain.

3) I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking Fentanyl Citrate.

4) I understand how I should take Fentanyl Citrate, including how much I can take, and how often I can take it.

5) I understand that Fentanyl Citrate can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take Fentanyl Citrate exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if Fentanyl Citrate does not relieve my pain. I will not change my dose of Fentanyl Citrate myself or take Fentanyl Citrate more often than my prescriber has directed.

7) I agree that I will never give Fentanyl Citrate to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store Fentanyl Citrate in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of unused and remaining Fentanyl Citrate and will dispose of Fentanyl Citrate as soon as I no longer need it.

10) I understand that selling or giving away Fentanyl Citrate is against the law.

11) I have asked my prescriber all the questions I have about Fentanyl Citrate. If I have any additional questions or concerns in the future about my treatment with Fentanyl Citrate, I will contact my prescriber.

12) [placeholder for sponsor to add HIPAA/privacy statement language]

i) I will provide a completed, signed copy of the *Patient-Prescriber Agreement* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the Fentanyl Citrate REMS program (by fax, scan and e-mail, mail or through the Fentanyl Citrate REMS website) within ten (10) working days.

j) At all follow-up visits, I agree to assess the patient for appropriateness of the dose, and for signs of misuse and abuse.

k) I understand that Fentanyl Citrate is only available through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for prescribers.

b. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new *Patient-Prescriber Agreement* at least every two (2) years.

c. Watson will:

i. Ensure that prescriber enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, prescribers receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Prescriber Education Program*
- *Prescriber Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement*

iii. Ensure that prescribers have successfully completed the knowledge assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the Fentanyl Citrate REMS program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, are certified to prescribe Fentanyl Citrate.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

2. Fentanyl Citrate will only be dispensed by pharmacies that are specially certified.

a. Watson will ensure that Fentanyl Citrate will only be dispensed by certified pharmacies. To become certified to dispense Fentanyl Citrate, each pharmacy must be enrolled in the Fentanyl Citrate REMS program.

b. Each pharmacy will be required to designate an authorized pharmacist to complete enrollment on behalf of the pharmacy.

c. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals, hospices, and long-term care facilities that dispense for inpatient use).

d. ***Outpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to enroll their **outpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program)* and successfully complete the *Pharmacy Knowledge Assessment.*

ii. Ensure the pharmacy enables their pharmacy management system to support communication with the Fentanyl Citrate REMS system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Pharmacy Enrollment Form.* In signing the *Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I understand the risks and benefits associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing Fentanyl Citrate have been educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program.* This training should be documented and is subject to audit.

c) I understand that Fentanyl Citrate is not bioequivalent with other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for any other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for <u>all</u> patients is the lowest dose.

f) I understand the importance of discussing the risks and benefits of Fentanyl Citrate with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the Fentanyl Citrate Medication Guide must be given to the patient or their caregiver each time Fentanyl Citrate is dispensed.

h) I understand that Fentanyl Citrate will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL Fentanyl Citrate prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the Fentanyl Citrate REMS program to dispense Fentanyl Citrate.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program and successfully complete the enrollment requirements every two (2) years.

n) I understand that Fentanyl Citrate is only available through the REMS program. I understand that the pharmacy must comply with the Fentanyl Citrate REMS program requirements for outpatient pharmacies.

e. ***Inpatient Pharmacies:***

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy**:

i. Review the Fentanyl Citrate REMS education program (*Pharmacy Education Program*) and successfully complete the *Pharmacy Knowledge Assessment*

ii. Complete and sign the *Pharmacy Enrollment Form*. In signing the *Pharmacy Enrollment Form* the authorized pharmacist is required to acknowledge the following:

a) I understand the benefits and risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with Fentanyl Citrate and the requirements of the Fentanyl Citrate REMS program, as described in the *Pharmacy Education Program*.

c) I understand that Fentanyl Citrate is not bioequivalent to other fentanyl products on a microgram-per-microgram basis and therefore must not be substituted for other fentanyl products.

d) I understand that Fentanyl Citrate is contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of Fentanyl Citrate for all patients is the lowest dose.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the Fentanyl Citrate REMS program to dispense Fentanyl Citrate to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy is not to dispense Fentanyl Citrate for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with an Fentanyl Citrate prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the REMS program, as described in section B.1 of this REMS.

i) I will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the Fentanyl Citrate REMS.

j) I understand that our pharmacy will not sell, loan or transfer Fentanyl Citrate inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that Fentanyl Citrate can only be obtained from wholesalers/distributors that are enrolled in the Fentanyl Citrate REMS program.

l) I understand that our pharmacy must re-enroll in the Fentanyl Citrate REMS program every two (2) years.

m) I understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program. I understand and agree to comply with the Fentanyl Citrate REMS program requirements for inpatient pharmacies.

f. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years

g. Watson will:

i. Ensure that pharmacy enrollment can successfully be completed via the Fentanyl Citrate REMS website, mail, fax, or by scanning and e-mailing the forms.

ii. Ensure that, as part of the enrollment process, pharmacies receive the following materials that are part of the Fentanyl Citrate REMS program and are appended:

- *Pharmacy Education Program*
- *Pharmacy Enrollment Form*
- *Pharmacy Knowledge Assessment*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the knowledge assessment before activating a pharmacy's enrollment in the Fentanyl Citrate REMS program. For outpatient pharmacies only, Watson will also ensure that the upgrades to the pharmacy management system have been validated before enrolling a pharmacy in the Fentanyl Citrate REMS program.

iv. Ensure that pharmacies are notified when they are successfully enrolled in the Fentanyl Citrate REMS program, and therefore, certified to dispense Fentanyl Citrate.

v. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

3. Fentanyl Citrate will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. Watson will ensure that Fentanyl Citrate will only be dispensed for outpatient use if there is documentation in the Fentanyl Citrate REMS system that the dispensing pharmacy, prescriber, and patient are all enrolled and active in the Fentanyl Citrate REMS program.

b. Patients are passively enrolled in the Fentanyl Citrate REMS program when their first Fentanyl Citrate prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be captured in the Fentanyl Citrate REMS system. Prescribers and outpatient pharmacies are enrolled, as previously described in sections B.1 and B.2.a-d, respectively.

c. Prior to dispensing Fentanyl Citrate, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the Fentanyl Citrate prescription through their pharmacy management system.

i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient

ii. If one or more of the required enrollments can not be verified, the Fentanyl Citrate REMS system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. Following initial activation, patients remain active until a trigger for inactivation occurs. Triggers for patient inactivation include:

i. The patient has not filled a prescription for more than six (6) months

ii. The patient receives prescriptions for Fentanyl Citrate from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction.

e. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the Fentanyl Citrate REMS program cannot fill the prescription for Fentanyl Citrate until the new prescriber is active in the Fentanyl Citrate REMS program.

f. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for Fentanyl Citrate are not for the same or overlapping period of treatment.

g. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. Watson will ensure that wholesalers/distributors who distribute Fentanyl Citrate are enrolled in the Fentanyl Citrate REMS program. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving Fentanyl Citrate inventory for distribution:

a. Review the distributor Fentanyl Citrate REMS program materials

b. Complete and sign the *Distributor Enrollment Form* and send it to the Watson (by fax, scan and e-mail, mail or through the TIRF website). In signing the *Distributor Enrollment Form*, each distributor is required to indicate they understand that Fentanyl Citrate is available only through the Fentanyl Citrate REMS program and that they must comply with program requirements, and acknowledge that:

i. I will ensure that relevant staff are trained on the Fentanyl Citrate REMS program procedures and will follow the requirements of the Fentanyl Citrate REMS program.

ii. I will ensure that Fentanyl Citrate is only distributed to pharmacies whose enrollment has been validated in the Fentanyl Citrate REMS program.

iii. I will provide data to the Fentanyl Citrate REMS program including information on shipment to enrolled pharmacies.

iv. I will cooperate with periodic audits or non-compliance investigations to ensure that Fentanyl Citrate is distributed in accordance with the program requirements.

c. Watson will ensure that all forms are complete, prior to enrolling a distributor in the Fentanyl Citrate REMS program.

d. Watson will notify distributors when they are enrolled in the Fentanyl Citrate REMS program, and therefore, able to distribute Fentanyl Citrate.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the Fentanyl Citrate REMS program every two (2) years.

g. The following distributor materials are part of the Fentanyl Citrate REMS program and are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*

2. Watson will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the Fentanyl Citrate REMS requirements.

3. Watson will develop a REMS system that uses existing pharmacy management systems that allow for the transmission of REMS information using established telecommunication standards. The REMS system should incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the REMS requirements, if deemed necessary in the future.

4. Watson will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing Fentanyl Citrate. Additionally, Watson will monitor to ensure that Fentanyl Citrate is only being dispensed for outpatient use to actively enrolled patients of actively

enrolled prescribers. Corrective action or inactivation will be instituted by Watson if non-compliance is found.

5. Watson will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement* with each Fentanyl Citrate patient, and to submit it to the REMS program within ten (10) business days. This will be accomplished through patient surveys and by reconciling the *Patient-Prescriber Agreements* submitted to the REMS program with patient enrollment data captured through the pharmacy management system.

6. Watson will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the Fentanyl Citrate REMS program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

7. Prostraken will evaluate enrolled inpatient pharmacies' compliance with REMS requirements through surveys.

8. Watson will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the Fentanyl Citrate REMS program.

9. Watson will ensure that all materials listed in or appended to the Fentanyl Citrate REMS will be available through the Fentanyl Citrate website www. Fentanyl CitrateREMS.com or by calling the Fentanyl Citrate REMS call center at XXX-XXX-XXXX.

10. Watson will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the REMS program. Notifications for patients will be sent to the patient's prescriber.

11. If there are substantive changes to the Fentanyl Citrate REMS Program, Watson will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the Fentanyl Citrate REMS program are defined as:

    a. Significant changes to the operation of the Fentanyl Citrate REMS program for outpatient pharmacies.

    b. Changes to the Prescribing Information and Medication Guide that affect the risk benefit profile of Fentanyl Citrate.

12. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, Watson will take reasonable steps to improve implementation of these elements and to maintain compliance with the Fentanyl Citrate REMS program requirements, as applicable.

Appendix B

REMS Supporting Document Template

This REMS Supporting Document should include the following listed sections 1 through 5, as well as a table of contents. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 3 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Background

2. Goals

3. Supporting Information on Proposed REMS Elements

    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System

4. Information Needed for Assessments

5. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST
11/12/2010
Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

IMPORTANT NOTICE

Office of Generic Drugs
New Mailing Address

Dear Applicants:

Effective 01-Aug-2010, the new mailing address for Abbreviated New Drug Application (ANDA) and Abbreviated Investigational New Drug Application (AINDA) Regulatory Documents will be:

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, Maryland 20855

After the effective date, 01-Aug-2010, ANDAs will only be accepted at the new mailing address listed above. DO NOT **submit your ANDA Regulatory documents to this address prior to** 01-Aug-2010. For further information, please refer to the following websites prior to submitting your ANDA and AINDA Regulatory documents:

- Office of Generic Drugs (OGD)
http://www.fda.gov/cder/ogd

- Federal Register
http://www.gpoaccess.gov/fr/

Watson

June 19, 2015

Kathleen Uhl, M.D.
Director, OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville MD 20855

PROPOSED REMS for ANDA 079075

Electronic Submission (eCTD)
via Gateway

RE: Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base
ANDA 079075, Sequence #0062

Dear Dr. Uhl:

Watson Laboratories, Inc., ("Watson") is submitting this electronic Proposed Risk Evaluation and Mitigation Strategy (REMS) to its ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base, in response to the General Advice Letter received from FDA dated January 9, 2015 (**please see attached**).

As requested by the reviewer in the FDA's General Advice Letter, Watson has joined the FDA's approved shared system TIRF REMS, the TIRF REMS Access Program, and submits the proposed REMS. The proposed REMS submission includes two parts: a "proposed REMS" and a "REMS supporting document." Additionally, all relevant proposed REMS materials are appended to the proposed REMS. The documents are in accordance with the most currently approved TIRF class shared system REMS, approved by the Agency on December 24, 2014, and are provided in **Module 1.16**. As requested by the reviewer, the proposed REMS and other REMS-related materials are provided in Microsoft Word format.

Please note that Watson's most current labeling and Medication Guide for its Fentanyl Buccal Tablets was provided in **Module 1.14** of CBE-0 Labeling Supplement, Sequence 0061, submitted on February 27, 2015. In this supplement, Watson's labeling was updated in accordance with the most recently approved labeling for the RLD Fentora® Tablets, approved on February 21, 2013. The Agency approved this supplement on May 3, 2015.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. An MS Word file of this cover letter is provided for the reviewer's convenience. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

Watson trusts this information is sufficient for the submission to be evaluated. Should you have any questions or comments, please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

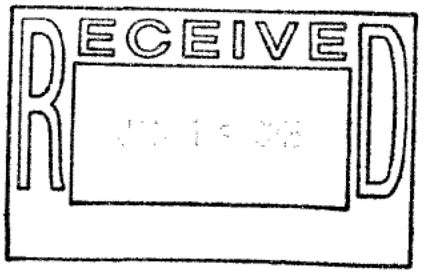
Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 079075

GENERAL ADVICE



Watson Laboratories; Inc.
Attention: Kelly Delgado
Manager, Regulatory Affairs
311 Bonnie Circle
Corona, CA 92880

Dear Ms. Delgado:

Please refer to your Abbreviated New Drug Application (ANDA) submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg.

We also refer to our November 12, 2010, letter notifying you that, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for products containing transmucosal immediate release fentanyl (TIRF), including Fentanyl Citrate Buccal Tablets, to ensure the benefits of the drug outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors. Our November 12, 2010, letter also advised you of our determination that a single, shared system should be used to implement the elements to assure safe use (ETASU) for all members of the TIRF class.

We further refer to your email correspondence dated September 2, 2011, informing us that due to ongoing litigation with Cephalon (the application holder of Fentora (fentanyl citrate), the applicable listed drug for your product), you have not marketed your Fentanyl Citrate Buccal Tablets, and therefore requested to submit a commitment to FDA ensuring that you will be in the TIRF shared REMS program at the time you market your product. In our letter dated September 20, 2011, we informed you that you could submit a proposed REMS for Fentanyl Citrate Buccal Tablets before you market this product, provided that your Fentanyl Citrate Buccal Tablets is not marketed until you have an approved REMS.

The shared system REMS for TIRF products, the TIRF REMS Access Program, was approved on December 28, 2011, and the most recent REMS modification was approved on December 24, 2014. Cephalon is a member of the shared system REMS for TIRF products. The TIRF REMS Access Program is the only approved REMS program for the TIRF products.

We also refer to your subsequent correspondence, dated November 7, 2012 and received November 8, 2012, withdrawing your proposed REMS for supplements 006, 007, and 008, and stating that you have not marketed the Fentanyl Citrate Buccal Tablets and are committed to submitting the TIRF REMS at the time you do intend to market the product.

This letter is to inform you that we have determined that under section 505-1 of the FDCA, you must have a REMS approved as part of your application in order to maintain approval of your ANDA. Accordingly, you must either submit a proposed REMS and join the shared system TIRF REMS, or request withdrawal of approval of your ANDA.

If you choose not to request withdrawal of approval of your ANDA and to submit a proposed REMS, please contact Karla Werre at Mallinckrodt Pharmaceuticals, who has been identified as the current point of contact for the TIRF REMS, regarding your participation in the shared system REMS. She can be reached at (314) 654-3517 or karla.werre@mallinckrodt.com

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Fentanyl Citrate Buccal Tablets pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Fentanyl Citrate Buccal Tablets. FDA has determined that Fentanyl Citrate Buccal Tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Fentanyl Citrate Buccal Tablets. FDA has also determined that Fentanyl Citrate Buccal Tablets is a product for which patient labeling could help prevent serious adverse events.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fentanyl Citrate Buccal Tablets.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your proposed REMS must include elements to manage these risks, including the following:

- Healthcare providers are specially certified or trained
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Additionally, all relevant proposed REMS materials should be appended to the proposed REMS. The REMS, once approved, will create enforceable obligations.

For administrative purposes, designate the proposed REMS submission **"PROPOSED REMS for ANDA 079075"** and all subsequent submissions related to the proposed REMS **"PROPOSED REMS-AMENDMENT for ANDA 079075"** If you do not submit electronically, please send 5 copies of your REMS-related submissions.

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in a single Word document.

In accordance with section 505-1 of the FDCA, submit a response with either the above proposed REMS or a request to withdraw approval of your ANDA within 30 days of receipt of this letter,

If you have any questions, call Chantal Phillips, REMS Coordinator, at (301) 796-2259.

Sincerely,

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R PETERS
01/09/2015

July 10, 2015

Kathleen Uhl, M.D.
Director, OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville MD 20855

PROPOSED TIRF REMS for ANDA 079075 –
Resubmission as Prior Approval Supplement (PAS)
Electronic Submission (eCTD)
via Gateway

RE: Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base
ANDA 079075, Sequence #0063

Dear Dr. Uhl:

Watson Laboratories, Inc., ("Watson") hereby re-submits this electronic Proposed Risk Evaluation and Mitigation Strategy (REMS) as a Prior Approval Supplement (PAS) to its ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base, in response to the FDA's General Advice Letter dated January 9, 2015 (**attached**).

Actavis confirms that it has paid the fee for review of this PAS as required by the Generic Drug User Fee Act Amendment 2012 (GDUFA). The GDUFA Cover Sheet (FDA Form 3794) (PIN GD8010026) for this PAS is provided in **Module 1.1.3** of this Supplement.

As requested by the reviewer in the FDA's General Advice Letter, Watson has joined the FDA's approved shared system TIRF REMS, the TIRF REMS Access Program, and submits the proposed REMS. The proposed REMS submission includes two parts: a "proposed REMS" and a "REMS supporting document." Additionally, all relevant proposed REMS materials are appended to the proposed REMS. The documents are in accordance with the most currently approved TIRF class shared system REMS, approved by the Agency on December 24, 2014, and are provided in **Module 1.16**. As requested by the reviewer, the proposed REMS and other REMS-related materials are provided in Microsoft Word format.

Please note that Actavis is now a TRIG member and authorizes FDA to reference DMF No. 27320 for future TIRF REMS submissions. Additionally, FDA can refer to the DMF 27320 12/10/2014 Sequence No. 0013 for the most recent, approved TIRF REMS and appended materials.

Watson's most current labeling and Medication Guide for its Fentanyl Buccal Tablets was provided in **Module 1.14** of CBE-0 Labeling Supplement, Sequence 0061, submitted on February 27, 2015. In this supplement, Watson's labeling was updated in accordance with the most recently approved labeling for the RLD Fentora® Tablets, approved on February 21, 2013. The Agency approved this supplement on May 3, 2015.

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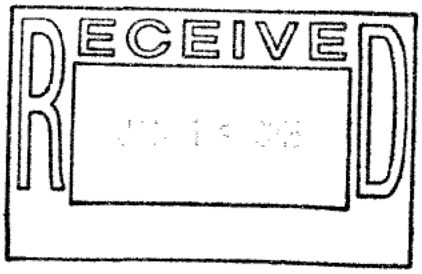
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 079075

GENERAL ADVICE



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If you have any questions, call Chantal Phillips, REMS Coordinator, at (301) 796-2259.

Sincerely,

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R PETERS
01/09/2015

1.16 Risk Management Plans

Following documents are provided in **this Module** in support of the PROPOSED REMS for ANDA 079075.

Description	Format
REMS and Appended Materials	PDF
Risk Evaluation and Mitigation Strategy (REMS)	MS Word
Risk Evaluation and Mitigation Strategy (REMS) Supporting Document	MS Word
Appended Materials	
TIRF REMS Access Program: An Overview for Prescribers	MS Word
TIRF REMS Access Education Program	MS Word
TIRF REMS Access Program: Knowledge Assessment	MS Word
TIRF REMS Access Program: Prescriber Enrollment Form	MS Word
TIRF REMS Access Program: Patient-Prescriber Agreement Form	MS Word
TIRF REMS Access Program: An Overview for Patients and Caregivers	MS Word
TIRF REMS Access Program: Frequently Asked Questions	MS Word
TIRF REMS Access Program: Web Prototype	MS Word
TIRF REMS Access Program: Dear Healthcare Provider Letter	MS Word
TIRF REMS Access Program: An Overview for Independent Outpatient Pharmacies	MS Word
TIRF REMS Access Program: An Overview for Chain Outpatient Pharmacies	MS Word
TIRF REMS Access Program: An Overview for Closed System Outpatient Pharmacies	MS Word
TIRF REMS Access Program: An Overview for Inpatient Pharmacies	MS Word
TIRF REMS Access Program: Independent Outpatient Pharmacy Enrollment Form	MS Word
TIRF REMS Access Program: Chain Outpatient Pharmacy Enrollment Form	MS Word
TIRF REMS Access Program: Closed System Outpatient Pharmacy Enrollment Form	MS Word
TIRF REMS Access Program: Inpatient Pharmacy Enrollment Form	MS Word
TIRF REMS Access Program: Dear Outpatient Pharmacy Letter	MS Word
TIRF REMS Access Program: Dear Inpatient Pharmacy Letter	MS Word
TIRF REMS Access Program: Dear Distributor Letter	MS Word
TIRF REMS Access Program: Wholesaler / Distributor Enrollment Form	MS Word

October 26, 2015

Kathleen Uhl, M.D.
Director, OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville MD 20855

PROPOSED TIRF REMS for ANDA 079075 – Resubmission of Prior Approval Supplement (PAS) to Correct Inactive Hyperlinks in Module 1.16 Electronic Submission (eCTD) via Gateway

RE: Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base ANDA 079075, Sequence #0064

Dear Dr. Uhl:

Watson Laboratories, Inc., ("Watson") hereby re-submits this electronic Prior Approval Supplement (PAS) for its Proposed Risk Evaluation and Mitigation Strategy (REMS) to its ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base, in order to replace Module 1.16 in order to include active hyperlinks which were inadvertently broken when submitting Sequence 0063.

The request to replace Module 1.16 with corrected hyperlinks was received from FDA, via Email on October 2, 2015 (**see attached**).

Actavis confirms that it has paid previously paid the fee for review of this PAS as required by the Generic Drug User Fee Act Amendment 2012 (GDUFA). The GDUFA Cover Sheet for this PAS **(FDA Form 3794) (PIN GD8010026)** is resubmitted with this resubmission, Sequence 0064.

As previously noted in the Sequence 0063 cover letter, Watson has joined the FDA's approved shared system TIRF REMS, the TIRF REMS Access Program, and submits the proposed REMS. The proposed REMS submission includes two parts: a "proposed REMS" and a "REMS supporting document." Additionally, all relevant proposed REMS materials are appended to the proposed REMS. The documents are in accordance with the most currently approved TIRF class shared system REMS, approved by the Agency on December 24, 2014, and are provided in **Module 1.16**. As requested by the reviewer, the proposed REMS and other REMS-related materials are provided in Microsoft Word format. Please note, Watson has also provided PDF versions of each document in Module 1.16.

Please note that Actavis is now a TRIG member and authorizes FDA to reference DMF No. 27320 for future TIRF REMS submissions. Additionally, FDA can refer to the DMF 27320 12/10/2014 Sequence No. 0013 for the most recent, approved TIRF REMS and appended materials.

Watson's most current labeling and Medication Guide for its Fentanyl Buccal Tablets was provided in **Module 1.14** of CBE-0 Labeling Supplement, Sequence 0061, submitted on February 27, 2015. In this supplement, Watson's labeling was updated in accordance with the most recently approved labeling for the RLD Fentora® Tablets, approved on February 21, 2013. The Agency approved this supplement on May 3, 2015.

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Watson trusts this information is sufficient for the submission to be evaluated. Should you have any questions or comments, please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

kelly.delgado@actavis.com

Digitally signed by kelly.delgado@actavis.com
DN: cn=kelly.delgado@actavis.com
Reason: I am approving this document
Date: 2015.10.26 15:14:36 -07'00'

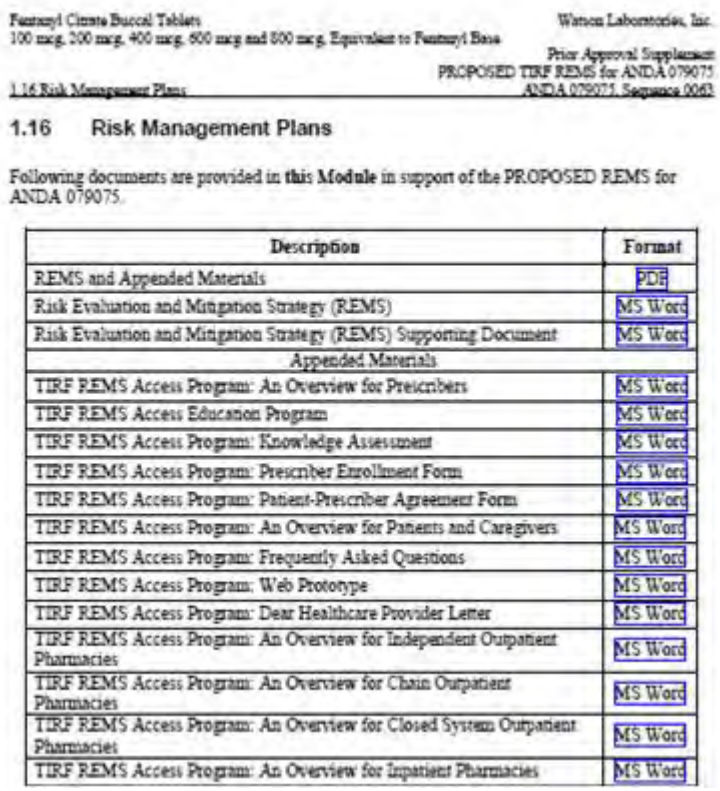
Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

Delgado, Kelly

From: Gooding, Valerie <Valerie.Gooding@fda.hhs.gov>
Sent: Friday, October 02, 2015 6:54 AM
To: Regulatory Affairs US
Cc: CDER ESUB
Subject: ANDA 079075 - sequence 0063 - REMS document - links not working

Dear Kelly,

It was brought to our attention that the REMS document in the above submission has links that are inactive (see snapshot below).



Fentanyl Citrate Buccal Tablets
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base

Watson Laboratories, Inc.

Prior Approval Supplement
PROPOSED TIRF REMS for ANDA 079075
ANDA 079075, Sequence 0063

1.16 Risk Management Plans

1.16 Risk Management Plans

Following documents are provided in **this Module** in support of the PROPOSED REMS for ANDA 079075.

Description	Format
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Risk Evaluation and Mitigation Strategy (REMS) Supporting Document	MS Word
Appended Materials	
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TIRF REMS Access Program: An Overview for Closed System Outpatient Pharmacies	MS Word
TIRF REMS Access Program: An Overview for Inpatient Pharmacies	MS Word

Please resubmit the document using the “replace” operator and make sure the hyperlinks are active.

Best Regards,

Valerie M.D. Gooding, GWCPM
Regulatory Information Specialist
Office of Strategic Programs (OSP)
Electronic Submissions Capability Team
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22 Room 1223
Silver Spring MD 20993
valerie.gooding@fda.hhs.gov

301-796-0902
For the FDA CDER eCTD web page, please visit
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
To submit electronically via the Gateway: http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/ucm114831.htm
For Pre-assigned Numbers:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm163184.htm

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	December 14, 2015
Reviewer(s):	Somya Dunn, M.D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D. DRISK
Office Director:	Claudia Manzo, Pharm.D Office of Medication Error Prevention & Risk Management (OMEPRM)
Drug Name(s):	FentanylBuccal Tablet
Therapeutic Class:	Opioid Analgesic
Dosage and Route:	100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg tablet for buccal or sublingual administration
Application Type/Number:	ANDA 79075
Submission Number:	Supplement 10 and 11 (eCTD Sequence 0063 and 0065)
Applicant/Sponsor:	Watson Laboratories, Inc.
OSE RCM #:	2015-1633
TSI #:	290

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the proposed Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) for Fentanyl Buccal tablet, Abbreviated New Drug Application (ANDA) 79075. This ANDA was submitted by Watson Laboratories, Inc. as Supplement 10 on July 10, 2015. The Sponsor is a member of the TIRF REMS Industry Group (TRIG) and will market their product under the single, shared system TIRF REMS. This review documents the final agreed upon TIRF REMS.

1.1 PRODUCT BACKGROUND

Fentanyl Buccal tablet is an opioid agonist with the proposed indication for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. The Sponsor is plans to market the following strengths: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg tablets

On September 25, 2006, Fentora (NDA 021947), the reference listed drug (RLD) for Fentanyl Buccal tablets, was approved for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. It was approved with a Risk Minimization Action Plan (RiskMAP) to minimize the use of Fentora by opioid non-tolerant individuals and minimize misuse and unintended (accidental) exposure to Fentora.

During the review of postmarketing data between 2006 and 2009, FDA had determined that, in the interest of public health and to minimize the burden on the healthcare system, a SSS REMS would be required for all TIRF products. On November 12, 2010, FDA sent all TIRF medication sponsors, including Cephalon, a REMS Notification Letter informing them of the need for a SSS REMS and the details for the REMS requirements. On July 20, 2011, a single REMS was approved for Fentora and Actiq.

On December 28, 2011, FDA approved a SSS REMS for all TIRF products, including Fentora, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. The TIRF REMS was approved with the following elements:

- Medication Guide
- Elements to Assure Safe Use
  - Prescriber Certification
  - Pharmacy Certification
  - Documentation of safe use conditions
- Implementation System
- Timetable for Submission of Assessments

The TIRF REMS Access Program was launched on March 12, 2012. The TIRF REMS was modified June 5, 2012, November 7, 2013 and December 24, 2014.

1.2 REGULATORY HISTORY

Regulatory History relevant to this review:

On July 10, 2007, Watson submitted Abbreviated New Drug Application (ANDA) 79075 providing for the manufacture of Fentanyl Buccal Tablet, citing the reference listed drug (RLD) Fentora NDA 021947.

On November 12, 2010, the FDA sent a Pre-Approval REMS Nofication Letter notifying Watson that they would need to sumbit a REMS and join the process currently in place of of the TIRF single shared system REMS development.

On January 7, 2011, Fentanyl buccal tablet, ANDA 79075, was approved.

On September 2, 2011, Watson emailed the FDA to inform them that there was ongoing litigation with Cephalon to explain why they have not marketed the approved fentanyl buccal tablet (ANDA 79075). They submitted a commitment to ensure the FDA that they plan to be in the TIRF single shared REMS program at the time of marketing.

On September 20, 2011, the FDA sent a General Advice Letter to Watson informing them that a proposed REMS would be needed before marketing.

On December 28, 2011, the TIRF single shared REMS program was approved.

On November 7, 2012 Watson sent communication to the FDA stating that they are still not marketing their fentanyl buccal tablet (ANDA 79075) and are still committed to submit the REMS when they intend to market.

On January 9, 2015, the FDA sent a General Advice Letter informing Watson that the FDA determined that under section 505-1 of the Federal Food, Drug and Cosmetic Act (FDCA), they must have a REMS approved as part of the application in order to maintain approval of the ANDA. Accordingly, they must either submit a proposed REMS and join the shared system TIRF REMS, or request withdrawal of approval of the ANDA.

On July 10, 2015, Watson submitted Supplement 10 indicating that they are now a member of the TRIG and that the FDA can refer to the DMF 27320 for the approved TIRF REMS. They reference the DMF in their submission.

On October 2, 2015, the FDA sent an email to Watson informing them that the hyperlinks of Supplement 10 are not functional and the REMS documents could not be opened.

On October 26, 2015, Watson sumitted an amendment to Supplement 10, which contained corrected hyperlinks.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSIONS

July 10, 2015**:** Watson's submission of proposed REMS for ANDA 79075 (eCTD Seq. No. 0063, Supplement 10) TIRF REMS, REMS materials and Supporting Document last modified 2014; however hyperlinks were not functional. This submission included a Cover Letter that referenced the approved TIRF Medication Guide.

October 26, 2015: Watson's submission of amendment to the REMS for ANDA 79075 (eCTD Seq. No. 0065, Supplement 10) TIRF REMS, REMS materials and Supporting Document last modified 2014 with functional hyperlinks.

3 RESULTS OF THE REVIEW OF PROPOSED RISK EVALUATION AND MITIGATION

The Sponsor did not propose any revisions to the TIRF REMS document, appended materials, or the REMS Supporting Document. The Sponsor is a member of the TIRF REMS Industry Group (TRIG), and thus has access to the most current approved TIRF REMS documents which were submitted to the DMF and referenced by the Sponsor as stated in the Regulatory History (see Section 1.2).

The Medication Guide was reviewed under separate cover by OGD Division of Labeling Review (see section 2.1; this is referenced in the Cover Letter for Supplement 10). The labeling reviewers found the MG submission to be acceptable.

4 DISCUSSION AND CONCLUSION

As stipulated in FDAAA, a drug that is subject of an abbreviated new drug application is subject to the elements to assure safe use as required for the listed drug. The listed drug and the ANDA shall use a single, shared system. Therefore, Watson must join the TRIG and Fentanyl Buccal tablet will be subject to the already established single, shared system utilized by the RLD, Fentora (TIRF REMS).

The attached REMS for Fentanyl Buccal tablet (ANDA 79075), originally submitted on July 10, 2015 referencing the DMF 27320, contains the currently approved TIRF REMS document and appended materials as stipulated by the Agency on December 24, 2014 (approval date of most recent TIRF REMS modification). Therefore, the TIRF REMS is acceptable to the Division of Risk Management.

5 RECOMMENDATIONS

DRISK recommends approval of the TIRF REMS for Fentanyl Buccal tablets (ANDA 79075) as appended to this review.

DRISK recommends that OGD inform the Office of Compliance to update the "List of Approved Application Numbers and Sponsors" on the FDA's Approved Risk Evaluation

and Mitigation Strategies (REMS) website, available at: http://www.fda.gov/downloads/Drugs/DrugSafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm289730.pdf

6 ATTACHMENTS

TIRF REMS document and appended materials

Initial REMS approval: 12/2011

Most recent modification: XX/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for <u>outpatient</u> use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **<u>outpatient</u>** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**
  - i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.
  - ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
  - iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?
Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?
Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?
Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?
Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Additional Prescriber Information (All Fields Required)

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued* _____
DEA Number* _____

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

Site Name* _____
Address* _____
City* _____
State* _____ **ZIP*** _____
Phone Number* _____
Fax Number* _____

State License Number* _____
State Issued*
DEA Number*

***Required Fields**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/ProductList.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

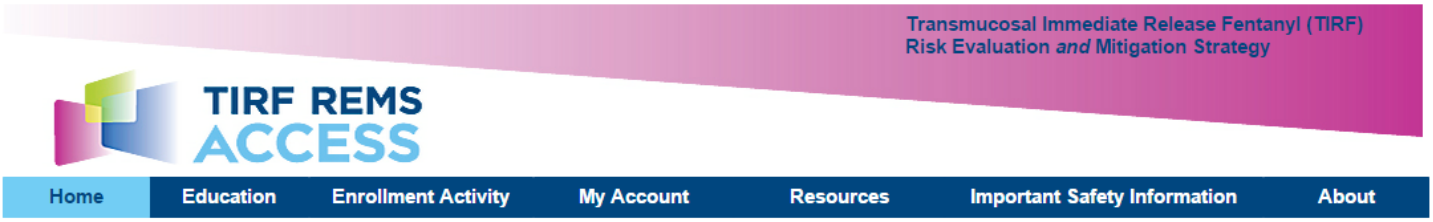
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

- Patient First Name,
- Patient Last Name,
- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

*Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Chain Outpatient Pharmacies”, “An Overview for Independent Outpatient Pharmacies” or “An Overview for Inpatient Pharmacies” for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*: _____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

- Patient First Name..... TIRFREMSTEST
- Patient Last Name..... Smithers
- Date of Birth..... 19841105
- Patient ZIP/Postal Zone..... 07921
- Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
- Quantity Dispensed..... 12
- Days Supply..... 4
- Prescriber ID..... BA1111119
- Prescriber Last Name..... REMSTEST

- Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “NN”
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... “R” (Rejected)
° Reject Code..... “Will vary based upon missing/invalid required field”
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
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- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
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The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

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- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

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Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

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Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

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Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOMYA V DUNN
12/14/2015

CLAUDIA B MANZO
12/15/2015
concur

From: Sarchet, Jennifer
To: "Delgado, Kelly"; "Regulatory Affairs US"
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number; Supplement 010; Medication Guide
Date: Tuesday, December 22, 2015 9:12:00 AM
Attachments: A079075G002DLR_AP.pdf
Importance: High

Kelly,

In reference to ANDA 079075/S-010; Fentanyl Citrate (TIRF): Could you please submit an UPDATED Medication Guide ASAP, but no later than 12/30/2015 (preferable sooner if possible)? Could you also e-mail me when this is complete? The updated Medication Guide for ANDA 079075/S-010 would include the changes related to S-002 and S-009 which involves "including all references to the TIRF REMS Access program throughout the insert and medication guide." (Please see attached letter for reference).

Please note, you only need to submit the Medication Guide **NOT** the package insert.

Please confirm receipt of this e-mail and let me know if you have any questions and when you think you will be able to submit this?

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

From: Delgado, Kelly [mailto:Kelly.Delgado@actavis.com]
Sent: Wednesday, December 16, 2015 1:39 PM
To: Sarchet, Jennifer
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hi Jennifer,

Thank you for the confirmation. Happy Holidays!

Kelly Delgado
Regulatory Affairs
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880 USA
Ph: 951-493-4440
Cell: 951-310-1194
Fax: 951-493-5806
Email: kelly.delgado@actavis.com

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To: Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hello Kelly,

Correct, no additional action on your part is necessary at this time. Many thanks for double checking.

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

From: Regulatory Affairs US [mailto:RegulatoryAffairsUS@actavis.com]
Sent: Thursday, December 10, 2015 2:44 PM
To: Sarchet, Jennifer; Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hi Jennifer,
This is good news! Watson apologizes for any confusion with the reference to Actavis in the body of the cover letter. As we discussed, it is confirmed that the sponsor for this ANDA remains as Watson Laboratories, Inc. That being said, I wanted to confirm that no action is needed at this time relative to this REMS supplement, and that for future submissions we are to ensure that this reference is not introduced again, is that correct?

Thanks again for your follow-up. Have a nice afternoon!
Kelly Delgado
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Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880 USA
Ph: 951-493-4440
Cell: 951-310-1194
Fax: 951-493-5806
Email: kelly.delgado@actavis.com

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Thursday, December 10, 2015 6:45 AM
To: Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hello Ms. Delgado,

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Thank you,
Jennifer

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CDR, U.S. Public Health Service Corps
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Office of Generic Drugs
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240-402-4275 (office)

APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify me immediately me by telephone at 240-402-4275. Thank you.

From: Regulatory Affairs US [mailto:RegulatoryAffairsUS@actavis.com]
Sent: Thursday, December 03, 2015 5:52 PM
To: Sarchet, Jennifer
Cc: Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hi Jennifer,
We are in receipt of your inquiry. For clarity, Watson submitted its proposed REMS on June 19, 2015 (Sequence 0062) but resubmitted the proposed REMS as a PAS on July 10, 2015, Sequence 0063 (believe this was assigned as Supplement 0010, correct).

When we were requested to replace Module 1.16 with "working" hyperlinks, we submitted an amendment to Sequence 0063 on October 26,2015 (the Regional Metadata was coded as "Amendment") in Sequence 0064 and in this amendment, we resubmitted the REMS files using the "replace" lifecycle tag for the REMS Word documents. However, due to a software glitch with this ANDA, we continued to have link issues when linking to a previous eCTD submission, so we also provided PDF versions of the respective REMS MS Word documents for hyperlinking purposes. So, both MS Word and PDF files were provided in Sequence 0064.

Since the October 26, 2015 submission was coded as an Amendment and the lifecycle tags were used (where possible), I am a little unclear as to what is needed to satisfy your concerns. Therefore, I would like to discuss with you on the phone, if possible. Since I am on the West Coast, I will try to call you tomorrow.

Thanks in advance,

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Regulatory Affairs
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880 USA
Ph: 951-493-4440
Cell: 951-310-1194
Fax: 951-493-5806
Email: kelly.delgado@actavis.com

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Thursday, December 03, 2015 10:13 AM
To: Regulatory Affairs US

Subject: ANDA 079075; Fentanyl Citrate; Supplement Submission Number

Hello Ms. Delgado,

In reference to ANDA 079075; Fentanyl Citrate and the submission dated and received October 26, 2015: It appears to be coded as a new supplement (supplement 011) in the Gateway Global Submit System. I believe this submission is related to supplement 010 and not supplement 011 (as I do not believe there is a supplement 011 as of yet).

Could you confirm and fix the submission in the Gateway Global Submit System?

Thank you,
Jennifer

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CDER/FDA
240-402-4275 (office)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER S SARCHET
12/22/2015

From: Sarchet, Jennifer
To: "Regulatory Affairs US"
Cc: Phillips, Chantal; Snyder, Kyle
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number; Supplement 010; Medication Guide
Date: Thursday, December 24, 2015 5:55:00 AM

Hello Kelly,

Thank you for your telephone message. I checked with labeling and they indeed would like you to submit an updated Medication Guide ***and*** Package Insert based off the RLD's most current Medication Guide and Package Insert. My apologies for incorrectly stating previously that the Package Insert was not needed.

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

From: Regulatory Affairs US [mailto:RegulatoryAffairsUS@actavis.com]
Sent: Tuesday, December 22, 2015 11:33 AM
To: Sarchet, Jennifer
Cc: Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number; Supplement 010; Medication Guide

Hi Jennifer,
I confirm receipt of this email. We are working to respond by 12/30 or sooner, as requested. If there is any change, we will be in touch.

Thank you and Happy Holidays,

Kelly Delgado
Regulatory Affairs
Watson Laboratories, Inc.
311 Bonnie Circle
Corona, CA 92880 USA
Ph: 951-493-4440
Cell: 951-310-1194
Fax: 951-493-5806
Email: kelly.delgado@actavis.com

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Sent: Tuesday, December 22, 2015 6:13 AM
To: Delgado, Kelly; Regulatory Affairs US
Subject: RE: ANDA 079075; Fentanyl Citrate; Supplement Submission Number; Supplement 010; Medication Guide
Importance: High

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Regulatory Affairs

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Email: kelly.delgado@actavis.com

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To: Regulatory Affairs US
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Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JENNIFER S SARCHET
12/24/2015

ANDA 079075/S-010

SUPPLEMENT
APPROVAL

Watson Laboratories, Inc.
Attention: Kelly Delgado
Manager, Regulatory Affairs
311 Bonnie Circle
Corona, CA 92880

Dear Ms. Delgado:

Please refer to your supplemental Abbreviated New Drug Applications (sANDA) dated and received July 10, 2015, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), regarding your abbreviated new drug application (ANDA) for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg.

Reference is also made to the General Advice letter issued by this office on January 9, 2015, and to your amendment dated October 26, 2015.

This supplemental ANDA, submitted as a "Prior Approval Supplement," provides for the approval and inclusion of your products in the single, shared system for products containing transmucosal immediate release fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS).

We have completed our review of this ANDA, as amended. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated November 12, 2010. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your proposed REMS, submitted on July 10, 2015, amended on October 26, 2015, and appended to this letter, is approved. The REMS consists of a Medication Guide, ETASU, and an implementation system.

The REMS uses a shared system for the ETASU, implementation system, and the REMS assessments. This shared system, known as the Transmucosal Immediate Release Fentanyl (TIRF) REMS Program, includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 079075 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 079075/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 079075/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 079075/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 079075

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your sANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

The material submitted is being retained in our files.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Acting Director, Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
REMS
Medication Guide

Initial REMS approval: 12/2011

Most recent modification: 12/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**
  - i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.
  - ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
  - iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?

Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?

Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?

Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?

Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** _____ **DEA Number*** _____
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/ProductList.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

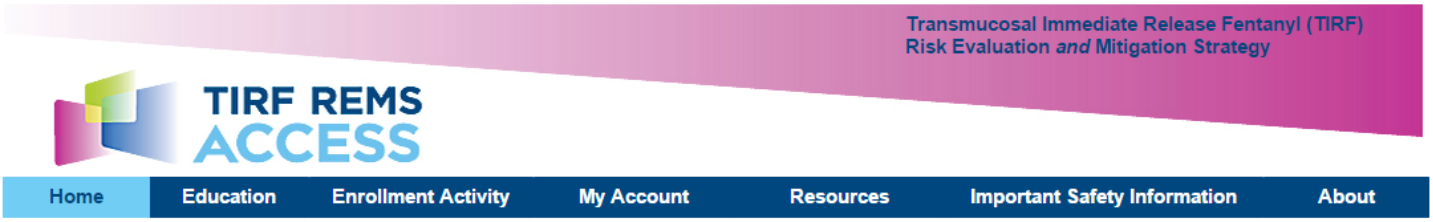
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

- Patient First Name,
- Patient Last Name,
- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

*Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Chain Outpatient Pharmacies”, “An Overview for Independent Outpatient Pharmacies” or “An Overview for Inpatient Pharmacies” for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____

Address* _____

City* _____

State* _____ **ZIP** _____

Phone Number* _____

Fax Number* _____

DEA Number* _____

National Provider Identifier (NPI)* _____

Medicaid ID _____

State Issued _____

NCPDP Number* _____

Store Number* _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

- Patient First Name..... TIRFREMSTEST
- Patient Last Name..... Smithers
- Date of Birth..... 19841105
- Patient ZIP/Postal Zone..... 07921
- Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
- Quantity Dispensed..... 12
- Days Supply..... 4
- Prescriber ID..... BA1111119
- Prescriber Last Name..... REMSTEST

- Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
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- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

MEDICATION GUIDE
Fentanyl (Fen-te-nil) Buccal Tablets CII
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:
Do not use fentanyl buccal tablets unless you are regularly using another opioid pain medicine around-the-clock for your cancer pain and your body is used to these medicines (this means you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep fentanyl buccal tablets in a safe place away from children.

Get emergency help right away if:

- **a child takes fentanyl buccal tablets. Fentanyl buccal tablets can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed fentanyl buccal tablets uses it**
- **an adult who is not already taking opioids around-the-clock, uses fentanyl buccal tablets.**

These are medical emergencies that can cause death. If possible, try to remove fentanyl buccal tablets from the mouth.

Read this Medication Guide completely before you start using fentanyl buccal tablets, and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment. Share this important information with members of your household and other caregivers.

What is the most important information I should know about fentanyl buccal tablets?

Fentanyl buccal tablets can cause life-threatening breathing problems which can lead to death.

1. **Do not use fentanyl buccal tablets if you are not opioid tolerant.**
2. If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using fentanyl buccal tablets. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use fentanyl buccal tablets exactly as prescribed by your healthcare provider.**

    - You must not use more than 2 doses of fentanyl buccal tablets for each episode of breakthrough cancer pain.

    - You must wait at least 4 hours before treating a new episode of breakthrough pain with fentanyl buccal tablets. **See the Medication Guide section "How should I use fentanyl buccal tablets?" and the Instructions for Use at the end of this Medication Guide for detailed information about how to use fentanyl buccal tablets the right way.**

4. **Do not switch from fentanyl buccal tablets to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tablets is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of fentanyl buccal tablets that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use fentanyl buccal tablets for short-term pain that you would expect to go away in a few days, such as:
    - pain after surgery

- headache or migraine
- dental pain

6. **Never give fentanyl buccal tablets to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

Fentanyl buccal tablets are a federally controlled substance (CII) because it is a strong opioid (narcotic) pain medicine that can be misused by people who abuse prescription medicines or street drugs.

- **Prevent theft, misuse or abuse. Keep fentanyl buccal tablets in a safe place** to protect it from being stolen. Fentanyl buccal tablets can be a target for people who abuse (narcotic) medicines or street drugs.
- **Selling or giving away this medicine is against the law.**

7. Fentanyl buccal tablets are available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive fentanyl buccal tablets, you must:

- talk to your healthcare provider
- understand the benefits and risks of fentanyl buccal tablets
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form.

What are fentanyl buccal tablets?

- Fentanyl buccal tablets are a prescription medicine that contains the medicine fentanyl.
- Fentanyl buccal tablets are used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- Fentanyl buccal tablets are started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use fentanyl buccal tablets if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using fentanyl buccal tablets.
- Fentanyl buccal tablets are only:
  - o available through the TIRF REMS Access program
  - o given to people who are opioid tolerant

It is not known if fentanyl buccal tablets are safe and effective in children under 18 years of age.

Who should not use fentanyl buccal tablets?

Do not use fentanyl buccal tablets:

- **if you are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for your cancer pain, and your body is used to these medicines.**
- for short-term pain that you would expect to go away in a few days, such as:
  - o pain after surgery
  - o headaches or migraine
  - o dental pain

- if you are allergic to any of the ingredients in fentanyl buccal tablets. See the end of this Medication Guide for a complete list of ingredients in fentanyl buccal tablets.

What should I tell my healthcare provider before using fentanyl buccal tablets?
Before using fentanyl buccal tablets, tell your healthcare provider if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have or had a head injury or brain problem
- have liver or kidney problems
- have seizures
- have a slow heart rate or other heart problems
- have low blood pressure
- have mental problems including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)
- have a past or present drinking problem (alcoholism), or a family history of drinking problems
- have a past or present drug abuse problem or addiction problem, or a family history of a drug abuse problem or addiction problem
- have any other medical conditions
- are pregnant or plan to become pregnant. Fentanyl buccal tablets may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. Fentanyl passes into your breast milk. It can cause serious harm to your baby. You should not take fentanyl buccal tablets while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening side effects when taken with fentanyl buccal tablets. Sometimes, the doses of certain medicines and fentanyl buccal tablets need to be changed if used together.

- **Do not take any medicine while using fentanyl buccal tablets until you have talked to your healthcare provider. Your healthcare provider will tell you if it is safe to take other medicines while you are using fentanyl buccal tablets.**
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use fentanyl buccal tablets?

Before you can begin to use fentanyl buccal tablets:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- Fentanyl buccal tablets are only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your fentanyl buccal tablets prescription filled.

Using fentanyl buccal tablets:

- **Use fentanyl buccal tablets exactly as prescribed. Do not use fentanyl buccal tablets more often than prescribed.**
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Instructions for Use at the end of this Medication Guide for information about how to use fentanyl buccal tablets the right way.**
- **Use fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using fentanyl buccal tablets. If there is any of the fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- You must not use more than 2 doses of fentanyl buccal tablets for each episode of breakthrough cancer pain.
  - Use **1** dose of fentanyl buccal tablets for an episode of breakthrough cancer pain.
  - If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of fentanyl buccal tablets, you can use **only 1** more dose of fentanyl buccal tablets as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of fentanyl buccal tablets, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tablets at this time.**

- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tablets.
  - If you only need to take 1 dose of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.

- It is important for you to keep taking your around-the-clock opioid pain medicine while using fentanyl buccal tablets.
- Talk to your healthcare provider if your dose of fentanyl buccal tablets does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tablets needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.
- If you use too many fentanyl buccal tablets or overdose, you or your caregiver should call for emergency medical help or have someone take you to the nearest hospital emergency room.

What should I avoid while using fentanyl buccal tablets?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy. Ask your healthcare provider when it is okay to do these activities.

- **Do not drink alcohol while using fentanyl buccal tablets.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of fentanyl buccal tablets?

Fentanyl buccal tablets can cause serious side effects, including:

1. **Breathing problems that can become life-threatening.** See "**What is the most important information I should know about fentanyl buccal tablets?**" **Call your healthcare provider or get emergency medical help right away if you:**
    - have trouble breathing
    - have drowsiness with slowed breathing
    - have slow, shallow breathing (little chest movement with breathing)
    - feel faint, very dizzy, confused, or have unusual symptoms

These symptoms can be a sign that you have taken too many fentanyl or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not take any more fentanyl buccal tablets until you have talked to your healthcare provider.**

2. **Decreased blood pressure.** This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
3. **Physical dependence. Do not stop using fentanyl buccal tablets or taking any other opioid without talking to your healthcare provider.** You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
4. **A chance of abuse or addiction.** This chance is higher if you are or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental health problems.
5. **Pain, irritation, or sores at the application site (on your gum, on the inside of your cheek, or under your tongue).** Tell your healthcare provider if this is a problem for you.

The most common side effects of fentanyl buccal tablets are:
- nausea
- vomiting
- dizziness
- low red blood cell count
- tiredness
- swelling of the arms, hands, legs and feet
- headache

Constipation (not often enough or hard bowel movements) is a very common side effect of pain medicines (opioids) including fentanyl buccal tablets and is unlikely to go away without treatment. Talk to your healthcare provider about dietary changes, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking fentanyl buccal tablets.

Talk to your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of fentanyl buccal tablets. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1800-FDA-1088.

How should I store fentanyl buccal tablets?

- **Always keep fentanyl buccal tablets in a safe place away from children and from anyone for whom it has not been prescribed**. Protect fentanyl buccal tablets from theft.
- Store fentanyl buccal tablets at room temperature, 68°F to 77°F (20° C to 25°C) until ready to use. Do not freeze fentanyl buccal tablets.
- Keep fentanyl buccal tablets in the original blister unit. Do not remove fentanyl buccal tablets from its blister packaging for storage in a temporary container, such as a pill box.
- Keep fentanyl buccal tablets dry.

How should I dispose of unused fentanyl buccal tablets when they are no longer needed?

- Dispose of any unused fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.
  - o Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablet packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets, call Watson Laboratories Inc., at 1-800-272-5525 or call your local Drug Enforcement Agency (DEA) office.

General information about fentanyl buccal tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use fentanyl buccal tablets only for the purpose for which it was prescribed**. **Do not give fentanyl buccal tablets to other people, even if they have the same symptoms you have.** Fentanyl buccal tablets can harm other people and even cause death. Sharing fentanyl buccal tablets is against the law.

This Medication Guide summarizes the most important information about fentanyl buccal tablets. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about fentanyl buccal tablets that is written for health professionals.

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients in fentanyl buccal tablets?

Active Ingredient: fentanyl citrate

Inactive Ingredients: mannitol, sodium starch glycolate, potassium bicarbonate, and magnesium stearate.

Instructions for Use

Before you use fentanyl buccal tablets, it is important that you read the Medication Guide and these Instructions for Use. Be sure that you read, understand, and follow these Instructions for Use so that you use fentanyl buccal tablets the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use fentanyl buccal tablets.

When you get an episode of breakthrough cancer pain, use the dose of fentanyl buccal tablets prescribed by your healthcare provider as follows:

- Fentanyl buccal tablets come packaged as a blister card containing 4 blister units. Each blister unit contains 1 fentanyl buccal tablet. **Do not open a blister until ready to use.**

The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as **XXX mcg** (See Figure 1).

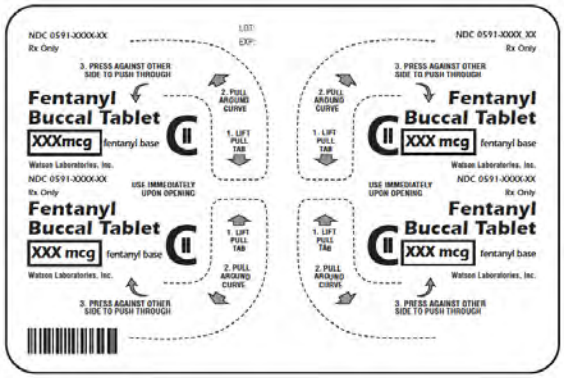


Figure 1

- Lift the pull tab where indicated. Pull the tab around the curve and press the blister against the other side, pushing the tablet through. (See Figure 2).

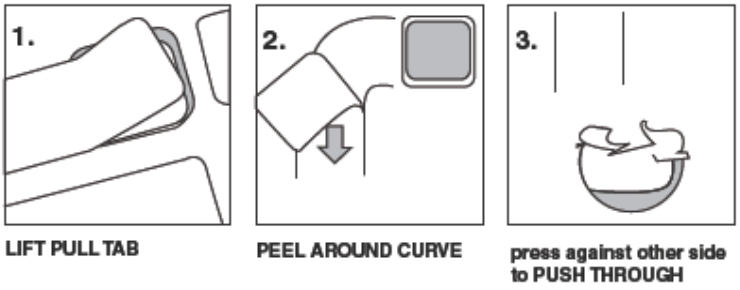


Figure 2

- Do not push the tablet through the foil on the blister unit because this could damage the tablet.
- When removed from the blister unit, fentanyl buccal tablet must be used right away.
- **Use fentanyl buccal tablets whole**.
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- You can place a fentanyl buccal tablet:
  - o in your mouth above a rear molar tooth between the upper cheek and gum (See Figure 3). Switch (alternate) sides of your mouth for each dose.

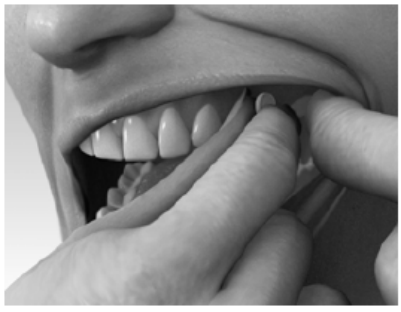


Figure 3

OR,

o on the floor of your mouth, under your tongue (See Figures 4a, 4b, 4c, 4d).

- When placing the tablet under your tongue, first lift your tongue (4b), then place the tablet under your tongue (4c), and lower your tongue over the tablet (4d).

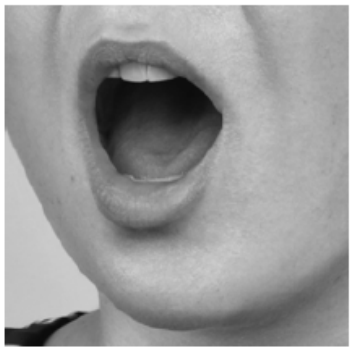


Figure 4a

Figure 4b

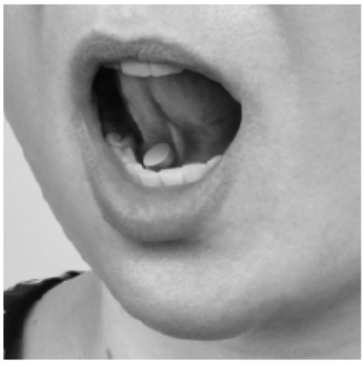


Figure 4c

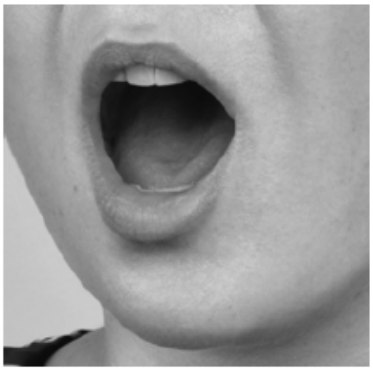


Figure 4d

- **Leave the tablet in place until it dissolves.** A fentanyl buccal tablet generally takes between 14 to 25 minutes to dissolve.
- After 30 minutes, if there is any fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use fentanyl buccal tablets in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Watson Laboratories, Inc.
Corona, CA 92880

Revised: December 2015

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DALE P CONNER
01/08/2016

May 17, 2016

Kathleen Uhl, M.D.
Director, OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville MD 20855

TIRF REMS CORRESPONDENCE
48-MONTH REMS SUPPLEMENTAL ASSESSMENT REPORT
Electronic Submission (eCTD)
via Gateway

RE: Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base
ANDA 079075, Sequence #0069

Dear Dr. Uhl:

Watson Laboratories, Inc., ("Watson") hereby submits this electronic TIRF REMS Correspondence, 48-Month REMS Supplemental Assessment Report to its approved ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base. Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011, for Watson's above reference product which is contained in DMF #027320. A copy of the Letter of Authorization (LOA) for DMF #027320 is provided in **Module 1.4.1** of this submission.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Watson hereby notifies FDA of submission of the 48-month REMS Supplemental Assessment Report to DMF #027320 in eCTD Sequence 0023, submitted on May 4, 2016.

A copy of the current Medication Guide for this product was provided as PDF format and MS Word format in **Module 1.14.2.2** and **Module 1.14.2.3**, respectfully in the Supplement – Changes Being Effected (CBE-0), Sequence 0066, submitted on December 30, 2015.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. An MS Word file of this cover letter is provided for the reviewer's convenience. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

Watson trusts this information is sufficient for the submission to be evaluated. Should you have any questions or comments, please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

eunmin.choi@actavis.com
Digitally signed by eunmin choi@actavis com
DN: cn=eunmin choi@actavis com
Date: 2016 05 17 12:49 06 07'00'

Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

Accenture LLP
1160 West Swedesford Road
Berwyn, PA 19312
www.accenture.com

Date: June 17, 2015

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

DMF#: 027320
Holder: McKesson Specialty Health (McKesson)
Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Letter of Authorization for: Not applicable because DMF does not cover multiple items.

McKesson hereby authorizes Actavis Laboratories Inc. to incorporate by reference information regarding the Transmucosal Immediate Release Fentanyl (TIRF) Access Program in DMF Number 027320 into any application filed by Actavis Laboratories Inc. We also authorize the FDA to review the aforementioned specific information in DMF Number 027320 when considering any application filed by Actavis Laboratories Inc.

The entire DMF can be referenced, which was submitted on August 20, 2013.

McKesson states that DMF Number 027320 is current and McKesson will comply with the statements made within it. McKesson will notify FDA through an amendment to DMF Number 027320 of any addition, change, or deletion of information in the DMF. McKesson will also notify in writing Actavis Laboratories Inc. that an addition, change, or deletion of information has been made to the DMF.

Sincerely,

Jann A. Kochel, U.S. Agent
Associate Director, Regulatory Affairs
Accenture, LLP
610-407-1738
610-407-8433 (Fax)
jann.a.kochel@accenture.com

August 19, 2016

Kathleen Uhl, M.D.
Director, OGD, CDER, FDA
Document Control Room
7620 Standish Place
Rockville MD 20855

TIRF REMS Correspondence
DMF ANNUAL REPORT
(Reporting Period: August 21, 2015 – August 20, 2016)
Electronic Submission (eCTD)
via Gateway

RE: ANDA 079075, Sequence #0070
Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base

TIRF REMS Correspondence: DMF Annual Report

Dear Dr. Uhl:

Watson Laboratories, Inc., ("Watson"), indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc., hereby submits this electronic TIRF REMS Correspondence, DMF Annual Report (Reporting Period: August 21, 2015 – August 20, 2016) to its approved ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base. Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011, for Watson's above reference product which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 which was provided in **Module 1.4.1** of TIRF REMS Correspondence, Sequence 0069, on May 17, 2016.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF,*" Watson hereby notifies FDA of submission of the DMF Annual Report for the reporting period August 21, 2015 – August 20, 2016, to DMF #027320 in eCTD sequence 0024 on August 18, 2016.

A copy of the current Medication Guide for this product was provided in **Module 1.14.2.2** of the Labeling Supplement, Sequence 0066, submitted on December 30, 2015.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. An MS Word file of this cover letter is provided for the reviewer's convenience. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

Watson trusts this information is sufficient for the submission to be evaluated. Should you have any questions or comments, please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

eunmin.choi
@actavis.com
Digitally signed by eunmin.choi@actavis.com
DN: cn=eunmin.choi@actavis.com
Date: 2016.08.19 14:24:41 -07'00'

For: Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

REMS CORRESPONDENCE
60-MONTH ASSESSMENT REPORT

December 28, 2016

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 079075, Sequence #0071
Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base

TIRF REMS Correspondence: DMF 60-Month Assessment

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories, Inc.1, ("Watson")'s ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in provided in Module 1.4.1 of TIRF REMS Correspondence, Sequence 0069, on May 17, 2016.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Watson hereby notifies FDA of submission of the 60-month REMS Assessment Report to DMF #027320 in eCTD sequence 0027 on December 28, 2016.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

1 An indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

Watson trusts this information is sufficient for the submission to be evaluated. Please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

kelly.delgado@actavis.com

Digitally signed by kelly.delgado@actavis.com
DN: cn=kelly.delgado@actavis.com
Reason: I am approving this document
Date: 2016.12.28 10:38:58 -08'00'

Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

TIRF REMS CORRESPONDENCE
CONSOLIDATED RESPONSES TO INFORMATION REQUESTS
FROM THE 48-MONTH ASSESSMENT REPORT

January 31, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 079075, Sequence #0072
Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories, Inc.[1], ("Watson")'s ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 previously submitted in Module 1.4.1 of TIRF REMS Correspondence, Sequence 0069, on May 17, 2016.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Watson hereby notifies FDA of submission of the Consolidated Responses to Information Requests for the 48-month REMS Assessment submitted to DMF #027320 in eCTD sequence 0026 on January 30, 2017.

Please note, the current medication guide for the above listed drug product may be referenced in Module1.14.2 of Watson's ANDA 079075, in eCTD sequence 0066.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

[1] An indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

Watson trusts this information is sufficient for the submission to be evaluated. Please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

kelly.delgado@actavis.com

Digitally signed by kelly.delgado@actavis.com
DN: cn=kelly.delgado@actavis.com
Reason: I am approving this document
Date: 2017.01.30 21:15:49 -08'00'

Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

TIRF REMS CORRESPONDENCE
60-MONTH SUPPLEMENTAL ASSESSMENT REPORT

February 21, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

RE: ANDA 079075, Sequence #0073
Fentanyl Citrate Buccal Tablets,
100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base

TIRF REMS Correspondence: DMF 60-Month Supplemental Assessment Report

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories, Inc.1, ("Watson")'s ANDA 079075 for Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg, Equivalent to Fentanyl Base which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Module 1.4.1 of TIRF REMS Correspondence, Sequence 0069, on May 17, 2016.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Watson hereby notifies FDA of submission of the 60-month REMS Supplemental Assessment Report to DMF #027320 in eCTD sequence 0028 on February 17, 2017.

A copy of the current Medication Guide for this product was provided as PDF format and MS Word format in Module 1.14.2.2 and Module 1.14.2.3, respectfully in the Supplement – Changes Being Effected (CBE-0), Sequence 0066, submitted on December 30, 2015.

This is an electronic submission (eCTD) submitted in the XML backbone via OGD's Gateway. This submission is virus-free and has been checked using Network Associates' McAfee VirusScan Enterprise or Norton Antivirus by Symantec. Watson has a letter of Non-Repudiation on file, dated October 8, 2001.

1 An indirect, wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc.

Watson trusts this information is sufficient for the submission to be evaluated. Please contact me by telephone at (951) 493-4440, by facsimile at (951) 493-4581 or by email at RegulatoryAffairsUS@actavis.com, if you have any questions or if I can assist you with the review of this application.

Sincerely,

kelly.delgado@actavis.com

Digitally signed by kelly.delgado@actavis.com
DN: cn=kelly.delgado@actavis.com
Reason: I am approving this document
Date: 2017.02.21 09:49:17 -08'00'

Kelly Delgado
Manager, Regulatory Affairs
Watson Laboratories, Inc.

U.S. Generics

June 12, 2017

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

NEW SUPPLEMENT FOR ANDA 079075/0079
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT March 27, 2017/S-0077

ANDA # 079075 / Sequence # 0079
Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg

Dear Sir or Madam:

Reference is made to the Single, Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories Inc., an indirect wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.'s, Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of TIRF REMS Correspondence, Sequence 0069, on May 17, 2016. Please find the GDUFA fee payment coversheet enclosed in Module 1.2.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Teva hereby notifies FDA of submission of the REMS modification, to update the REMS materials with the recent safety label changes as requested by the FDA in the REMS Modification Notification letter, to the DMF #027320 in eCTD sequence 0029 on June 09, 2017. As requested by the agency the proposed modified REMS and other REMS-related materials were submitted in Microsoft Word format.

In addition to the above REMS modification, as proposed in the response to the 60-Month Assessment Report Information Request 1a by the TRIG, the proposed Dear Healthcare Provider Letter is submitted to the DMF eCTD in Sequence 0030 on June 09, 2017. The Dear Healthcare Provider Letter is provided in a separate sequence as a stand-alone submission to clarify it as a one-time (single-use) communication rather than a new document being appended into the REMS itself.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission size is approximately 3 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150, antivirus engine 9.900.1008, pattern 13.465.00 with a release date of 06/12/2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Jennifer Costello at 215-293-6103 or via email at jennifer.costello@tevapharm.com.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact either Elisabeth Gray (by phone: 973-658-2883 or email: elisabeth.gray@tevapharm.com) or Rich Leone (by phone: 215-293-6330 or email: rich.leone@tevapharm.com).

Thank you for your prompt attention to this submission.

Sincerely,

Elisabeth Gray
Director, Regulatory Affairs, US Generics (for)

Rich Leone
Senior Director, Regulatory Affairs, US Generics

RL/nr

U.S. Generics

June 15, 2017

Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
RESPONSE TO INFORMATION REQUEST-REMS ASSESSMENT

ANDA # 079075 / Sequence # 0080
Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg

Dear Sir or Madam:

Reference is made to the FDA Information Request for REMS Assessment Requirement received January 23, 2017, requesting to submit results of the evaluation of utilization of individual TIRF products in opioid non-tolerant patients using initial class-wide fill.

Additional reference is made to the teleconference between the TRIG and the FDA on March 03, 2017, where TRIG provided another approach utilizing initial fill based on the specific product.

Watson Laboratories Inc., an indirect wholly owned subsidiary of Teva Pharmaceuticals USA, Inc. hereby acknowledges FDA request and the QuintilesIMS report submission by other TIRF sponsors. Teva did not have product available during the report time period and therefore does not have IMS data to submit to response.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission size is approximately 3 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150, antivirus engine 9.900.1008, pattern 13.471.00 with a release date of 06/15/2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Jennifer Costello at 215-293-6103 or via email at jennifer.costello@tevapharm.com.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact either Elisabeth Gray (by phone: 973-658-2883 or email: elisabeth.gray@tevapharm.com) or Rich Leone (by phone: 215-293-6330 or email: rich.leone@tevapharm.com).

Teva Pharmaceuticals USA, Inc.
425 Privet Road | Horsham, PA 19044 | Tel. 215.591.3153 | Fax 215.591.8812 | www.tevapharm-na.com

Thank you for your prompt attention to this submission.

Sincerely,

Elisabeth Gray
Director, Regulatory Affairs, US Generics (for)

Rich Leone
Senior Director, Regulatory Affairs, US Generics

RL/nr

U.S. Generics

August 21, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
REMS Final for Approved ANDA 079075/0081
PRIOR APPROVAL SUPPLEMENT

ANDA # 079075 / Sequence # 0081
Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg

Dear Dr. Uhl:

Reference is made to the Single, Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories Inc., an indirect wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.'s, Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on May 17, 2016. Reference is also made to the Information Request E-mail communication received on July 12, 2017, from Safety Regulatory Project Manager Wendy Brown to incorporated agency's comments on the REMS Materials. Please find the GDUFA fee payment coversheet enclosed in Module 1.2.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Teva Pharmaceuticals USA, Inc., hereby notifies FDA of submission of the REMS modification, including the final formatted REMS document, materials including website screenshots, and REMS Supporting Document as separate files, as well as a compiled document for posting on the FDA REMS website requested by the FDA in the Information request, to the DMF #027320 in eCTD sequence 0031 on August 18, 2017.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission size is approximately 3 MB. All files were checked and verified to be free of

Teva Pharmaceuticals USA, Inc.
425 Privet Road | Horsham, PA 19044 | Tel. 215.591.3153 | Fax 215.591.8812 | www.tevapharm-na.com

viruses using Trend Micro OfficeScan, client 11.0.4150, antivirus engine 9.950.1006, pattern 13.607.00 with a release date of 08/21/2017 or later. If there are any technical questions

regarding the format, validation, or electronic delivery of this submission, please contact Jennifer Costello at 215-293-6103 or via email at jennifer.costello@tevapharm.com.

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact either Elisabeth Gray (by phone: 973-658-2883 or email: elisabeth.gray@tevapharm.com) or Rich Leone (by phone: 215-293-6330 or email: rich.leone@tevapharm.com).

Thank you for your prompt attention to this submission.

Sincerely,

Elisabeth Gray
Director, Regulatory Affairs, US Generics (for)

Rich Leone
Senior Director, Regulatory Affairs, US Generics

RL/nr

U.S. Generics

August 21, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
ANDA # 079075 / Sequence # 0082
Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg
DMF Annual Report (Reporting Period: August 21, 2016 – August 20, 2017)

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories Inc., an indirect wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.'s Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on May 17, 2016

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Teva Pharmaceuticals USA, Inc. hereby notifies FDA of submission of the DMF Annual Report for the reporting period August 21, 2016 – August 20, 2017, to DMF #027320 in eCTD sequence 0032 on August 18, 2017.

The current medication guide may be referenced in Module 1.14.2.

This submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission size is approximately 3 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150, antivirus engine 9.950.1006, pattern 13.607.00 with a release date of 08/21/2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Jennifer Costello at 215-293-6103 or via email at jennifer.costello@tevapharm.com.

Teva Pharmaceuticals USA, Inc.
425 Privet Road | Horsham, PA 19044 | Tel. 215.591.3153 | Fax 215.591.8812 | www.tevapharm-na.com

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact either Elisabeth Gray (by phone: 973-658-2883 or email: elisabeth.gray@tevapharm.com) or Rich Leone (by phone: 215-293-6330 or email: rich.leone@tevapharm.com).

Thank you for your prompt attention to this submission.

Sincerely,

Elisabeth Gray
Director, Regulatory Affairs, US Generics (for)

Rich Leone
Senior Director, Regulatory Affairs, US Generics

RL/nr

U.S. Generics

August 30, 2017

Kathleen Uhl, MD
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

TIRF REMS CORRESPONDENCE
REMS Final for Approved ANDA 079075/0083
Amendment to Prior Approval Supplement Sequence # 0079

ANDA # 079075 / Sequence # 0083
Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg

Dear Dr. Uhl:

Reference is made to the Single, Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Watson Laboratories Inc., an indirect wholly owned subsidiary of Teva Pharmaceuticals USA, Inc.'s, Fentanyl Citrate Buccal Tablets, 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg which is contained in DMF #027320. Additional reference is made to the Letter of Authorization (LOA) for DMF #027320 submitted in Section 1.4.1 of this application on May 17, 2016. Reference is also made to the Information Request E-mail communication received on July 12, 2017, from Safety Regulatory Project Manager Wendy Brown to incorporated agency's comments on the REMS Materials.

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Teva Pharmaceuticals USA, Inc., hereby notifies FDA of the re-submission of the REMS modification, including the final formatted REMS document, REMS Supporting Document and appended materials along with the original Dear Stakeholder letters requested by the FDA in the Information request, to the DMF #027320 in eCTD sequence 0033 on August 29, 2017.

The submission is being sent to the Agency through the Electronic Submissions Gateway (ESG). The submission size is approximately 3 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150, antivirus engine 9.950.1006, pattern 13.625.00 with a release date of 08/30/2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Jennifer Costello at 215-293-6103 or via email at jennifer.costello@tevapharm.com.

Teva Pharmaceuticals USA, Inc.
425 Privet Road | Horsham, PA 19044 | Tel. 215.591.3153 | Fax 215.591.8812 | www.tevapharm-na.com

This information is submitted for your review and approval. If there are any questions, please do not hesitate to contact either Elisabeth Gray (by phone: 973-658-2883 or email: elisabeth.gray@tevapharm.com) or Rich Leone (by phone: 215-293-6330 or email: rich.leone@tevapharm.com).

Thank you for your prompt attention to this submission.

Sincerely,

Elisabeth Gray
Director, Regulatory Affairs, US Generics (for)

Rich Leone
Senior Director, Regulatory Affairs, US Generics

RL/ye

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 079075/S-013
Communication Type:	Correspondence
Communication Group:	sANDA Action
Communication Name:	Approval
Communication ID:	COR-SANDAACTION-05
Drafted by:	J. Sarchet 7/18/2017
Clearance History by:	DRISK 8/9/2017; SRT 8/9/2017
Finalized:	J. Sarchet 8/10/2017 and 9/6/2017
Filename:	
Signatory Authority:	OND Division Director or Deputy Division Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change) **For CMC Supplements with Labeling:** OPQ Division Director or Branch Chief
Use Statement:	Use to notify applicant of an approval action for a supplemental application that includes changes to the labels or labeling
Notes:	USE "sANDA Approval [OTC ONLY]" template for Over-the-Counter sANDA Approvals USE COR-SNDAACTION-06 FOR sANDA CMC APPROVALS USE COR-SANDAACTION-09 FOR sANDA TENTATIVE APPROVALS If supplement approval also fulfills a PMR/PMC, this letter will need to be double-coded as PMR-PMC Fulfilled. **Note:** Remember to check for acceptability of facility **prior to issuing approval letter**.

Version: 05/04/2017

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

ANDA 079075/S-013

SUPPLEMENT APPROVAL

Watson Laboratories, Inc.
Indirect, wholly-owned subsidiary of
Teva Pharmaceuticals, USA, Inc.
425 Privet Road
Horsham, Pennsylvania 19044

Attention: Mr. Rich Leone
Senior Director, Regulatory Affairs, US Generics

Dear Mr. Leone :

Please refer to your Supplemental Abbreviated New Drug Application (sANDA) dated June 12, 2017, and your amendments, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fentanyl Citrate Buccal Tablets.

We also refer to our REMS Modification Notification letter dated April 10, 2017, informing you that the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) must be modified to ensure that the benefits of the drug outweigh its risks.

This supplemental abbreviated new drug application proposes modifications to the approved TIRF REMS to align the REMS document and materials with the labeling approved on December 16, 2016.

We have completed our review of this supplemental application. It is approved, effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for TIRF products, of which Fentanyl Citrate is a member, was originally approved on December 28, 2011, and the most recent REMS modification was approved on December 24, 2014. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submissions of assessments of the REMS.

In order to ensure the benefits of Fentanyl Citrate outweigh its risks, we determined that you were required to make changes to the REMS document and appended materials consistent with the safety label changes approved on December 16, 2016, as well as additional minor modifications.

Your proposed modified REMS, submitted to Drug Master File (DMF) 27320 on June 9, 2017, amended August 29, 2017 and appended to this letter, is approved.

This shared system, known as the TIRF REMS Access Program, currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C), FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA XXXXX REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA XXXXX/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA XXXXX/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA XXXXX/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR ANDA XXXXX

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved ANDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jennifer Sarchet, REMS Coordinator, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Trueman W. Sharp, M.D., M.P.H.
Deputy Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

Initial REMS approval: 12/2011

Most recent modification: 08/2017

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment*).

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS

Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that TIRF medicines are not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.

4) I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.

5) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

6) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

7) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

8) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not

been prescribed can result in a fatal overdose.

D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place, out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

- *TIRF REMS Access Prescriber Program Overview*
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Prescriber Enrollment Form*
- *Patient-Prescriber Agreement Form*
- *TIRF REMS Access Patient and Caregiver Overview*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care

physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**

  i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e., chain stores) in the TIRF REMS Access program.

  ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

  iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method

of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form.* In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

   a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

   b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

   c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

   d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

   e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

   f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

   g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

   h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

a. Review the distributor TIRF REMS Access program materials

b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e., EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance

investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e., active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access

program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.
8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

  NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

  How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction, and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age and older **who are already receiving and who are tolerant to around-the-clock opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - 60 mg oral hydrocodone/day
  - OR an equianalgesic dose of another oral opioid daily
- Patients must remain on around-the-clock opioids when taking a TIRF medicine.

Appropriate Patient Selection (cont.)

- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients or in
    - the management of acute or postoperative pain including headache/migraine, dental pain, or acute pain in the emergency department,
    - acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment,
    - known or suspected gastrointestinal obstruction, including paralytic ileus,
    - known hypersensitivity to fentanyl, or components of the TIRF medicine.

Appropriate Patient Selection (cont.)

Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction, and Overdose

- **TIRF medicines contain fentanyl, an opioid ago**nist and Schedule II controlled substance. TIRF medicines contain fentanyl, which has a high potential for abuse similar to other opioids. TIRF medicines can be abused and are subject to misuse, addiction, and criminal diversion.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Drug seeking tactics include:
  - emergency calls or visits near the end of office hours
  - refusal to undergo appropriate examination, testing, or referral
  - repeated loss of prescriptions
  - tampering with prescriptions

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction, and Overdose (cont.)

- reluctance to provide prior medical records or contact information for other treating healthcare providers
- “doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction

- Concerns about abuse and addiction should not prevent the proper management of pain.

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction, and Overdose (cont.)

- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- TIRF medicines, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.

Determine Patient-Specific Risk Factors

2. Accidental Ingestion or Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- Instruct patients to take steps to store TIRF medicines in a safe place out of reach of children.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Determine Patient-Specific Risk Factors

2. Accidental Ingestion or Exposure (cont.)

- Any accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may increaseplasma concentrations of fentanyl and prolong opioid adverse reactions which may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.
- Due to the additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

Determine Patient-Specific Risk Factors

3. Drug Interactions (cont.)

- The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
- Monoamine Oxidase Inhibitors (MAOIs) interactions with opioids may manifest as serotonin syndrome.
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics may reduce the analgesic effect of TIRF medicines and/or precipitate withdrawal symptoms.
- Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Determine Patient-Specific Risk Factors

4. Pregnancy

- Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts.
- If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.
- Substantial differences exist in the pharmacokinetic profiles of different fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in a fatal overdose.

Dosage and Administration General

Appropriate Conversion (cont.)

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a dose that provides adequate analgesia and minimizes adverse reactions is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Patients must wait at least 2 or 4 hours before treating another episode of breakthrough pain with their TIRF medicines. Please refer to the TIRF medicine's Full Prescribing Information to determine the time between doses.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
    - **Pharmacists:** Instruct patients to consult with their prescriber.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**
- Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting the TIRF medicine or when the dosage is increased, and that it can occur even at recommended dosages.
- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.

Patient Counseling

Tell the patient (cont.):

- **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You must take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.

Patient Counseling

Tell the patient (cont.):

- Potentially fatal additive effects may occur if the TIRF medicine is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider.
- The use of the TIRF medicine, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death.
- Opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs.
- Avoid taking their TIRF medicine while using any drugs that inhibit monoamine oxidase.
- Opioids could cause adrenal insufficiency, a potentially life-threatening condition.
- Their TIRF medicine may cause orthostatic hypotension and syncope.

Patient Counseling

Tell the patient (cont.):

- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated.
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, because it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits (cont.):**

- TIRF medicines, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12-year-old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?

Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?

Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?

Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?

Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain or acute pain in the emergency department.
C. Instruct patients that, if they stop taking their around -the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

Prescriber Name* (please print):

11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____	**State License Number*** _____
Address* _____	**State Issued*** _____
City* _____	**DEA Number*** _____
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (Actiq and its generic equivalents are approved for 16 years of age and older), who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that TIRF medicines are not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.
4. I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.
5. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
6. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
7. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
8. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Prescriber Name* (please print):_____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?
Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?
No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?
Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?
The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-

Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?
The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?
An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at

www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822--1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e., workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?
The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com).
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

This letter ceased distribution in November 2013.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or

order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in

clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

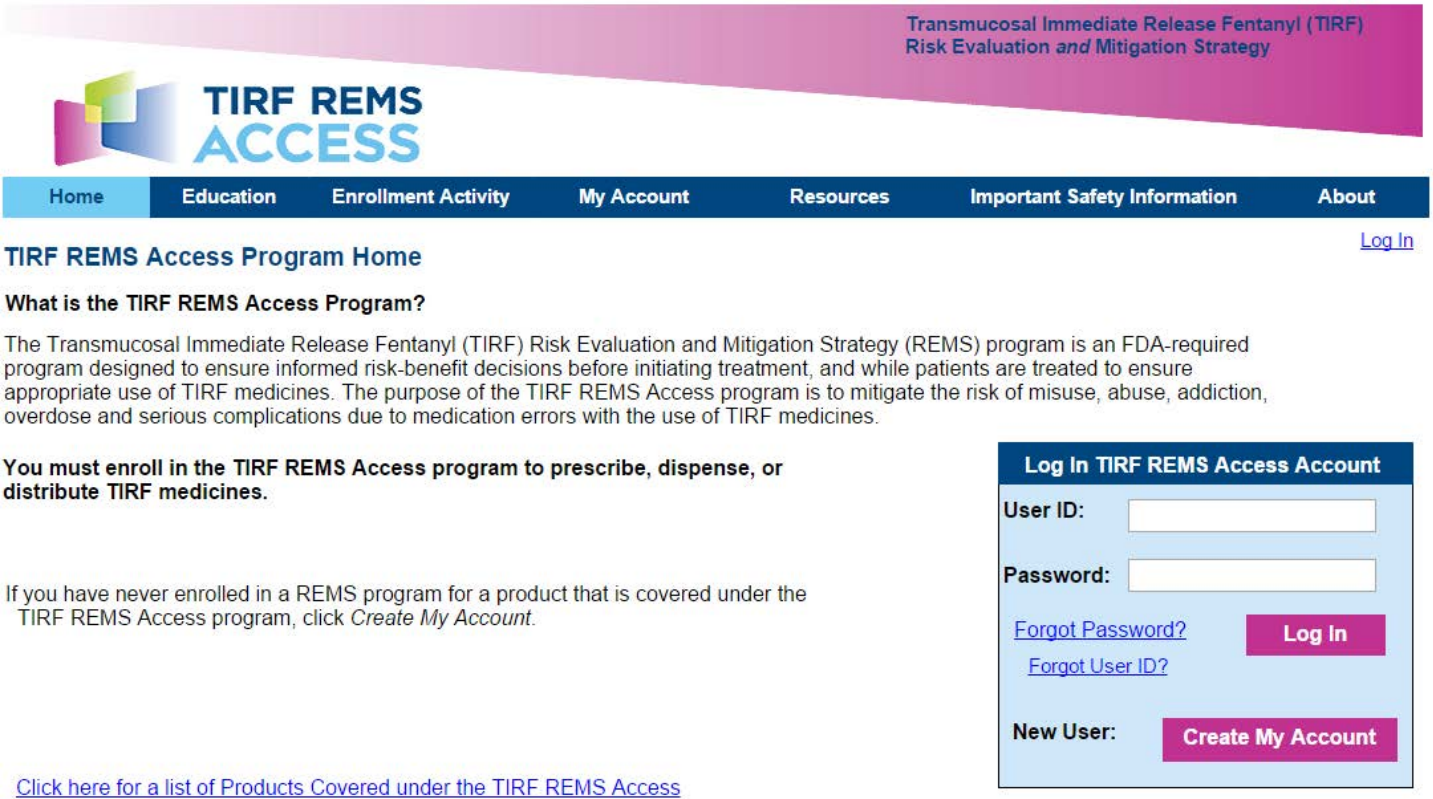
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6: Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7: Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.

- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Chain Outpatient Pharmacies", "An Overview for Independent Outpatient Pharmacies" or "An Overview for Inpatient Pharmacies" for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5: Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e., workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.
- Create User ID and password and select 'Create My Account'

- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/rems/pdf/NDC_listing.pdf) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____

Address* _____

City* _____

State* _____ **ZIP** _____

Phone Number* _____

Fax Number* _____

DEA Number* _____

National Provider Identifier (NPI)* _____

Medicaid ID _____

State Issued _____

NCPDP Number* _____

Store Number* _____

***Required Fields**

Chain ID*:

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/rems/pdf/NDC_listing.pdf) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

This letter ceased distribution in November 2013.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
  - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions

- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in

clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

• Patient First Name..... TIRFREMSTEST
• Patient Last Name..... Smithers
• Date of Birth..... 19841105
• Patient ZIP/Postal Zone..... 07921
• Drug Name..... TIRFPRODUCT 100 mcg – NDC # 42747-0221-32
• Quantity Dispensed..... 12
• Days Supply..... 4
• Prescriber ID..... BA1111119
• Prescriber Last Name..... REMSTEST

• Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

This letter ceased distribution in November 2013.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to

outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in

clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should

be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

This letter ceased distribution in November 2013.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1*: *If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

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- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/rems/products.action.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TRUEMAN W SHARP
09/07/2017

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	ANDA 207338
Communication Type:	Correspondence
Communication Group:	Safety
Communication Name:	Pre-Approval REMS Notification for ANDA
Communication ID:	
Drafted by:	C.Phillips/1-2-15
Clearance History:	SRT/1-16/15
Finalized:	
Filename:	
Use Statement:	Inform applicant that REMS is required
Notes:	

Version: DARRTS 2/10/2012

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 207338

PRE-APPROVAL REMS NOTIFICATION

Actavis Laboratories FL, Inc.
Attention: Janet Vaughn
Director, Regulatory Affairs
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Ms. Vaughn,

Please refer to your Abbreviated New Drug Application (ANDA) dated and received June 19, 2014, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Fentanyl Citrate Sublingual Tablets, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8mg (base equivalent).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS (REMS)

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Fentanyl Citrate Sublingual Tablets, to ensure the benefits of the drugs outweigh the risks of overdose, abuse, misuse, addiction, and serious complications due to medication errors.

Pursuant to section 505-1(i) of the FDCA, a drug that is the subject of an ANDA and the listed drug it references must use a single shared system for the elements to assure safe use (ETASU), unless FDA waives the requirement. There is a shared system REMS program approved for products containing transmucosal immediate-release fentanyl (TIRF), the TIRF REMS Access Program. Therefore, you should contact Karla Werre at Mallinckrodt Pharmaceuticals, who has been identified as the current point of contact for the TIRF REMS, regarding your participation in the shared system REMS. She can be reached at (314) 654-3517 or karla.werre@mallinckrodt.com.

The REMS for the TIRF products was originally approved on December 28, 2011 and the most recent modification was approved on November 7, 2013.

Your proposed REMS program must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a

Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Fentanyl Citrate Sublingual Tablets poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Fentanyl Citrate Sublingual Tablets. FDA has determined that Fentanyl Citrate Sublingual Tablets is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Fentanyl Citrate Sublingual Tablets. FDA has also determined that Fentanyl Citrate Sublingual Tablets is a product for which patient labeling could help prevent serious adverse events.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Fentanyl Citrate Sublingual Tablets.

Elements to Assure Safe Use: We have determined that elements to assure safe use are necessary to mitigate serious risks listed in the labeling of the drug. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including, at a minimum, the following:

- Healthcare providers are specially certified or trained [section 505-1(f)(3)(A)]
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified [section 505-1(f)(3)(B)]
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions [section 505-1(f)(3)(D)]

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Additionally, all relevant proposed REMS materials should be appended to the proposed REMS.

Your application cannot be approved without a REMS. Once FDA finds the content acceptable, and determines that the application can be approved, we will include the REMS as an attachment to the approval letter. The REMS, once approved, will create enforceable obligations.

Use the following designator at the top of the first page of your proposed REMS submission in bold, capital letters: **"PROPOSED REMS for ANDA 207338"** and all subsequent submissions

related to the proposed REMS as **"PROPOSED REMS AMENDMENT for ANDA 207338."** If you do not submit electronically, please send 5 copies of your REMS-related submissions.

To facilitate review of your submission, we request that you submit your proposed REMS and other REMS-related materials in Microsoft Word format. . If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many documents as possible in Word format.

If you have any questions, call Julia Lee, Regulatory Project Manager, at (240) 402-8685.

Sincerely,

John R. Peters, M.D.
Acting Director
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R PETERS
01/20/2015

PROPOSED REMS for ANDA 207338

Sequence # 0003
ANDA # 207338
Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent)

April 3, 2015

Kathleen Uhl, M.D.
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

RE: PRE-APPROVAL REMS NOTIFICATION

Dear Dr. Uhl:

Reference is made to Actavis Laboratories FL, Inc.'s (Actavis-FL)'s Abbreviated New Drug Application for Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent), ANDA # 207338, and to FDA's PRE-APPROVAL REMS NOTIFICATION letter dated January 9, 2015 (copy attached). In accordance with 21 C.F.R. § 314.96, Actavis-FL is submitting an amendment to its ANDA, updating the REMS as requested by the FDA.

Actavis-FL is providing its submission in eCTD format through the FDA Electronic Submission Gateway (ESG) Web Interface according to the Applicability Statement 2 (AS2) standards. The following documents are being provided in **Section 1.16** of this submission:

- REMS (PDF and Word formats)
- REMS Supporting Documents (PDF and Word formats)
- TIRF REMS Access Program - Education Program for Prescribers and Pharmacists (PDF and Word formats)
- TIRF REMS Access Program - Web Prototype (PDF and Word formats)
- An Overview for Chain Outpatient Pharmacies (PDF and Word formats)
- Chain Outpatient Pharmacy Enrollment Form (PDF and Word formats)
- An Overview for Closed System Outpatient Pharmacies (PDF and Word formats)
- Closed System Outpatient Pharmacy Enrollment Form (PDF and Word formats)

- An Overview for Independent Outpatient Pharmacies (PDF and Word formats)
- Independent Outpatient Pharmacy Enrollment Form (PDF and Word formats)
- An Overview for Inpatient Pharmacies (PDF and Word formats)
- Inpatient Pharmacy Enrollment Form (PDF and Word formats)
- Inpatient Pharmacy Letter (PDF and Word formats)
- An Overview for Patients and Caregivers (PDF and Word formats)
- Outpatient Pharmacy Letter (PDF and Word formats)
- An Overview for Prescribers (PDF and Word formats)
- Prescriber Enrollment Form (PDF and Word formats)
- Patient-Prescriber Agreement Form (PDF and Word formats)
- Healthcare Provider Letter (PDF and Word formats)
- Wholesaler / Distributor Enrollment Form (PDF and Word formats)
- Wholesaler / Distributor Letter (PDF and Word formats)
- Knowledge Assessment (PDF and Word formats)
- Frequently Asked Questions (FAQs) (PDF and Word formats)

This supplement is an electronic submission organized in accordance with ICH-CTD format (eCTD). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface in accordance with Applicability Statement 2 (AS2) standards.

Should you have any questions or comments concerning this submission, please contact the undersigned at RegulatoryAffairsUS@actavis.com (*e-mail*), (954) 358-6125 (*telephone*), or 954-358-6350 (*fax*).

Sincerely,

Frida Navarro

Digitally signed by Frida Navarro
DN: cn=Frida Navarro o=Actavis Laboratories FL Inc ou=Regulatory Affairs email=frida navarro iriarte@actavis com c=US
Reason: I attest to the accuracy and integrity of this document
Date: 2015 04 03 16 05:14 04'00'

For: Janet Vaughn
Director, Regulatory Affairs

Initial REMS approval: 12/2011

Most recent modification: XX/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**

  i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.

  ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

  iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment.*

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.*

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

Transmucosal Immediate Release Fentanyl (TIRF)

Sponsors:

TIRF REMS Industry Group (TRIG) of Companies

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS) SUPPORTING DOCUMENT

1. TABLE OF CONTENTS

2. BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended release and immediate release products. Extended release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. Fentanyl, an opioid agonist and a Schedule II controlled substance, is approximately 100-fold more potent than morphine as an analgesic [Biedrzycki et al, 2009]. Secondary effects of fentanyl on central nervous system, respiratory and gastro-intestinal functions are typical of opioid analgesics and are considered to be an effect [Simpson et al, 2007].

TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' the chronic pain control (breakthrough pain, BTP). All the TIRF medicines as such, are short acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with the use and misuse of TIRF medicines, including acute respiratory depression which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose and prescribing to opioid-non-tolerant patients have led to serious and on occasion fatal, adverse events demonstrating that short-acting fentanyl products can pose a health risk if not used appropriately.

In order to mitigate these risks, TIRF Sponsors will implement a Risk Evaluation and Mitigation Strategy (REMS) for the transmucosal immediate release fentanyl products (or "TIRF medicines"), intended for use in breakthrough pain (BTP) in patients with cancer, while ensuring treatment access for patients who would benefit from this therapy.

Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. These products are currently used for the treatment of BTP in adult patients with cancer who are already receiving, and are tolerant to, around-the-clock (ATC) routine opioid therapy. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

The TIRF REMS Access proposal presented here addresses the current requirements set forth by the FDA provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

A. Clinical Features of BTP

BTP is a transient exacerbation of pain of moderate to severe intensity that occurs on a background of otherwise stable pain in a patient receiving regular, continuous opioids. It is characterized by rapid onset, with pain reaching maximal intensity within 3 minutes and lasting approximately 30 minutes [Laverty, 2007]. Often classified by its relationship to specific events or spontaneous onset, BTP arises as a consequence of the cancer, the anticancer treatment or a concomitant illness. BTP can affect up to two-thirds of patients with cancer, and can have a significant impact on patient quality of life [Breivik et al., 2009]. Moreover, a number of patients remain inadequately treated for their BTP or feel dissatisfied with their pain control [Fishbain, 2008]. There is therefore a need for effective pharmacologic treatments that will help relieve and control the symptoms of BTP. An ideal treatment for BTP is an analgesic with good efficacy, rapid onset and short duration of action, with minimal adverse effects in appropriately selected patients, and is easy and quick for a patient or caregiver to administer.

B. Assessment of Key Risks of TIRF Medicines

The TIRF REMS Access program will address the primary risks of overdose, misuse, abuse, addiction and serious complications due to medication errors. These are broad risks relating to the distribution, sale, use and misuse of opioids in the US and are not unique to TIRF medicines. However, TIRF medicines are absorbed transmucosally and partially bypass gastrointestinal absorption and first-pass metabolism, resulting in rapid onset of analgesic effect, and potentially, adverse effects. The key acute risk for any individual exposed to TIRF medicines is excessive respiratory depression which can be fatal if untreated. This risk is highest in opioid non-tolerant patients. Therefore, TIRF medicines must not be used by opioid non-tolerant patients. Patients considered opioid tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg of oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid; for one week or longer.

By restricting the use of TIRF medicines to opioid tolerant patients the risk of serious outcomes such as severe respiratory depression should be minimized. Opioid addiction arising in palliative care patients is rare [Hojsted et al, 2007**].**

3. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

4. SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors will execute the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program including patients, prescribers, pharmacists and distributors will be enrolled in the TIRF program, educated on the requirements of the program and required to document that they understand and will abide by the "elements to assure safe use."

Program materials will be provided on the TIRF medicines in addition to product-specific materials. The Educational Program and Knowledge Assessment components of the program will contain both TIRF medicine class and product-specific components. Enrollment forms, the *Patient-Prescriber Agreement Form* (PPAF), and overview documents containing program information will be provided to stakeholders as TIRF medicine materials. In addition, the Medication Guides will be provided to stakeholders in product-specific material format unique to the respective TIRF medicine being prescribed / dispensed.

The program procedures will be monitored for adherence and will be modified as necessary to ensure optimal effectiveness. The TIRF Sponsors will conduct ongoing and retrospective analysis as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

A. Additional Potential Elements

a. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF medicine prescription. Every TIRF medicine will have a unique Medication Guide. There will be sufficient copies distributed by each Sponsor to ensure that every patient receives a copy with each prescription. Medication Guides will be available through individual TIRF Sponsors, the TIRF REMS Access website, and the TIRF REMS Access call center.

The Medication Guide contains FDA approved language including an explanation of the risks associated with the use or misuse of TIRF medicines, augmented with information on precautions for safe use of the product, a brief explanation of essential elements of the TIRF REMS Access program, and contact information for customer assistance (i.e., call center with toll-free number and website). The TIRF medicine Medication Guides are developed to enhance patient awareness and understanding of the potential serious risks associated with the use of TIRF medicines with the intent of increasing the patients' appropriate use of TIRF medicines. The Medication Guides include critical information that every patient and caregiver should know about TIRF medicines including, but not limited to:

- Patients should not use a TIRF medicine unless they are regularly using another opioid pain medicine around-the-clock for their constant cancer pain and their body is used to these medicines (opioid tolerant).
- TIRF medicines must be kept in a safe place away from children.

- If a child, or an adult who is not already taking opioids regularly, takes a TIRF medicine, this is a medical emergency and can cause death. Get emergency help right away.

A copy of each product specific Medication Guide is distributed with every TIRF medicine.

TIRF Sponsors will supply all enrolled prescribers and pharmacies with sufficient copies of the Medication Guides to ensure that every patient who is prescribed and dispensed a prescription will have access to the specific TIRF medicine Medication Guide each time it is prescribed or dispensed.

The Medication Guide will be available through the TIRF REMS Access website, www.TIRFREMSaccess.com. Copies can also be obtained by calling the TIRF REMS Access program at **1-866-822-1483**.

b. Other Information Materials for Patients

The prescriber will discuss the benefits and risks of TIRF medicines as outlined in the Medication Guide with the patient, including proper dosing and administration, appropriate use and handling and storage of TIRF medicines.

The prescriber will discuss enrollment in the TIRF REMS Access program. The prescriber and the patient will review and sign the TIRF REMS Access program *Patient-Prescriber Agreement Form* (not required for inpatients) and a copy will be provided to the patient or caregiver. The prescriber will also provide the patient or caregiver with a copy of the Medication Guide.

The patient or caregiver will be offered counseling on the specific TIRF medicine by the dispensing pharmacist on appropriate use, storage and disposal, and receive an additional copy of the Medication Guide each time a TIRF medicine is dispensed.

The prescriber will have access to the *TIRF REMS Access Program: An Overview for Patients and Caregivers* to utilize with patients during discussions regarding the use of TIRF medicines. In patient-friendly language, the materials will focus on a description of the TIRF REMS Access program, including enrollment details and contact information (call center with toll-free telephone number and website address). This overview will also be available for download on www.TIRFREMSaccess.com.

c. Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS is not required. However, TIRF Sponsors will send Dear Healthcare Professional letters to targeted stakeholders to support implementation of the TIRF REMS Access program. These communications will include Dear Healthcare Provider and Dear Pharmacy letters, and will inform prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means of reporting adverse events.

TIRF Sponsors will send letters to healthcare professionals approximately 2 weeks prior to first availability of TIRF REMS Access program.

The target audience for the *Dear Healthcare Provider* letter will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians and primary care physicians), oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters* will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

Additional materials will be available via the TIRF REMS Access program website or through the TIRF REMS Access program toll-free number.

B. Elements to Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This can be achieved by prescriber's enrollment through a review of the *TIRF REMS Access Education Program* including the TIRF medicine's Full Prescribing Information, successful completion of the *Knowledge Assessment*, and completion of the enrollment form.

TIRF medicines will only be available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies will be enrolled into the TIRF REMS Access program. There is a different set of enrollment requirements for **outpatient pharmacies** (e.g. retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and **inpatient pharmacies** (e.g. hospitals that dispense for inpatient use only). For Long-Term Care (LTC) and Hospice patients whose prescriptions are obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access program.

There are three (3) types of outpatient pharmacies:

> **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.
>
> **Independent Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy.

Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.

For chain outpatient pharmacies, an authorized chain outpatient pharmacy representative must complete enrollment. The authorized chain outpatient pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the *TIRF REMS Access Education Program* and *Knowledge Assessment* are completed, the authorized chain outpatient pharmacy representative, on behalf of the chain, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form. Pharmacy sites that have been trained may be updated by the authorized chain outpatient pharmacy representative using an online dashboard.

Independent outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to undergo enrollment through review of the *TIRF REMS Access Education Program* and successful completion of the *Knowledge Assessment* on behalf of the pharmacy. The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transactions to validate the system enhancements and submit a completed and signed TIRF REMS Access enrollment form. The authorized pharmacist will be responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training must be documented and is subject to audit. At a minimum this documentation should include the store name, the store number, the pharmacist/pharmacy staff member's name, and the date training was completed.

For closed system outpatient pharmacies, an authorized closed system outpatient pharmacy representative must complete enrollment. The authorized closed system outpatient pharmacy representative must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. Once the *TIRF REMS Access Education Program* and *Knowledge Assessment* are completed, the authorized closed system outpatient pharmacy representative, on behalf of the closed system, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form. A list of closed system outpatient pharmacy sites that have been trained must be provided to the program via a standard electronic file format for processing.

For inpatient pharmacy enrollment, the authorized pharmacist must undergo the *TIRF REMS Access Education Program*, successfully complete the *Knowledge Assessment*, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist must also acknowledge that they understand that outpatient pharmacies within their facility must be separately enrolled.

Pharmacies will not be able to successfully order TIRF medicines from distributors unless they are enrolled in the TIRF REMS Access program.

All patients (excluding inpatients) must complete and sign a *Patient-Prescriber Agreement Form* (PPAF) with their healthcare provider, documenting safe-use conditions. Their healthcare provider will submit a copy of the PPAF to the TIRF REMS Access program via the website at www.TIRFREMSaccess.com, fax at 1-866-822-1487, or regular mail at (Address: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038). Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program. A completed *Patient-Prescriber Agreement Form* needs to be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

a. Prescriber Education and Enrollment

The TIRF REMS Access program education materials are the primary tool for educating prescribers about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The *Prescriber Enrollment Form* also includes information for prescribers on the requirement to complete a *Patient-Prescriber Agreement Form* before writing the first prescription for a TIRF medicine (not required for inpatients). For inpatient administration of TIRF medicines prescriber enrollment in the TIRF REMS Access program is not required.

The *TIRF REMS Access Educational Program* for prescribers comprises the Education Program and *Knowledge Assessment* that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available on the TIRF REMS Access website (www.TIRFREMSaccess.com):

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Chain Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Independent Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Outpatient Pharmacies

If the prescriber does not want to perform the Education Program and Knowledge Assessment online, all of these documents can be downloaded on the TIRF REMS Access website, or requested as a hardcopy from the TIRF REMS Access program call center.

Review of the Knowledge Assessment

Following review of the *TIRF REMS Access Education Program*, the program *Knowledge Assessment* must be successfully completed. A description of the process followed in reviewing the Knowledge Assessments is presented below, and this description applies equally to prescribers and pharmacists.

Manual Knowledge Assessment Review (i.e. on receipt of printed materials)

The prescriber should review the *TIRF REMS Access Education Program*, complete the paper *Knowledge Assessment* and return it by fax to the TIRF REMS Access program.

Upon receipt of a manual program *Knowledge Assessment*, a TIRF REMS specialist will review the assessment and determine the stakeholder type.

The TIRF REMS specialist will enter each answer to the assessment question in the validated TIRF REMS Access database.

If the answers are correct (the user has passed the assessment with a score of 100%) and all other enrollment criteria have been met, the user will be enrolled in the program by notice through email or fax.

If answers are incorrect a *Knowledge Assessment* feedback fax will be generated and sent to the enrolling user that only addresses the incorrect questions received. If answers are missing an "Incomplete" fax is generated and sent to the user advising them to resend a completed *Knowledge Assessment* to allow for successful processing of the assessment.

Website Knowledge Assessment Review (web-based materials)

Upon completion of the review of the *Education Program*, the user is required to successfully complete the *Knowledge Assessment* prior to enrolling in the program.

The user is presented with one question at a time and required to provide an answer.

Upon completion of all program assessment questions, the system calculates a score. The score is presented to the user.

If the score is 100%, then the user has passed the program assessment.

If the user's score is less than 100%, they will be presented with the incorrectly answered question that they will be required to retake, in addition to further feedback on the incorrect answer.

The *Knowledge Assessment* (manual or website) may be attempted up to three times. If a score of 100% is not achieved after three attempts, the *TIRF REMS Access Education Program* must be reviewed again before retaking the *Knowledge Assessment*. Having performed the training again, a further three unsuccessful attempts at the *Knowledge Assessment* are permitted before enrollment is denied.

Successful completion of the *Knowledge Assessment* is required in order for the prescriber to enroll in the TIRF REMS Access program. Prescribers may enroll online or by paper by completing the *TIRF REMS Access Prescriber Enrollment Form*.

Verification of prescribers having successfully enrolled will be recorded in the TIRF REMS Access program and will allow them to access the full TIRF REMS Access program and to prescribe TIRF medicines. Prescribers will receive a user ID and password as part of the enrollment process. In addition, these forms will also be available as printed materials and can be downloaded from the website for stakeholders that prefer not to enroll electronically. These forms along with the *Knowledge Assessment* may be completed on paper and faxed to the TIRF REMS Access call center at 1-866-822-1487.

Manual Enrollment

Upon receipt of a paper enrollment form, a TIRF REMS specialist will review the form for completeness and determine the enrolling stakeholder type (i.e., prescriber or pharmacy). The TIRF REMS specialist will enter all data on the form into the TIRF REMS Access database.

Required for successful enrollment form:

1. All required fields are completed on the form.
2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation
4. The program *Knowledge Assessment* has been passed successfully.
5. All enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation is sent to the stakeholder via the preferred method of communication (fax or email) that is indicated on the enrollment form.

An enrollment form is considered incomplete where:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

If the enrollment form is incomplete, a fax is generated clearly listing all incomplete fields and a description of the action required to resolve the issue. The fax is sent to the fax number provided by the enrolling user on the enrollment form (email or phone can be used to send/discuss the incomplete form if the fax number is not available). The enrolling user must provide the incomplete information and return it to the TIRF REMS Access program for reprocessing. The enrollment is not considered complete until all required fields have been received and validated.

Web-based Enrollment

The enrolling user will be required to review the *TIRF REMS Access Education Program*, complete the *Knowledge Assessment* with a score of 100%, and complete the appropriate enrollment form.

Required for successful enrollment:

1. All required fields are completed on the form.

2. All field validation edits have been passed successfully.
3. Successful Identifier Authentication Validation.
4. The enrollment data are saved in the TIRF REMS Access database.

Upon successful enrollment, an enrollment confirmation and completed enrollment form are sent via the indicated preferred method of communication (fax or email) provided by the enrolling user on the enrollment form. In the case that email is not available, a fax confirmation will be sent. Enrollment confirmation is also provided via the website.

An enrollment form is considered incomplete when:

1. Required fields are missing.
2. Required fields did not pass field validation edits.

Unsuccessful Enrollment: The field edit messages are displayed back to the enrolling user. The enrolling user cannot progress further with the enrollment process until errors are corrected. Only the user's initial registration information will be retained; no enrollment data are saved to the TIRF REMS Access database.

TIRF Sponsors will maintain a database containing a list of all enrolled prescribers and their status (i.e. active or inactive). Upon initial activation, prescribers remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate prescribers for non-compliance reasons.

If a previously active prescriber becomes inactive, the prescriber will become re-activated by successfully completing the standard *TIRF REMS Access Education Program*, *Knowledge Assessment*, and the enrollment form in its entirety.

While a prescriber is inactive, prescriptions from that prescriber can no longer be filled under the TIRF REMS Access program. If the prescriber is providing care for patients using TIRF medicines at the time of prescriber inactivation, it is the prescriber's responsibility to ensure that the patients continue to receive appropriate pain medication via referral to another prescriber in the TIRF REMS Access program.

Prescribers are re-educated and re-enrolled in the TIRF REMS Access program every two years. TIRF Sponsors will notify prescribers of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify prescribers of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program
b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of TIRF medicines.

All communication methods utilized by the TIRF REMS Access program will provide information on how to report any suspected adverse events, including reports of misuse and abuse to TIRF Sponsors.

b. Outpatient Pharmacies: Education and Enrollment

The *TIRF REMS Access Education Program* is the primary tool for educating pharmacists about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines.

The TIRF REMS Access education for pharmacists comprises the *TIRF REMS Access Education Program* and *Knowledge Assessment* that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Chain Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Independent Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Outpatient Pharmacies

If the pharmacy does not want to perform the *Education Prog*ram and *Knowledge Assessment* online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested from the TIRF REMS Access program call center.

The *Education Program* will cover information regarding how to validate prescriptions via the TIRF REMS Access program before they are filled as well as information on appropriate dispensing and use of TIRF medicines. Following review of the *Education Program,* the authorized pharmacist may enroll the pharmacy by successful completion of the *Knowledge Assessment* and the appropriate TIRF REMS Access program pharmacy enrollment form. On receipt of a valid enrollment form, the independent and chain outpatient pharmacies will be sent by fax or email the instruction guide on the test transactions they will be required to run to verify that their pharmacy management system has been configured. The authorized outpatient pharmacy representative would ensure completion of system testing to verify their pharmacy management system has been configured. If the test transactions have been completed successfully, the pharmacy will be enrolled and confirmation will be sent to the pharmacy. If the test transactions are not completed successfully, the pharmacy will not be enrolled and a message will be sent to contact the call center in order to further explain the need to configure the pharmacy management system.

The authorized pharmacist will be responsible for educating all pharmacy staff that participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program. This training should be documented and is subject to audit.

An authorized chain outpatient pharmacy representative or closed system outpatient pharmacy representative may complete the TIRF REMS Access training, *Knowledge Assessment* and enrollment on behalf of all their pharmacies within the chain or closed system outpatient pharmacy and then document and manage training of all pharmacy staff according to their internal processes. The authorized chain outpatient pharmacy representative may update trained stores on their chain outpatient pharmacy dashboards or submit a list to the TIRF REMS Access program for uploading into the database. The authorized closed system outpatient pharmacy representative would ensure their trained closed system dispensing locations were placed into their closed system enrollment file according to the standard file format and submitted to the TIRF REMS Access program for uploading into the database.

Enrolled pharmacies will be recorded in the system which will allow them access to the TIRF REMS Access program to dispense TIRF medicines. Following enrollment and successful completion of the test transactions (for chain outpatient pharmacies,) the authorized pharmacist will receive a username and enrollment ID, where the user can then create a password for the TIRF REMS Access website.

Independent and chain outpatient pharmacies have the option of enrolling on-line at www.TIRFREMSaccess.com or by fax to the TIRF REMS Access program at 1-866-822-1487. Independent and chain outpatient pharmacy enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. Closed system outpatient pharmacies must enroll by fax or by email to information@TIRFREMSAccess.com Closed system outpatient pharmacy enrollment forms may be requested by sending an email to information@TIRFREMSAccess.com. Enrollment forms may be completed along with the Knowledge Assessment and submitted to the TIRF REMS Access program.

A database will be maintained containing a list of all enrolled pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, the pharmacy will become re-activated by successfully completing the standard *TIRF REMS Access Education Program*, Knowledge Assessment and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines or dispense TIRF medicines under the TIRF REMS Access program.

Pharmacies are re-educated and re-enrolled every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies, of forthcoming enrollment expiration and the need to re-enroll in the REMS program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update

all affected materials and notify pharmacies of the changes, as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program

b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any TIRF medicine.

The pharmacist will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

c. Inpatient Pharmacies: Education and Enrollment

The *TIRF REMS Access Education Program* is the primary tool for educating inpatient pharmacies about TIRF medicines and the TIRF REMS Access program. These materials include information on proper patient selection, dosing and administration, general opioid use and risks of TIRF medicines. The Education Program also includes information about the requirements of the TIRF REMS Access program in the inpatient setting.

The TIRF REMS Access education materials for inpatient pharmacies comprise the Educational Program and Knowledge Assessment that can be accessed from the TIRF REMS Access website or requested from the TIRF REMS Access program call center. The following documents are also available as resources within this Education Program:

- Individual product Full Prescribing Information
- Individual product Medication Guides
- The TIRF REMS Access Program: An Overview for Patients & Caregivers
- The TIRF REMS Access Program: An Overview for Prescribers
- The TIRF REMS Access Program: An Overview for Chain Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Independent Outpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Inpatient Pharmacies
- The TIRF REMS Access Program: An Overview for Closed System Outpatient Pharmacies

An authorized pharmacist of the inpatient pharmacy is required to undergo the *TIRF REMS Access Pharmacy Education Program*. If the pharmacist does not want to perform the Education Program and *Knowledge Assessment* online, all of these documents can be downloaded using the download education link on the TIRF REMS Access website or requested as a hardcopy enrollment from the TIRF REMS Access program call center.

The Education Program will cover information about the requirements of the TIRF REMS Access program. Following review of the Education Program, the authorized pharmacist may

enroll the pharmacy by successfully completing of the Knowledge Assessment and the TIRF REMS Access Inpatient Pharmacy Enrollment Form.

Inpatient pharmacy enrollment will be recorded in the system. Upon successful enrollment the inpatient pharmacy will have the ability to order TIRF medicines for inpatient dispensing. Pharmacies will receive a user ID and password as part of the enrollment process.

In addition, enrollment forms can be printed from the website for stakeholders that prefer not to enroll electronically. These forms may be completed along with the *Knowledge Assessment* and faxed to the TIRF REMS Access program at 1-866-822-1487.

A database will be maintained containing a list of all enrolled inpatient pharmacies and their status (i.e. active or inactive).

Upon initial activation, pharmacies remain active until inactivation occurs; or expiration of the enrollment period. TIRF Sponsors may inactivate enrolled inpatient pharmacies for non-compliance reasons.

If a previously active pharmacy becomes inactive, it will become re-activated by successfully completing the standard TIRF REMS Access Education Program, Knowledge Assessment, and the enrollment process in its entirety, except in some cases of inactivation due to non-compliance.

While a pharmacy is inactive they will not be able to receive shipments of TIRF medicines.

Inpatient pharmacies are re-educated and re-certified every two years or following substantive changes to the TIRF REMS Access program. TIRF Sponsors will notify pharmacies of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.

If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies of the changes as applicable.

Substantive changes to the TIRF REMS Access program are defined as:

a. Significant changes to the operation of the TIRF REMS Access program.

b. Changes to the Prescribing Information and Medication Guides that affect the benefit-risk profile of any TIRF medicine.

The inpatient pharmacy will be encouraged to report any adverse events, product quality complaints, including reports of misuse, abuse, and diversion to TIRF Sponsors that are brought to their attention.

d. Patient Enrollment and Counseling

Patient enrollment is not required for inpatient use of TIRF medicines.

- Prescribers for outpatients will be provided with copies of a TIRF medicine Medication Guide and materials to use in counseling patients. Medication Guides are product specific and can be accessed from the specific TIRF Sponsor, the TIRF REMS Access website, or the TIRF REMS Access call center. Patients will be counseled on the TIRF REMS product by enrolled prescribers, supported by review of the Medication Guide and

the overview of the TIRF REMS Access program for Patients and Caregivers. Patients will also have the opportunity to discuss any questions or concerns they have with their prescriber. Together the prescriber and patient will review and sign the *Patient-Prescriber Agreement Form.*

- The patient will be counseled by the prescriber and personally sign the *Patient-Prescriber Agreement Form* unless they are unable to act on their own behalf. For incapacitated patients, the patient counseling can be provided to and signed by the patient's legally authorized representative or medical guardian.
- Both the prescriber and patient must complete the *Patient-Prescriber Agreement Form* and the prescriber must provide a completed copy by fax or through the TIRF REMS Access website to the TIRF REMS Access program within 10 working days. Patients will be enrolled in the TIRF REMS Access program when their first prescription is processed at the pharmacy. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This enrollment will be part of the normal prescription processing at the pharmacy and will be performed by the TIRF REMS Access program.
- The *TIRF REMS Access Program: An Overview for Patients and Caregivers* will be available for distribution to the patient by the prescriber or through the program website. This overview details the steps the patient must follow. Further information will be available on the TIRF REMS Access program website or at the TIRF REMS Access call center.
- Patients will be offered counseling by the dispensing pharmacist on the responsible use, handling and disposal of TIRF medicines. A copy of a specific TIRF medicine's Medication Guide will be provided by the pharmacist when their prescriptions are dispensed by the pharmacy.
- A database will be maintained containing a list of all enrolled patients and their PPAF status (i.e. active or inactive). Upon initial activation, PPAFs remain active until a trigger for inactivation occurs. The triggers for PPAF inactivation include: a prescription has not been filled for more than 6 months, PPAF has expired, patient is deceased, patient chooses to no longer participate.
- If a previously active PPAF becomes inactive, the PPAF can become active again by the patient completing the standard patient counseling and re-evaluation by their prescriber (i.e. a complete review of the current TIRF medicine's Medication Guide) and completing a new *Patient-Prescriber Agreement Form.*
- If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot authorize the prescription for the TIRF medicines to be filled until the new prescriber is active in the TIRF REMS Access program.
- Patients will be re-counseled and required to complete a new *Patient-Prescriber*

Agreement Form every 2 years. TIRF Sponsors will notify the patient's prescriber of forthcoming enrollment expiration and the need to complete a new *Patient-Prescriber Agreement Form*.

- If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify the patient's prescriber of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program
    b. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of any and all TIRF medicines.

e. Prescription Verification

Following initial patient enrollment on processing of a patient's first TIRF medicine prescription, pharmacies must verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

TIRF Sponsors will use a model that uses a pharmacy billing claim and engages a switch provider in the validation process for independent and chain outpatient pharmacies. The switch provider provides information to pharmacists at point-of-dispensing via their pharmacy terminals. Their secure connectivity network provides a single point of access between pharmacies and payers so that transactions are routed quickly and reliably, instantly transmitting claims to the appropriate processor and returning the adjudicated response to the pharmacy within seconds.

Patients must complete a *Patient-Prescriber Agreement Form* (PPAF) prior to being given a prescription for a TIRF medicine. This may be done in two ways – online at www.TIRFREMSaccess.com or paper based. If conducted online, the PPAF will be recognized immediately. Paper based PPAFs must be faxed to the program within 10 working days to complete enrolment.

Independent and Chain Outpatient Pharmacies: Prescription Verification

On receipt of a prescription for a TIRF medicine at an enrolled independent or chain outpatient pharmacy, the pharmacist will enter the prescription details in their pharmacy management systems and send the transaction to the TIRF REMS Access program via the Switch Provider. The TIRF REMS Access program will use this transaction data to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the REMS database will then be interrogated, via the Switch Provider, in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, a billing request will be sent to the payer by the Switch. Once the payer authorizes payment the switch provider will then authorize the pharmacy to dispense

the TIRF medicine as with a normal prescription, returning an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will reject the claim (prior to the claim being forwarded to the payer) and the pharmacy will receive a rejection notice from the Switch Provider. This automated feedback will indicate the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notify the pharmacist to contact the TIRF REMS Access call center for further information. The current switch authorization process typically takes 3-5 seconds to complete. Interrogation of the TIRF REMS Access program enrollment database should add not more than 1 second to the overall process. This method of verification is designed to integrate into normal pharmacy workflow patterns and therefore minimize burden to the pharmacy while providing a robust control on ability to dispense TIRF medicines outside of the TIRF REMS Access program.

The TIRF REMS Access system communicates an authorization number when the submitted prescription billing request passes all qualification rules and the processor approves the billing request. The switch provider appends the authorization to a message field before delivering the response to the pharmacy practice management system.

If the pharmacy is enrolled and the electronic prescription verification process fails, prescription verification can be facilitated through the call center. The call center representative can enter the required fields necessary to provide prescription verification.

The 'back-up' process/system is not the primary method for verification, and will only be available to enrolled, active pharmacies. All instances where the back-up process is used will be adequately documented, including the specific reason it is being used. A report on back-up system use will be included in the REMS Assessment.

Back-up system utilization will be incorporated into compliance monitoring; if excessive use is observed corrective action will be implemented.

Closed System Outpatient Pharmacies: Prescription Verification

On receipt of a prescription for a TIRF medicine at an enrolled closed system outpatient pharmacy, the pharmacist will contact the TIRF REMS Access program via phone or fax to provide prescription details for verification. The TIRF REMS Access program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for enrollment. If the prescriber is enrolled and active, dispensing of the TIRF medicine is allowed. In the event that the PPAF was not completed online, prescribers are allowed up to 10 working days to fax or send it to the TIRF REMS Access program. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received.

For all prescriptions that follow, the closed system outpatient pharmacist will continue to contact the TIRF REMS Access program via phone or fax with prescription information in order to validate the enrollment status of the prescriber, patient and pharmacy.

In the case of a valid prescription, the closed system outpatient pharmacy will be provided an authorization number which will be captured by the TIRF REMS Access program.

If the prescription is not valid (e.g. one of the stakeholders is not enrolled), the TIRF REMS Access program will not provide an authorization number and the closed system outpatient pharmacy will receive a rejection notice. This feedback will be provided to the closed system outpatient pharmacy via phone or fax and will include the reason for rejection, information on how the rejection may be resolved and instructions on not dispensing the TIRF prescription until resolution is reached.

f. The TIRF REMS Access Program Website

- The TIRF REMS Access program website (www.TIRFREMSaccess.com) contains information about the TIRF REMS Access program and serves as one method by which prescribers can receive education and enroll themselves in the TIRF REMS Access program. The prescriber will also be able to complete and submit a *Patient-Prescriber Agreement Form* via the website.
- Chain outpatient, independent outpatient and inpatient pharmacies can use the website for education and enrollment, including a dashboard functionality to allow chain outpatient pharmacies to manage their stores
- Closed system outpatient pharmacies can use the website for education.
- The website includes the *TIRF REMS Access Education Program, Knowledge Assessment* and enrollment forms that must be reviewed and completed before enrolling. The website is referenced in all TIRF REMS Access program and TIRF medicine related materials.
- Prescribers can use the website to inform patients of enrolled pharmacies that can dispense TIRF medicines.

  The TIRF REMS Access program Website also serves as a resource for:
  - Description of the TIRF REMS Access program
  - Ordering TIRF REMS Access Medication Guides
  - Full Prescribing Information for all TIRF medicines
  - Medication Guides for all TIRF medicines
  - Patient/Caregiver, Prescriber, Chain Outpatient Pharmacy, Independent Outpatient Pharmacy, Closed System Outpatient Pharmacy and Inpatient Pharmacy TIRF REMS Access program overviews in on-screen and printer friendly format
  - TIRF REMS Access program contact information
  - Frequently Asked Questions

g. The Key Elements of this REMS that Mitigate the Risks Associated with the Use of TIRF medicines are:

i. A certified prescriber who has acknowledged and agreed to adhere to the conditions that must be met for the appropriate outpatient use of each TIRF medicines.

- Prescribers will be educated and certified on the risks of inappropriate patient selection, including non-opioid tolerant patients. In order to become enrolled, outpatient prescribers will be required to complete the *TIRF REMS Access Education Program* and *Knowledge Assessment*. Enrollment is contingent upon prescribers documenting that they understand the risks of TIRF medicines and agree to the appropriate use of TIRF medicines (See appended *Prescriber Enrollment Form*).
- Without this enrollment, patients, with prescriptions from outpatient prescribers will be unable to have TIRF medicine prescriptions filled by an enrolled pharmacy.
- The TIRF REMS Access program will maintain a database of all enrolled prescribers.

ii. The certified independent or chain outpatient pharmacy has agreed to send all claims through the system to verify eligibility. The certified closed system outpatient pharmacy has agreed to contact the TIRF REMS Access program to verify eligibility and receive authorization prior to dispense.

- All pharmacies that intend to purchase and dispense TIRF medicines must be enrolled in the TIRF REMS Access program in order to receive product from distributors. Pharmacies will be enrolled only after an authorized pharmacist undergoes *TIRF REMS Access Education Program*, completes a *Knowledge Assessment* and submits an enrollment form.
- Pharmacies that are not enrolled will be unable to obtain supplies of TIRF medicines.
- The TIRF REMS Access program will maintain a database of all certified pharmacies.

<u>Outpatient Pharmacies</u>

- The independent or chain outpatient pharmacy will ensure that the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.
- The closed system outpatient pharmacy will have processes in place to ensure the TIRF REMS Access program is contacted and authorization has been received prior to the dispensing of a TIRF prescription.
- The authorized pharmacist will ensure that all pharmacy staff involved in dispensing TIRF medicines at their pharmacy have been educated on the risks associated with TIRF medicines, maintain auditable training records for pharmacy staff, and adhere to the requirements of the TIRF REMS Access program.
- The pharmacist must ensure that TIRF medicines have been dispensed under the following safe use conditions:

- The pharmacist has dispensed TIRF medicines only to enrolled patients, based on a valid Schedule II prescription from an enrolled prescriber and receipt of an authorization message from the TIRF REMS Access program.
- The pharmacist has offered counseling to patients on appropriate TIRF medicine use.
- The pharmacist has provided each patient with a product specific Medication Guide for every TIRF prescription dispensed, instructed the patient to read it and has answered any questions the patient may have.

- Additionally, all TIRF medicine prescriptions will be tracked based on the following:
  - Prescription validation and dispensing steps performed by enrolled pharmacists;
  - Generation of a prescription authorization number from the TIRF REMS Access database upon confirming enrollment status. This tracking will enable identification of prescriptions, as well as provide utilization information used in the evaluation of the TIRF REMS Access program.

Inpatient Pharmacies

- The authorized pharmacist for an inpatient pharmacy will establish or oversee the establishment of a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program. The authorized inpatient pharmacist acknowledges that Pharmacies within or associated with the healthcare facility that dispense to outpatients must also be enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
- An inpatient pharmacy is not to dispense TIRF medicines for outpatient use.
- A prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.

iii. An informed outpatient and/or caregiver should understand the inherent risks in the use of opioids and know how to administer TIRF medicines appropriately at home. Therefore, each patient must:

- Sign a TIRF REMS Access program *Patient-Prescriber Agreement Form* that documents appropriate use conditions and opioid tolerance (See appended *Patient-Prescriber Agreement Form*).
- Deliver the TIRF medicine prescription to an enrolled pharmacy.
- Understand that they must be regularly using another opioid pain medicine for their constant pain.

- Be counseled on responsible use and handling by the pharmacist at each dispensing when they receive an additional copy of the appropriate Medication Guide.
- These requirements do not apply to inpatient use of a TIRF medicine.

C. Implementation System

The Implementation System includes the following:

a. Wholesaler/Distributor Enrollment and Fulfillment

- TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

- For the purpose of the TIRF REMS Access program, the term distributor refers to wholesaler, distributor, and/or chain outpatient pharmacy distributor who take title to or direct sale or disposition of TIRF medicines to persons other than a consumer or patient. TIRF medicine distributors will be contacted and will receive a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies. The distributor's authorized representative reviews the distributor program materials. The distributor's authorized representative will complete and sign the *Distributor Enrollment Form* and fax it to the TIRF REMS Access program. TIRF Sponsors will not ship TIRF medicines to any distributor who has not completed and signed the enrollment form; by checking the status of the distributor prior to shipping the drug (See appended *Distributor Enrollment Form*).
- As part of the TIRF REMS Access program, distributors will need to enroll in the TIRF REMS Access program. Distributors will need to confirm their understanding of the distributor requirements in the TIRF REMS Access program, which includes verifying that pharmacies are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.
- The distribution process for TIRF medicines as it relates to drug distributors will consist of:
    - Only those TIRF medicine Sponsor contracted distributors will be eligible for TIRF REMS Access program enrollment.
    - TIRF medicine distributors will be contacted and will receive a communication describing the TIRF REMS Access program.
    - TIRF medicine distributors must acknowledge receipt and understanding of the TIRF REMS communication, by completing the TIRF REMS Access *Distributor Enrollment Form*, in order to become a customer eligible to receive and/or distribute TIRF medicines from TIRF Sponsors. In addition to the TIRF REMS Access *Distributor Enrollment Form*, the distributor's authorized contact will

receive communication on how to verify pharmacies that are enrolled in the TIRF REMS Access program prior to shipping TIRF medicines.

- The procedures for the TIRF REMS Access program will include the method for timely communications of newly enrolled as well as inactive pharmacies in the TIRF REMS Access program.
- The procedures for the TIRF REMS Access program will also include the procedure for reporting and management of non-compliance with the TIRF REMS Access distribution program.
- Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.
- Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years. TIRF medicine Sponsors will notify distributors (based on contractual relationships in place between Sponsor and distributors) of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program.
- If there are substantive changes to the TIRF REMS Access program, impacted TIRF Sponsor or TIRF Sponsor team will update all affected materials and notify distributors of the changes, as applicable. Substantive changes to the TIRF REMS Access program are defined as:
    i. Significant changes to the operation of the TIRF REMS Access program.
    ii. Changes to the Prescribing Information and Medication Guide that affect the benefit-risk profile of impacted TIRF medicine.

b. The TIRF REMS Access Program Database

- The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive).
- Management of the TIRF REMS Access database will be contracted to an appropriately qualified third party vendor and overseen by the TIRF Sponsors. Data for all users will be updated in the TIRF REMS Access database. This includes data received from both the call center manual process and web-based processes. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing their TIRF medicine. Additionally, TIRF Sponsors will monitor to ensure their TIRF medicine is only being dispensed for outpatient use to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by the TIRF Sponsors if noncompliance is found.
- TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a

Patient-Prescriber Agreement Form with each TIRF medicine patient, and to submit it to the REMS program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TIRF REMS Access program will assess how often this occurs. This will be accomplished by reconciling the *Patient-Prescriber Agreement Forms* submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system.

- TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
- TIRF Sponsors will monitor the prescribing and dispensing of TIRF medicines to enrolled patients. If non-compliance is found, TIRF Sponsors will institute corrective actions. Please refer to Section 5(B) for further details.
- TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies, distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

Based on monitoring and evaluation of these elements to ensure safe use, TIRF Sponsors will work to improve implementation of these elements and to ensure compliance with the TIRF REMS Access program requirements, as applicable.

c. TIRF REMS Access Program Call Center

The TIRF REMS Access program includes a call center component. The call center will be staffed by qualified and trained specialists, who will provide TIRF REMS Access program support to patients, prescribers, pharmacies and distributors.

The call center specialists' responsibilities will include, but are not limited to, the following:

- Provide TIRF REMS Access program enrollment assistance to prescribers, pharmacies, distributors and patients
- Processing of prescriber, pharmacy and distributor enrollments and Knowledge Assessment forms
- Provide stakeholder enrollment verification in the TIRF REMS Access database
- Processing of *Patient- Prescriber Agreements Forms*
- Assist prescribers or patients in locating enrolled pharmacies
- Collect prescription information for enrolled closed system outpatient pharmacies and provide authorization numbers for each dispensing

- Identify and transfer product complaints and potential adverse event information to TIRF Sponsors

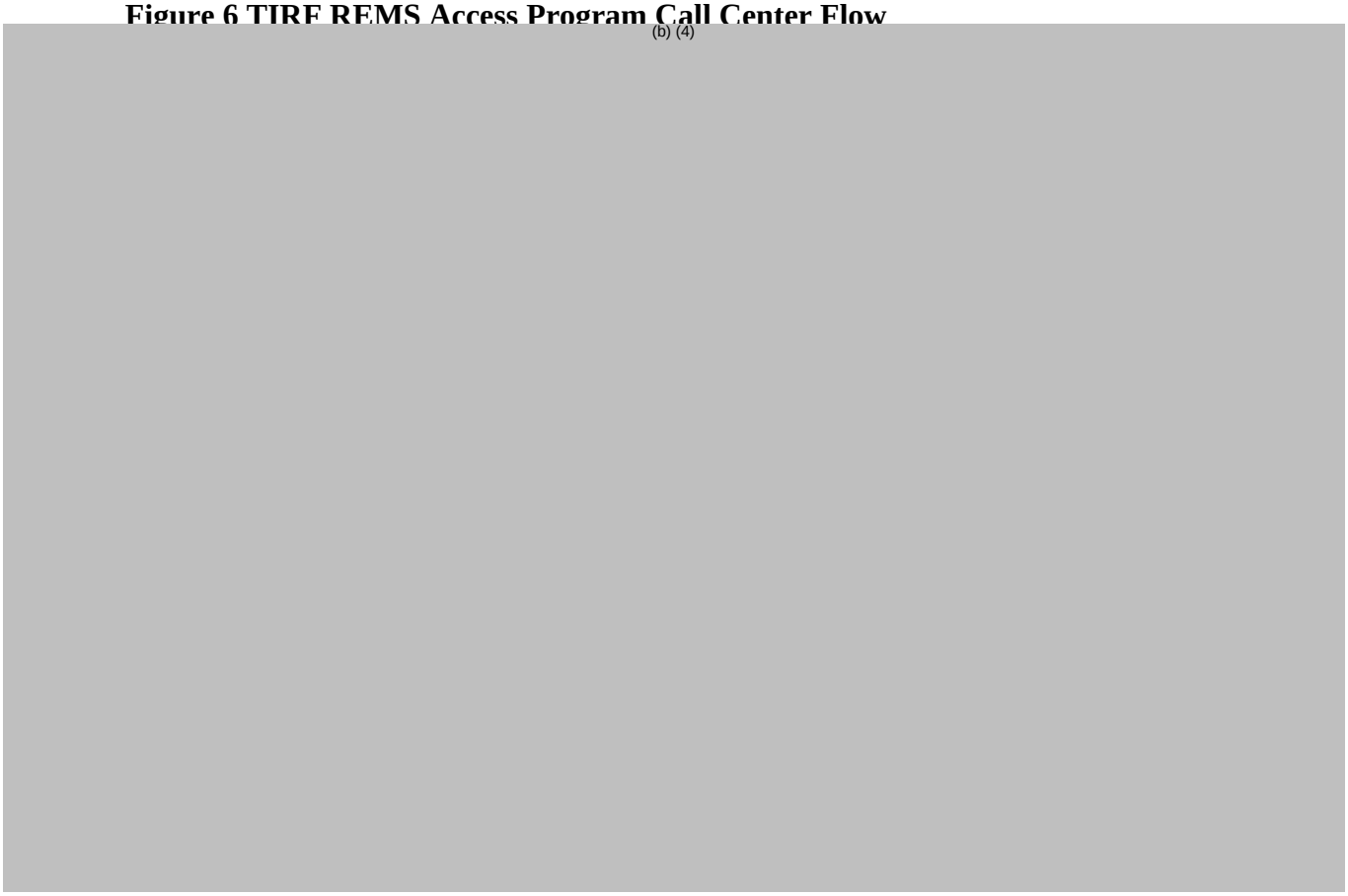
- Provide general program information and technical assistance to stakeholders interacting with the TIRF REMS Access website

The TIRF REMS Access program call center hours of operation are Monday – Friday, 8:00am to 8:00pm EST. Callers outside of these hours are instructed to leave a message that will be addressed at the beginning of the next business day. TIRF medicine Medication Guides may include the TIRF Sponsor phone number and may be contacted. TIRF Sponsors may refer caller to Emergency Room.

The TIRF REMS Access program call center flow is show below in Figure 6.

Figure 6 TIRF REMS Access Program Call Center Flow

(b) (4)



D. Timetable for Submission of Assessments of the REMS

TIRF Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the REMS approval, and annually thereafter. The knowledge, attitude, and behavior (KAB) surveys will be submitted at 12 and 24 months from the date of the REMS approval, and as needed thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment

should conclude no earlier than 60 days before the submission date for that assessment. TIRF Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

5. REMS ASSESSMENT PLAN

The aim of the TIRF REMS Access program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations will be used in an effort to improve the processes, over time, as needed.

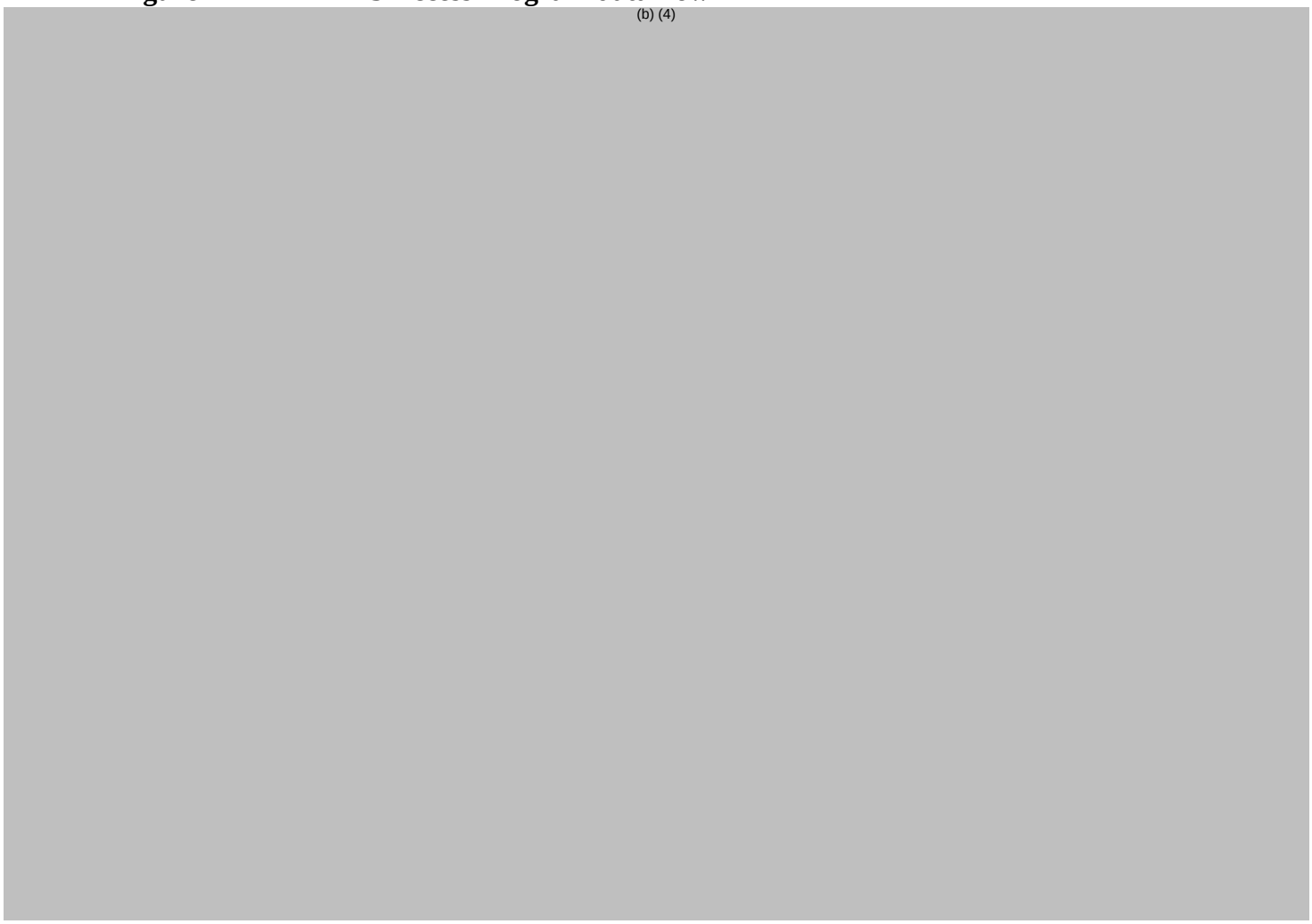
A Data Sources

Data will be collected from the following main sources as described in detail below: a) the TIRF REMS Access program utilization statistics, b) dispensing activity for enrolled pharmacies, c) program infrastructure and performance, d) TIRF REMS Access non-compliance plan, e) safety surveillance, e) periodic surveys of patients, healthcare providers, and pharmacies.

a. The TIRF REMS Access Product and Program Utilization Statistics (data presented per the current reporting period and cumulatively)

The TIRF REMS Access program data flow is show in Figure 7 below.

Figure 7 TIRF REMS Access Program data flow



For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and wholesalers, the following data will be tabulated for the current reporting period and cumulatively.

a. Patient Enrollment

1. Number of unique patients enrolled
2. Number of patients inactivated

b. Prescriber Enrollment

3. Number of prescribers enrolled
4. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending
5. Number of prescribers inactivated

c. Pharmacy Enrollment

6. Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities)
7. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type)
8. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system)

d. Distributor Enrollment

9. Number of distributors enrolled
10. Number of distributors inactivated

b. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)

11. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription/transactions per closed system entity
12. Number of prescriptions/transactions denied/rejected and the reasons for denial/rejection. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)
13. The mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
14. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF
15. Number of prescriptions dispensed after ten days without a PPAF in place

c. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be collected (per reporting period).

16. Number of times a backup system was used to validate a prescription, with reason(s) for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described
17. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions
18. Call center report with
    - Overall number of contacts
    - Summary of frequently asked questions
    - Summary of REMS-related problems reported
19. Description of corrective actions taken to address program/system problems

d. TIRF REMS Access Non-Compliance Plan

The TIRF sponsors should provide the following data regarding non-compliance in each assessment report (per reporting period).

20. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:
    - Verification of training for all pharmacists dispensing TIRF products
    - Numbers of prescription authorizations per closed system
    - Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program. Data to include the 12 month period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic versus manual process).
    - Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance
21. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance starting in the 48-Month Assessment Report. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period. These reports are to include:
    - Verification of training for all pharmacists dispensing TIRF products
    - Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program
    - Describe any corrective actions taken for any non-compliance identified during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events
22. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:
    - Description of how the NCRT defines a non-compliance event
    - Description of how non-compliance information is collected and tracked
    - Criteria and processes the Team uses to make decisions
    - Summary of decisions the Team has made during the reporting period
    - How the Team determines when the compliance plan should be modified
23. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action
24. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences
25. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

26. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
27. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
28. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

e. Safety Surveillance (data collected per reporting period)

29. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures
30. TIRF Sponsors will produce one comprehensive report that presents spontaneous adverse event data from all sponsors of the TIRF REMS Access program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:
    - Line listings under each category of adverse events of interest as listed above
    - Line listings should provide at a minimum the following information (see sample table provided):
        - Identifying case number
        - Age and Gender of the patient
        - Date of the event as well as of the report
        - The Preferred Terms
        - Indication of TIRF use
        - Duration of TIRF therapy
        - Concomitant medications
        - Event Outcome
    - Other metrics of interest include:
        - Number of event reports in each event category of interest
        - Counts of adverse events related to inappropriate conversions between TIRF products
        - Counts of adverse events related to accidental and unintentional exposures
        - Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients
    - Duplicate cases are identified and eliminated

- Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such
- For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events
- Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

31. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Metric 30 directly above:
    - Non-medical use of prescription drugs
    - Surveys conducted at substance abuse treatment programs
    - College surveys
    - Poison control center data
    - Impaired health care workers
    - Drug-related hospital emergency department visits
    - Drug-related deaths
    - Other databases as relevant

Table X. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Suspect Products	Event Outcome
	Age	Gender	Event	Report						

f. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Surveys will assess understanding of key messages.

B. TIRF REMS Access Non-Compliance Plan

GOALS & OBJECTIVES

The TIRF REMS Access program is in place to ensure the safe and appropriate use of TIRF medications. The goal of the non-compliance plan is to ensure that TRIG monitors the functioning of TIRF REMS Access and identifies and investigates deviations and non compliance with TIRF REMS requirements in order to ensure patient safety and continuously improve the program.

TIRF REMS ACCESS NON-COMPLIANCE REVIEW TEAM

A TIRF REMS Access Non-Compliance Review Team will be created. The team will have membership from the companies of the TRIG. A detailed plan for the TIRF REMS Access program will be created and implemented by the team.

The TIRF REMS Access Non-Compliance Review Team's responsibility will be to:

- Evaluate the compliance of patients, healthcare providers, distributors and pharmacies (stakeholders) with the TIRF REMS Access program
- Investigate potential non-compliance activity when events are referred to the team
- Devise corrective measures and issue notices, warnings, suspensions, or deactivations of stakeholders where warranted
- Review need for changes to the TIRF REMS Access program as a result of deviations or non-compliance

The TIRF REMS Access Non-Compliance Review Team will meet regularly.

Any needed program modifications or stakeholder notifications will be approved by TRIG prior to implementation.

SOURCES OF NON-COMPLIANT EVENTS

There are a variety of ways in which the TIRF REMS Access program can detect non compliance. Those potential sources include:

- TIRF REMS Assessment reports
- REMS database activity
- TRIG Member Company Adverse Event Reporting or Medical Information
- TIRF REMS Access Program Call Center
- Data Requests and Audits

TIRF REMS Access Assessment Reports

TIRF REMS Access program data will be collected from the following main sources: a) the TIRF REMS Access program outreach, b) TIRF REMS Access product and program utilization statistics, c) program performance, d) safety surveillance, e) periodic surveys of stakeholders. The TIRF REMS Access Non-Compliance Review Team will regularly review the assessment reports for evidence of non-compliance or deviation from program procedures.

REMS Database Activity

The TIRF REMS Access program will maintain a database of all enrolled prescribers, pharmacies, patients and distributors and their status (active or inactive). Data for all users will be updated in the TIRF REMS Access database including data from the call center manual process, web-based processes, pharmacy network and prescription authorizations for closed system outpatient pharmacies.

The TIRF REMS Access Non-Compliance Review Team will regularly analyze database reports to detect evidence of non-compliance or deviation from program procedures.

TRIG Member Company Adverse Event Reporting or Medical Information

Each company in the TRIG is responsible for the intake, investigation, review and reporting of adverse events and answering medical information queries for their own product. Each TRIG member will review adverse events or medical information queries received by that company and forward events which contain evidence of TIRF REMS Access non-compliance or deviation to the TIRF REMS Access Non-Compliance Review Team for further evaluation. For privacy or commercial confidentiality reasons, this information may be redacted before forwarding, and individual investigation for these events will be referred back to the company that initially received the event.

TIRF REMS Program Call Center

The TIRF REMS Access program will have a call center available for questions about the program, or to process non website enrollments. Enrollments or queries that contain evidence of non-compliance or deviation from program procedures will be referred to the TIRF REMS Access Non-Compliance Review Team.

Data Requests and Audits

TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

The TIRF REMS Access Non-Compliance Review Team will review information received from data requests and audit reports to detect evidence of non-compliance or deviation from program procedures.

EVALUATION PROCESS

Events of suspected non compliance or deviation from TIRF REMS Access program procedures will be evaluated by the TIRF REMS Access Non-Compliance Review Team. Further corrective actions for stakeholders may occur and are described below.

CORRECTIVE ACTION MEASURES

Stakeholders that fail to comply with one or more elements of the TIRF REMS Access program will be subject to corrective action in accordance with the TIRF REMS Access non-compliance plan. Corrective actions resulting from non-compliance will be determined by the TIRF REMS Access Non-Compliance Review Team according to the severity of the action. The stakeholders in this non-compliance plan include prescribers, patients, distributors, inpatient pharmacies, chain outpatient pharmacies, independent outpatient pharmacies and closed system outpatient pharmacies. The primary elements for corrective action include; notices, warnings, suspension, and deactivation, based on the incidence and outcomes of misuse, abuse, and overdose, in addition to accidental or intentional exposure. If a prescriber or pharmacy is suspended or

deactivated, information will be made available through the program to assist patients in finding alternative prescribers or pharmacies.

Notices

Notices are defined as minor violations that demonstrate a misunderstanding of the program requirements. Notices of non-compliance reinforce the program requirements and are intended to re-educate stakeholders. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

Warnings

Warnings are serious violations that result in an improper patient receiving a TIRF medicine. Warnings may be accompanied by other corrective actions (e.g. retraining) that may be required in order to avoid suspension.

Suspension

Suspension is a temporary deactivation from the program pending the completion of a Corrective Action Plan. Multiple warnings received by a stakeholder within a sixty day time-period will result in a Suspension. Multiple warnings received by a stakeholder over longer periods will accumulate, be logged in reports and may result in a suspension at the discretion of the TIRF REMS Access Non-Compliance Review Team.

A suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension, but may not purchase or acquire additional TIRF medicines until the suspension is removed. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension, and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity (e.g. a chain outpatient pharmacy or a multi-site distributor), the parent entity will be notified of the non-compliant activity and resultant suspension.

Deactivation

Deactivation is defined as an indefinite deactivation from the program. Deactivation may result from the failure of the stakeholder to implement corrective actions, multiple failures to comply with material program elements, and/or non-compliances where there is no feasible corrective action. Deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

A deactivated stakeholder may request reinstatement in the TIRF REMS Access program. Requests for reinstatement must be in writing (e.g. letter, fax, etc.) and contain sufficient details on corrective actions taken to prevent any future non-compliance with program elements. Patients that have been deactivated will only be reinstated by a request made by the patient's prescriber. Requests for reinstatement will be evaluated by the TIRF REMS Access Non-

Compliance Review Team which will make a recommendation to TRIG. TRIG will make the final determination on reinstatement.

TIRF REMS ACCESS PROGRAM AUDITS

As part of non-compliance monitoring, TIRF REMS Access program stakeholders will be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

C. Internal Quality and Compliance

The TIRF medicines REMS program team will be supported by written procedures to define process and will be audited against these for compliance.

6. OTHER RELEVANT INFORMATION

A. The TIRF REMS Access Program Transition Plan: From Individual to Shared REMS

Upon launch of the TIRF REMS Access program, all TIRF medicines in an individual REMS program will be transitioned to the TIRF REMS Access program. The transition for the TIRF REMS Access program will begin upon system availability. From this point onward all *new* stakeholders will be required to enroll in the TIRF REMS Access program.

Upon system availability the individual REMS program websites, call centers, and enrollment forms will be redirected to the TIRF REMS Access program. The TIRF REMS Access program will provide information and direction on why the individual REMS program website is no longer available, in addition to providing an introduction to the new TIRF REMS Access program and resources available to stakeholders. Historical data from all individual REMS programs will be referenced to determine the date of last prescription so that the TIRF REMS can accurately calculate 6 months of no prescription activity.

All pharmacies and prescribers already enrolled in an individual REMS program will be notified (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. They will also be notified in these letters that:

- They must review the Education Program on the TIRF REMS Access program website or request a copy from the call center.
- If the prescriber changes the patient's TIRF medicine at any time the prescriber is required to counsel the patient on the new product and provide the relevant Medication Guide but no new *Prescriber-Patient Agreement Form* (PPAF) is required.

Prescribers
Enrollment data for each enrolled prescriber will be transferred from the individual REMS program to the TIRF REMS Access program database when it is available. These prescribers will then be able to prescribe any TIRF medicine within the TIRF REMS Access program. Healthcare providers will be guided to review the educational program for the TIRF REMS Access program but will not be tested on these materials. These prescribers will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

Inpatient Pharmacies
Enrollment data for each enrolled inpatient pharmacy will be automatically transferred from the individual REMS program to the TIRF REMS Access program database when it is available. Inpatient pharmacies will then be able to order and dispense any TIRF medicine within the TIRF REMS Access program to inpatients.

Outpatient Pharmacies
All outpatient pharmacies in an individual REMS program will be automatically transitioned to the new TIRF REMS Access program.

However, chain outpatient pharmacies will need to execute a TIRF REMS Access program contract with their switch provider before they can order and dispense all TIRF medicines. Chain outpatient pharmacies that have not executed a TIRF REMS Access program contract with their switch provider will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If chain outpatient pharmacies do not execute a TIRF REMS Access program contract with their switch provider within six months, they will no longer be able to order or dispense any TIRF medicine.

Independent outpatient pharmacies will need to agree to the shared program terms and conditions before they can order and dispense all TIRF medicines. Independent outpatient pharmacies that have not agreed to the shared program terms and conditions will still be able to dispense those TIRF medicines with an individual REMS program, in which they previously enrolled, for up to 6 months from availability of the shared REMS program. If outpatient pharmacies do not sign the new business contracts within six months they will no longer be able to order or dispense any TIRF medicine, and will have to complete an updated contract if they wish to continue to dispense TIRF medicines.

All pharmacies that have been transitioned from an individual REMS program will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their original enrollment in the individual REMS program.

Patients
Enrollment data for patients will be automatically transferred from the individual REMS program to the TIRF REMS Access program database. Patients who have previously been

enrolled in an individual REMS and have completed a PPAF can be prescribed/receive any TIRF medicine within the TIRF REMS Access program. Patients will only be required to complete a new PPAF for the TIRF REMS Access program every 2 years from their last PPAF.

Distributors
Distributors already enrolled in a single product REMS program will be notified of the transition to the TIRF REMS Access program (by mail) ahead of the availability of the TIRF REMS Access program, of the transition to the TIRF REMS Access program. These letters will provide information about the TIRF REMS Access program inclusive of all transitioning activities. Enrollment data for distributors will be transferred from the individual REMS program to the TIRF REMS Access program database. Distributors will only be required to re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every 2 years from their last enrollment in the individual REMS program.

B. The TIRF REMS Access Program Steering Committee

A TIRF REMS Access program steering committee will be comprised of representatives from each Sponsor who will provide high level oversight and strategic direction for the TIRF REMS Access program. One voting member from each Sponsor company will be included in the Steering Committee. Significant issues and trends will be reviewed and appropriate recommendations made to the TIRF medicine Operations Team.

C. Abbreviations

The following abbreviations refer to the REMS program descriptors and products.

TIRF Medicines:	Transmucosal Immediate Release Fentanyl product(s)
TIRF REMS Access:	REMS program for TIRF medicines
TIRF Sponsors:	The group of sponsors that are submitting this REMS (please refer to the list of currently approved TIRF products located on the TIRF Products web page on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

7. REFERENCES

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Fishbain DA. Pharmacotherapeutic management of breakthrough pain in patients with chronic persistent pain. Am J Manag Care. 2008 May;14(5 Suppl 1):S123-8.

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June 19, 2015

REMS - INFORMATION REQUEST

Kathleen Uhl, M.D.
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

RE: Sequence # 0005
ANDA # 207338
Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent)

Dear Dr. Uhl:

Reference is made to Actavis Laboratories FL, Inc.'s (Actavis-FL)'s Abbreviated New Drug Application for Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent), ANDA # 207338, and to FDA's REMS information request email dated April 16, 2015 (copy attached). In accordance with 21 C.F.R. § 314.96, Actavis is amending the ANDA to provide a complete response to the comments included in the letter. For ease of review, the Agency's comments are provided in bold face type, followed by Actavis' response.

Comments:

1. **Your submission does not reference the DMF 27320 currently approved for the TIRF REMS. This is a requirement for any applicant holder who is either joining the TIRF or submitting modifications to their application.**

2. **We are also unable to locate a reference to a letter of authorization (LOA) from the TRIG that confirms you have joined the TIRF SSS. This is required.**

3. **You will need to submit a reference to letter of authorization (LOA) for joining the TIRF SSS REMS program referencing DMF No. 27320 held by McKesson Specialty Health. Submit a cover letter referencing the DMF 27320 12/24/2014 approved TIRF REMS. Your amended submission does NOT need to include the whole TIRF REMS and appended material – only reference to the DMF 27320 12/10/2014 Seq. No. 0013 submission of the most current TIRF REMS and LOA.**

Response:

Actavis is now a TRIG member and authorizes FDA to reference DMF No. 27320 for future TIRF REMS submissions. Additionally, the FDA can refer to the DMF 27320 12/10/2014 Sequence No. 0013 for the most recent, approved TIRF REMS and appended materials.

This supplement is an electronic submission organized in accordance with ICH-CTD format (eCTD). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface in accordance with Applicability Statement 2 (AS2) standards.

Should you have any questions or comments concerning this submission, please contact the undersigned at RegulatoryAffairsUS@actavis.com (*e-mail*), (954) 358-6125 (*telephone*), or 954-358-6350 (*fax*).

Sincerely,

Frida Navarro

Dig ta ly signed by Frida Nava ro
DN: cn=Frida Navarro, o=Actavis Labo atories FL Inc, ou=Regulatory
A fairs, ema l=frida.navarro @actavis com, c=US
Reason: I attest to the accuracy and integr ty of this document
Date: 201 5.06 19 17:21:13 -04'00'

For: Janet Vaughn
Director, Regulatory Affairs

Amir, Nazmin

From: Phillips, Chantal <Chantal.Phillips@fda.hhs.gov>
Sent: Thursday, April 16, 2015 3:49 PM
To: Regulatory Affairs US
Cc: Coogan, Andrew; Phillips, Chantal
Subject: ANDA 207338 REMS IR

Dear Ms. Vaughn,

In reference to your ANDA 207338 submitted 6/19/14, we have the following comments regarding your REMS:

1. Your submission does not reference the DMF 27320 currently approved for the TIRF REMS. This is a requirement for any applicant holder who is either joining the TIRF or submitting modifications to their application.

2. We are also unable to locate a reference to a letter of authorization (LOA) from the TRIG that confirms you have joined the TIRF SSS. This is required.

3. You will need to submit a reference to letter of authorization (LOA) for joining the TIRF SSS REMS program referencing DMF No. 27320 held by McKesson Specialty Health. Submit a cover letter referencing the DMF 27320 12/24/2014 approved TIRF REMS. Your amended submission does NOT need to include the whole TIRF REMS and appended material – only reference to the DMF 27320 12/10/2014 Seq. No. 0013 submission of the most current TIRF REMS and LOA.

Please let me know if you have any questions regarding this request.

Thank you,
Chantal

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
REMS Coordinator
Food and Drug Administration
Office of Generic Drugs
BLDG 75, Rm 2514

chantal.phillips@fda.hhs.gov
(301) 796-2259

TIRF REMS CORRESPONDENCE
CONSOLIDATED RESPONSES TO INFORMATION REQUESTS
FROM THE 36-MONTH ASSESSMENT REPORT

October 13, 2015

Kathleen Uhl, M.D.
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

RE: Sequence # 0006
ANDA # 207338
Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent)

Dear Dr. Uhl:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Actavis Laboratories FL, Inc.'s (Actavis)'s Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent), which is contained in DMF #027320. Additionally, a reference to the Letter of Authorization (LOA) for DMF #027320 was submitted to this application on June 19, 2015 (**sequence 0005**).

Per the guidelines in Section 1.5 of the DMF instruction document entitled, "*Process for Utilizing a Type V Drug Master File (DMF) for a Shared System Risk Evaluation and Mitigation Strategy (REMS) – Shared System REMS DMF*," Actavis hereby notifies FDA of submission of its Consolidated Responses to Information Requests from the 36-month REMS Assessment to DMF #027320 in eCTD sequence 0018 on October 12, 2015.

The current medication guide may be referenced in **sequence 0000**.

Should you have any questions or comments concerning this submission, please contact the undersigned at RegulatoryAffairsUS@actavis.com (*e-mail*), (954) 358-6125 (*telephone*), or 954-358-6350 (*fax*).

This is an electronic submission organized in accordance with ICH-CTD format (eCTD). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface in accordance with Applicability Statement 2 (AS2) standards.

Thank you for your prompt attention to this submission.

Sincerely,

Frida Navarro

Dig tally s gned by Frida Navarro
DN: cn=Frida Navarro o=Actavis Laboratories FL nc ou=Regulatory Affairs email=frida navarro r arte@actavis com c=US
Reason: I attest to the accuracy and integrity of th s document
Date: 2015 10 13 16 14:34 04 00

For: Janet Vaughn
Director, Regulatory Affairs

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	May 18, 2016
Reviewer:	LaShaun Washington-Batts, Pharm.D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Kimberly Lehrfeld, Pharm.D. DRISK
Division Director:	Cynthia LaCivita, Pharm.D. DRISK
Drug Name:	Fentanyl Sublingual Tablet
Therapeutic Class:	Opioid Analgesic
Dosage and Route:	100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg tablet for sublingual administration
Application Type/Number:	ANDA 207338
Applicant/Sponsor:	Activas Laboratories, Inc.
OSE RCM #:	2016-1238

1 INTRODUCTION

This review documents the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for fentanyl sublingual tablet, Abbreviated New Drug Application (ANDA) 207338. This ANDA was submitted by Actavis Laboratories, Inc. (Actavis) on June 19, 2014. Their proposed REMS was submitted to the Transmucosal Immediate-Release Fentanyl Products (TIRF) REMS drug master file #27320 (DMF #27320) on December 10, 2014 and referenced by Actavis in an amendment to the application on October 13, 2015. The Sponsor is a member of the TIRF REMS Industry Group (TRIG) and will market their product under the single, shared system (SSS) TIRF REMS. The Office of Generic Drugs (OGD) Division of Labeling Review will review the Medication Guide (MG) during their review of the label for ANDA 207338 and provide their comment under a separate cover.

1.1 PRODUCT BACKGROUND

Fentanyl sublingual tablet is an opioid agonist with the proposed indication for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

The Sponsor plans to market the following strengths: 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg tablets.

During the review of postmarketing data between 2006 and 2009, FDA had determined that, in the interest of public health and to minimize the burden on the healthcare system, a SSS REMS would be required for all TIRF products. On November 12, 2010, FDA sent all TIRF medication sponsors a REMS Notification Letter informing them of the need for a SSS REMS and the details for the REMS requirements.

On January 7, 2011, Abstral (NDA 022510), the reference listed drug (RLD) for fentanyl sublingual tablets, was approved for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. It was approved with a REMS to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors.

On December 28, 2011, FDA approved a SSS REMS for all TIRF products, including Abstral, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. The TIRF REMS was approved with the following elements:

- Medication Guide
- Elements to Assure Safe Use

- Prescriber Certification
- Pharmacy Certification
- Documentation of safe use conditions

· Implementation System
· Timetable for Submission of Assessments

The TIRF REMS Access Program was launched on March 12, 2012. The TIRF REMS was modified June 5, 2012, November 7, 2013 and December 24, 2014.

1.2 REGULATORY HISTORY

Regulatory History relevant to this review:

On December 28, 2011, the TIRF single shared REMS program was approved.

On June 19, 2014, Actavis submitted an ANDA for fentanyl sublingual tablets (ANDA 207338). This submission included the SSS TIRF REMS document, appended materials and a REMS Supporting document.

On, January 9, 2015, the Agency sent Actavis a Pre-Approval REMS Notification letter.

On April 3, 2015, Actavis amended their submission with the updated SSS TIRF REMS document, appended materials and a REMS Supporting document.

On June 19, 2015, the Agency sent Actavis an Information Request (IR) requesting Actavis submit a Letter of Authorization (LOA) referencing the TIRF REMS DMF #27320 and confirm their membership in the TIRF REMS Industry Group (TRIG).

On October 13, 2015, Actavis amended their submission providing documentation of TRIG membership and a LOA referencing the DMF# 27320. In addition, they referenced the submission to the DMF on December 10, 2014, which included the TIRF REMS document, appended materials and the REMS Supporting document approved by the Agency on December 24, 2014. This submission is the subject of this review.

2 MATERIALS REVIEWED

- Actavis Laboratories, Inc. reference to the proposed REMS for Fentanyl sublingual tablets (ANDA 207338) in DMF #27320, received on October 13, 2015 (Seq. No. 0006)
- Actavis Laboratories, Inc. proposed REMS for Fentanyl Sublingual tablets (ANDA 207338) in DMF#27320 received on December 10, 2014 (Seq. No. 0013) Transmucosal Immediate-Release Fentanyl Products REMS, approved on December 24, 2014.

3 RESULTS OF THE REVIEW OF PROPOSED RISK EVALUATION AND MITIGATION

The Sponsor did not propose any revisions to the TIRF REMS document, appended materials, or the REMS Supporting Document. The Sponsor reports that they are part of the single shared system REMS for TIRF products. It was confirmed via email from

TIRF REMS Industry Group (TRIG) that Actavis is part of the TRIG, and thus has access to the most current approved TIRF REMS documents which were submitted to the DMF and referenced by the Sponsor as stated in the Regulatory History (see Section 1.2).

The Medication Guide will be reviewed under separate cover by OGD Division of Labeling Review.

4 DISCUSSION AND CONCLUSION

As stipulated in FDAAA, a drug that is subject of an abbreviated new drug application is subject to the elements to assure safe use as required for the listed drug. The listed drug and the ANDA shall use a SSS.

This SSS TIRF REMS drug master file (DMF) 27320 contains the currently approved TIRF REMS document and appended materials as stipulated by the Agency on December 24, 2014 (approval date of most recent TIRF REMS modification). DRISK has reviewed the attached REMS and appended materials for fentanyl sublingual tablet (ANDA 203557) and finds it acceptable.

5 RECOMMENDATIONS

DRISK recommends approval of the TIRF REMS for fentanyl sublingual tablets (ANDA 207338), as appended to this review provided that the Office of Generic Drugs (OGD) Division of Labeling determines the Medication Guide is adequate prior to the approval of the application.

Upon approval, the list of approved products will be updated on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

If a classwide TIRF REMS modification is approved between the date of this review and action being taken on this application, this REMS review will no longer be applicable and the REMS should be considered deficient.

6 ATTACHMENTS

TIRF REMS document and appended materials

Initial REMS approval: 12/2011

Most recent modification: 12/2014

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF) RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

II. REMS ELEMENTS

A. Medication Guide

The product-specific TIRF Medication Guide will be dispensed with each TIRF prescription in accordance with 21 CFR 208.24.

The Medication Guides for TIRF medicines are part of the TIRF REMS Access program and will be available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified.

a. TIRF sponsors will ensure that healthcare providers who prescribe TIRF medicines for **outpatient** use are specially certified.

b. To become certified to prescribe TIRF medicines, prescribers will be required to enroll in the TIRF REMS Access program. Prescribers must complete the following requirements to be enrolled:

i. Review the TIRF REMS Access education materials (*TIRF REMS Access Education Program*), including the Full Prescribing Information (FPI) for each TIRF medicine, and successfully complete the Knowledge Assessment (*Knowledge Assessment).*

ii. Complete and sign the *Prescriber Enrollment Form.* In signing the *Prescriber Enrollment Form*, each prescriber is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.

b) I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations

where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.

c) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

e) I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the FPI, such as acute or postoperative pain, including headache/migraine.

f) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

g) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

h) I will provide a Medication Guide for the TIRF medicine that I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with, my patient or their caregiver.

i) I will complete and sign a TIRF REMS Access *Patient-Prescriber Agreement Form* with each new patient, before writing the patient's first prescription for a TIRF medicine, and **renew the agreement every two (2) years.**

j) I will provide a completed, signed copy of the *Patient-Prescriber Agreement Form* to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

k) At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

l) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.

m) I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

In signing the *Patient-Prescriber Agreement Form*, the prescriber documents the following:

1) I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.

2) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.

3) I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.

4) I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.

5) If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.

6) I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.

7) I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of TIRF medicines including communication of the following safety messages:

   A. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.

   B. NEVER share your TIRF medicine.

   C. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.

   D. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in

the product's Medication Guide.

I will ensure that the patient and/or caregiver understand that, in signing the *Patient-Prescriber Agreement Form*, they document the following:

1) My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.

2) I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.

3) I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock, for my constant pain, then I must also stop taking my TIRF medicine.

4) I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.

5) I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me to take it.

6) I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.

7) I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.

8) I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

9) I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine as soon as I no longer need it.

10) I understand that selling or giving away my TIRF medicine is against the law.

11) I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.

12) I have reviewed the "Patient Privacy Notice for the TIRF REMS Access

Program" and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in that document, with the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

c. Prescribers are required to re-enroll every two (2) years. Additionally, prescribers must re-counsel their patients and complete a new Patient-Prescriber Agreement Form every two (2) years.

d. TIRF Sponsors will:

   i. Ensure that prescriber enrollment can successfully be completed via the TIRF REMS Access website, or by mailing or faxing the forms.

   ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to prescribers. These materials are appended:

   - *TIRF REMS Access Prescriber Program Overview*
   - *TIRF REMS Access Education Program*
   - *Knowledge Assessment*
   - *Prescriber Enrollment Form*
   - *Patient-Prescriber Agreement Form*
   - *TIRF REMS Access Patient and Caregiver Overview*
   - *Frequently Asked Questions (FAQs)*
   - *TIRF REMS Access Website*

   iii. Ensure that prescribers have successfully completed the Knowledge Assessment, and ensure that enrollment forms are complete before activating a prescriber's enrollment in the TIRF REMS Access program.

   iv. Ensure that prescribers are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, are certified to prescribe TIRF medicines.

   v. Monitor education and enrollment requirements for prescribers and may inactivate non-compliant prescribers. Upon initial activation, prescribers remain active until inactivation occurs or expiration of the enrollment period.

   vi. Ensure that prior to the first availability of the TIRF REMS Access program/website, *Dear Healthcare Provider Letters* will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they

must enroll in the TIRF REMS Access program. The letters will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Healthcare Provider Letter* *is* part of the TIRF REMS Access program and is appended.

2. TIRF medicines will only be dispensed by pharmacies that are specially certified.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed by certified pharmacies. To become certified to dispense TIRF medicines, each pharmacy must be enrolled in the TIRF REMS Access program.

b. Each pharmacy will be required to designate an authorized pharmacy representative (chain and closed system outpatient pharmacies) or authorized pharmacist (independent outpatient and inpatient pharmacies) to complete enrollment on behalf of the pharmacy(s).

c. For the purposes of this REMS, there are different requirements for :

- **Outpatient Pharmacies**
  - i. **Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chain stores) in the TIRF REMS Access program.
  - ii. **Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.
  - iii. **Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that use a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program.
- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

d. ***Chain and Independent Outpatient Pharmacy(s):***

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **chain or independent outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program)* and successfully complete the *Knowledge Assessment*.

ii. Ensure the pharmacy enables its pharmacy management system to support communication with the TIRF REMS Access program system, using established telecommunication standards, and runs the standardized validation test transaction to validate the system enhancements.

iii. Complete and sign the *Independent Outpatient Pharmacy Enrollment Form* or the *Chain Outpatient Pharmacy Enrollment Form* for groups of associated pharmacies. In signing the *Independent Outpatient Pharmacy Enrollment Form or Chain Outpatient Pharmacy Enrollment Form,* the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program.* This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose of TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that TIRF medicines will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.

i) I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.

j) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

m) I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

n) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies.

o) I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Note: The '*or the designated chain pharmacy cash bin'* language will not be included in the attestation on the Independent Outpatient Pharmacy Enrollment Form

e. *Closed System Outpatient Pharmacies*:

The authorized pharmacist/pharmacy representative must complete the following requirements to enroll their **closed system outpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the *Knowledge Assessment*.

ii. Complete and sign the *Closed System Outpatient Pharmacy Enrollment Form*. In signing the *Closed System Outpatient Pharmacy Enrollment Form*, the authorized closed system outpatient pharmacy representative is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*. This training should be documented and is subject to audit.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located

on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.

g) I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.

h) I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated from the program.

i) I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines

j) I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

k) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

f. *Inpatient Pharmacies:*

The authorized pharmacist must complete the following requirements to successfully enroll their **inpatient pharmacy:**

i. Review the TIRF REMS Access Education Program (*TIRF REMS Access Education Program*) and successfully complete the pharmacy *Knowledge Assessment.*

ii. Complete and sign the *Inpatient Pharmacy Enrollment Form*. In signing the *Inpatient Pharmacy Enrollment Form*, the authorized pharmacist is required to acknowledge the following:

a) I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.

b) I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the *TIRF REMS Access Education Program*.

c) I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.

d) I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.

e) I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.

f) I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients, as described in section B.2.d, above.

g) I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.

h) I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program, as described in section B.1 of this REMS.

i) I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.

j) I understand that our pharmacy will not sell, loan or transfer any TIRF inventory to any other pharmacy, institution, distributor, or prescriber.

k) I understand that TIRF medicines can only be obtained from

wholesalers/distributors that are enrolled in the TIRF REMS Access program.

l) I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.

m) I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

g. Pharmacies (authorized pharmacist) are required to re-enroll every two (2) years.

h. TIRF Sponsors will:

i. Ensure that pharmacy enrollment can successfully be completed via the TIRF REMS Access website, by mailing or faxing the forms.

ii. Ensure that, as part of the enrollment process, the following materials that are part of the TIRF REMS Access program are available to pharmacies. These materials are appended:

- The TIRF REMS Access Program Overview (*Independent Outpatient Pharmacy, Chain Outpatient Pharmacy, Closed System Outpatient Pharmacy* or *Inpatient Pharmacy*, as applicable)
- *TIRF REMS Access Education Program*
- *Knowledge Assessment*
- *Pharmacy Enrollment Form (Independent Outpatient, Chain Outpatient, Closed System Outpatient, or Inpatient, as applicable)*
- *Frequently Asked Questions (FAQs)*
- *TIRF REMS Access Website*

iii. Ensure that all enrollment forms are complete, and that the authorized pharmacist has successfully completed the Knowledge Assessment before activating a pharmacy's enrollment in the TIRF REMS Access program.

iv. For **chain and independent outpatient pharmacies** only, TIRF Sponsors will also ensure that the configurations to the pharmacy management system have been validated before enrolling a pharmacy in the TIRF REMS Access program.

v. For **closed system outpatient pharmacies** only, TIRF Sponsors will ensure that, prior to authorizing a pharmacy's enrollment as a closed system outpatient pharmacy, the pharmacy meets the requirements of being deemed a closed system outpatient pharmacy (see II.B.2.c)

vi. Ensure that pharmacies are notified when they are successfully enrolled in the TIRF REMS Access program, and therefore, certified to dispense TIRF medicines.

vii. Monitor education and enrollment requirements for pharmacies and inactivate non-compliant pharmacies. Upon initial activation of enrollment, pharmacies remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

viii. Ensure that prior to first availability of the TIRF REMS Access program/website, *Dear*

Pharmacy Letters will be sent (one for inpatient pharmacies and one for outpatient pharmacies). The target audience for the letter will include outpatient and inpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and the requirements of the TIRF REMS Access program. The letter will be available on the TIRF REMS Access website for 1 year from the date of the mailing.

The *Dear Pharmacy Letters (Outpatient and Inpatient)* are part of the TIRF REMS Access program. These materials are appended.

3. TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

a. TIRF Sponsors will ensure that TIRF medicines will only be dispensed for outpatient use if there is documentation in the TIRF REMS Access program system that the dispensing pharmacy and prescriber are enrolled and active, and the patient is not inactive in the TIRF REMS Access program.

b. Patients are passively enrolled in the TIRF REMS Access program when their first TIRF medicine prescription is processed at the pharmacy. Patients may continue to receive TIRF medicines while passively enrolled, for up to ten working days, as described in section II.C.5. Prescribers and outpatient pharmacies (including closed system outpatient pharmacies) are enrolled, as previously described in sections B.1 and B.2, respectively.

c. For **chain and independent outpatient pharmacies**: Prior to dispensing TIRF medicines, enrolled outpatient pharmacies will electronically verify documentation of the required enrollments by processing the TIRF prescription through their pharmacy management system.

   i. If the required enrollments are verified, a unique authorization code will be issued to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, the TIRF REMS Access program system will reject the prescription (prior to a claim being forwarded to the payer) and the pharmacy will receive a rejection notice.

d. For **closed system outpatient pharmacies:** prior to dispensing TIRF medicines, enrolled closed system outpatient pharmacies will verify documentation of the required enrollments by contacting the TIRF REMS Access program at 1-866-822-1483, or via fax, and providing the required information from the TIRF prescription.

   i. If the required enrollments are verified, the TIRF REMS Access program will provide a unique authorization code to allow processing and dispensing of the prescription to the patient.

   ii. If one or more of the required enrollments cannot be verified, a rejection reason, and information regarding how to resolve the rejection, will be provided.

e. Following initial activation, patient PPAFs remain active until a trigger for inactivation occurs. Triggers for PPAF inactivation include:

   i. The patient has not filled a prescription for more than six (6) months.

ii. The PPAF has expired.

iii. The patient is deceased.

iv. The patient chooses to no longer participate in the TIRF REMS Access program.

f. If an active patient transfers from an enrolled prescriber to a non-enrolled or inactive prescriber, the TIRF REMS Access program cannot fill the prescription for TIRF medicines until the new prescriber is active in the TIRF REMS Access program.

g. A patient may have more than one current prescriber (e.g., pain management specialist, primary care physician) provided that prescriptions for TIRF medicines are not for the same or overlapping period of treatment.

h. Documentation and verification of safe-use conditions are not required for prescriptions ordered within an inpatient healthcare setting and given to an inpatient.

C. Implementation System

1. TIRF Sponsors will ensure that wholesalers/distributors who distribute TIRF medicines are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

2. The wholesaler/distributor enrollment process is comprised of the following steps that must be completed by the distributor's authorized representative, prior to receiving TIRF medicine inventory for distribution:

   a. Review the distributor TIRF REMS Access program materials

   b. Complete and sign the *Distributor Enrollment Form* and send it to the TIRF Sponsors (by fax or mail). In signing the *Distributor Enrollment Form*, each wholesaler/distributor is required to indicate they understand that TIRF medicines are available only through the TIRF REMS Access program and acknowledges that they must comply with the following program requirements:

      i. The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.

      ii. The Wholesaler/Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been validated in the TIRF REMS Access program.

      iii. The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies.

      iv. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements.

   c. TIRF Sponsors will ensure that all forms are complete prior to enrolling a distributor in the TIRF REMS Access program.

   d. TIRF Sponsors will notify distributors when they are enrolled in the TIRF REMS Access program and, therefore, able to distribute TIRF medicines.

e. Upon initial activation, distributors remain active until an action of inactivation occurs, expiration of the enrollment period, or failure to comply with the pharmacy enrollment verification obligations. If a previously active distributor becomes inactive, the distributor may become active again by completing the distributor enrollment process in its entirety.

f. Distributors will be re-educated and re-enrolled in the TIRF REMS Access program every two (2) years.

g. The following distributor materials are part of the TIRF REMS Access program. These materials are appended:

- *Dear Distributor Letter*
- *Distributor Enrollment Form*
- *Frequently Asked Questions*

3. TIRF Sponsors will maintain a database of all enrolled entities (prescribers, pharmacies, patients, and distributors) and their status (i.e. active or inactive), and will monitor and evaluate implementation of the TIRF REMS Access program requirements.

4. For **chain and independent outpatient pharmacies,** TIRF Sponsors will develop a TIRF REMS Access program system that uses existing pharmacy management systems that allow for the transmission of TIRF REMS Access information using established telecommunication standards. The TIRF REMS Access program system will incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to support the expansion or modification of the TIRF REMS Access program requirements, if deemed necessary in the future.

5. For **closed system outpatient pharmacies,** TIRF Sponsors will develop a system to allow enrollment and verification of safe use conditions through a telephone system and/or fax. TIRF Sponsors will monitor distribution data and prescription data to ensure that only actively enrolled distributors are distributing, actively enrolled pharmacies are dispensing, and actively enrolled prescribers for outpatient use are prescribing TIRF medicines. Additionally, TIRF Sponsors will monitor to ensure that, when dispensing in an outpatient setting, TIRF medicines are only being dispensed to actively enrolled patients of actively enrolled prescribers. Corrective action or inactivation will be instituted by TIRF Sponsors if non-compliance is found.

6. TIRF Sponsors will monitor prescribers' compliance with the requirement to complete a *Patient-Prescriber Agreement Form* with each TIRF patient, and to submit it to the TIRF REMS Access program within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed *Patient-Prescriber Agreement Form* is received. This will be accomplished by reconciling the Patient-Prescriber Agreements submitted to the TIRF REMS Access program with patient enrollment data captured through the pharmacy management system for **chain and independent outpatient pharmacies** or through the call center for **closed system outpatient pharmacies**.

7. TIRF Sponsors will monitor and evaluate all enrolled outpatient pharmacies (including closed system outpatient pharmacies), distributors, and the TIRF REMS Access program vendors to validate the necessary system upgrades and ensure the program is implemented as directed.

8. TIRF Sponsors will evaluate enrolled inpatient pharmacies' compliance with the TIRF REMS Access program requirements through surveys.
9. TIRF Sponsors will maintain a call center to support patients, prescribers, pharmacies, and distributors in interfacing with the TIRF REMS Access program.
10. TIRF Sponsors will ensure that all materials listed in or appended to the TIRF REMS Access program will be available through the TIRF REMS Access program website www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.
11. TIRF Sponsors will notify pharmacies, prescribers, and distributors of forthcoming enrollment expiration and the need to re-enroll in the TIRF REMS Access program. Notifications for patients will be sent to the patient's prescriber.
12. If there are substantive changes to the TIRF REMS Access program, TIRF Sponsors will update all affected materials and notify pharmacies, prescribers, and distributors of the changes, as applicable. Notifications for patients will be sent to the patient's prescriber. Substantive changes to the TIRF REMS Access program are defined as:
    a. Significant changes to the operation of the TIRF REMS Access program.
    b. Changes to the Prescribing Information and Medication Guide that affect the risk-benefit profile of TIRF medicines.
13. Based on monitoring and evaluation of the REMS Elements to Assure Safe Use, TIRF Sponsors will take reasonable steps to improve implementation of these elements and to maintain compliance with the TIRF REMS Access program requirements, as applicable.

III. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

TIRF NDA Sponsors will submit REMS Assessments to the FDA at 6 and 12 months from the date of the initial REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Sponsors will submit each assessment so that it will be received by the FDA on or before the due date.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Prescribers

To prescribe TIRF medicines for outpatient use, Prescribers must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

NOTE: There are different requirements for inpatient prescribers that only prescribe TIRF medicines for inpatient use. For inpatient administration (e.g. hospitals, in-hospital hospices, and long-term care facilities that prescribe for inpatient use), of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Only the inpatient pharmacy and distributors are required to be enrolled to be able to order and dispense TIRF medicines for inpatient use. Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Overview of the TIRF REMS Access Program for Prescribing to Outpatients: Steps for Enrollment and Program Requirements

Prescriber Education & Enrollment (Outpatient Use)

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS program do I need to enroll in the shared TIRF REMS Access Program?

All prescriber enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following three sections provide detailed information on the Enrollment Process (Section 1), the Patient Program Requirements (Section 2), and the Prescribing Process (Section 3) for outpatient prescribing of TIRF medicines.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Create an account and complete registration at www.TIRFREMSaccess.com.
2. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
3. Complete and submit a Prescriber Enrollment form.

Detailed Enrollment Process

Step 1: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account and complete registration at www.TIRFREMSaccess.com.

  How do I create an account and complete the TIRF REMS Access registration on-line?
  - Select the 'Create My Account' button on the home page
  - Complete the Create Account Information section
  - Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' question
  - Create User ID and Password and select 'Create My Account'
  - Select 'Prescriber' as the option to best describe you and select 'Continue'

- Complete required fields on the Prescriber Registration page and select 'Submit' to continue
- Complete required fields in the 'Site Information' section by adding your site and select 'Submit'

Step 2: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully
- Select 'Complete Enrollment' to continue

Step 3: Complete and submit Prescriber Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Prescriber Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to review the demographic information previously submitted, read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Patient Program Requirements

Summary of Patient Program Requirements

1. Identify appropriate patients
2. Counsel patients
3. Complete and submit the TIRF REMS Access Program Patient-Prescriber Agreement Form

Detailed Patient Program Requirements Process

Step 1: Identify appropriate patients

- Identify appropriate patients based on the guidance provided in the TIRF REMS Access Education Program and the product-specific Full Prescribing Information. Full Prescribing Information is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 2: Counsel Patients

- Counsel the patient about the benefits and risks of TIRF medicines and together review the appropriate product-specific Medication Guide. A Patient and Caregiver Overview is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Step 3: Complete and submit the TIRF REMS Access Patient-Prescriber Agreement Form

- Complete the TIRF REMS Access Program Patient-Prescriber Agreement Form, for each new patient, which must be signed by both you and your patient (not required for inpatients).

NOTE: A prescriber must be enrolled in the TIRF REMS Access program to submit a Patient-Prescriber Agreement Form for a patient.

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form by fax?

- Obtain a TIRF REMS Access Patient-Prescriber Agreement Form. A printable version of the Patient-Prescriber Agreement Form is available on-line at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Review the TIRF REMS Access Patient-Prescriber Agreement Form with your patient.
- Complete Prescriber required fields.
- Have the patient or caregiver complete the patient required fields.
- Submit Patient-Prescriber Agreement Form by fax to **1-866-822-1487.**

How do I complete the TIRF REMS Access Patient-Prescriber Agreement Form online?

- Log in to the TIRF REMS Access program from the home page by entering in your User ID and Password
- Select the heading labeled 'My Account'
- Select the 'PPAF' link
- Review the TIRF REMS Access Patient-Prescriber Agreement Form
- Enter your electronic signature, today's date, and check the attestation box
- Enter the required patient information
- Have the patient enter their electronic signature, today's date, and check the attestation box
    - (NOTE: If applicable, a Patient Representative can enter in their information in the required section on behalf of the patient)
- Print off two copies of the form by selecting the 'Print' button
- Provide one copy to the patient and keep one for your records
- Select the 'Submit' button to submit the PPAF for the patient
- You can print the confirmation by selecting the 'Print Confirmation' button

Section 3: Summary of Prescribing Process

1. Write TIRF medicine prescription.
2. Help patient find an enrolled pharmacy.

Detailed Prescribing Process

Step 1: Write TIRF medicine prescription

- Write a prescription for the appropriate TIRF medicine.

Step 2: Help patient find an enrolled pharmacy

- Help each patient find pharmacies which are enrolled in the TIRF REMS Access program. A list of enrolled pharmacies can be found on www.TIRFREMSaccess.com, or by calling **1-866-822-1483**.
- Inform patients that they can also find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or

- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Transmucosal Immediate Release Fentanyl (TIRF) Products Risk Evaluation and Mitigation Strategy (REMS)

TIRF REMS Access Program

Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl buccal tablet)
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys® (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

TIRF REMS Access Education Program:

- Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.
- The Education Program and enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.
- Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.
- Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

- This Education Program contains key safety information critical for minimizing the risks associated with TIRF medicines.
- The program will address:
  - Appropriate patient selection
  - Understanding each patient's risk factors for misuse, abuse, addiction and overdose
  - Dosage and administration
  - Patient counseling
  - Effective patient management and follow-up

TIRF REMS Access Education Program

Overview (cont.)

- Information on the TIRF REMS Access program requirements and operations is provided in the TIRF REMS Access program overviews for prescribers and pharmacies, which can be accessed at www.TIRFREMSaccess.com.
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**
  - The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.
- TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids.

Appropriate Patient Selection (cont.)

Definition of Opioid Tolerance:

- Patients considered **opioid-tolerant** are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - OR an equianalgesic dose of another oral opioid
- TIRF medicines are intended to be used only in the care of opioid-tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Appropriate Patient Selection (cont.)

Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients.
- TIRF medicines are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain. Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.
- TIRF medicines are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some fentanyl products.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, Addiction and Overdose

- TIRF medicines contain fentanyl, an opioid agonist and Schedule II controlled substance. TIRF medicines can be abused in a manner similar to other opioid agonists, legal and illicit.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Concerns about abuse and addiction should not prevent the proper management of pain.

Determine Patient-Specific Risk Factors

1. Risk of Misuse, Abuse, and Addiction and Overdose (cont.)

- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.
- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- Manage the handling of TIRF medicines to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting, and as required by law.

Determine Patient-Specific Risk Factors

2. Accidental Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- TIRF medicines must be stored safely and kept out of reach of children of all ages ***at all times***, including toddlers through teens.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.
- Any accidental exposure can be fatal. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

Determine Patient-Specific Risk Factors

3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CPY3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may result in potentially dangerous increases in fentanyl plasma concentrations, which could increase or prolong the drug effects and may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.

Dosage and Administration General

- **Patients beginning treatment with a TIRF medicine MUST begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine.** Carefully consult the initial dosing instructions in each product's specific Full Prescribing Information.

Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.

Dosage and Administration General

Appropriate Conversion

- **As a result of these differences, the conversion of a TIRF medicine for any other TIRF medicine may result in fatal overdose.**
- Converting from one TIRF medicine to a different TIRF medicine **must not be done on a microgram-per-microgram basis** and, must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine.
    - The only exception is for substitutions between a branded TIRF medicine and its generic equivalents.
- For patients being converted specifically from Actiq to Fentora, Actiq to Subsys, and Actiq to Abstral, you must refer to the Full Prescribing Information for detailed instructions.

Maintenance/Dose Adjustments for all TIRF Medicines

- Once a successful dose is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

Products** Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough pain episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Products** Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis® (fentanyl buccal soluble film)	Always 200 mcg.	**ONSOLIS should be used only once per breakthrough cancer pain episode**; i.e. ONSOLIS should not be redosed within an episode.	Patients must wait at least 2 hours before treating another breakthrough pain episode with ONSOLIS.	Titrate using **200 mcg ONSOLIS film increments.** Instruct patients not to use more than 4 films at once. When multiple films are used, **films should not be placed on top of each other** but may be placed on both sides of the mouth. If adequate pain relief is not achieved after 800 mcg (i.e. **four** 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using **one** 1200 mcg ONSOLIS film.
Subsys® (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ – please see Full Prescribing Information.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain.	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**

- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

Tell the patient:

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.
    - **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**

Patient Counseling

Tell the patient (cont.):

- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You much take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*

Patient Counseling

Tell the patient (cont.):

- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits:**

- Assess appropriateness of dose, and make any necessary dose adjustments to the TIRF medicine or of their around-the-clock opioid medicine.
- Assess for signs of misuse, abuse, or addiction.
- Be aware that abuse and addiction are separate and distinct from physical dependence and tolerance.
    - Abuse of opioids can occur in the absence of addiction, and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.
    - The possibility of physical and/or psychological dependence should be considered when a pattern of inappropriate behavior is observed.
- Careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

A. 12 year old sarcoma patient, using transdermal fentanyl for her underlying persistent cancer pain.
B. Adult female with advanced breast cancer; on 60 mg of oral morphine daily for the past 4 weeks.
C. Adult male with advanced lung cancer, his underlying persistent pain is managed with 25 mcg/hour transdermal fentanyl patches for the past 3 months.
D. Adult male with multiple myeloma who has bone pain currently managed with 50 mg oral oxymorphone daily for the last 2 weeks.

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

Certain factors may increase the risk of abuse and/or diversion of opioid medications. Which of the following is most accurate?

Select one option.

A. A history of alcohol abuse with the patient or close family members.
B. The patient has a household member with a street drug abuse problem.
C. The patient has a history of prescription drug misuse.
D. All of the above.

Question 4

A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. How should the prescriber proceed?

Select one option.

A. The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
B. The prescriber must not convert from the equivalent TIRF medicine dose to another TIRF medicine because they have different absorption properties and this could result in a fentanyl overdose.
C. Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
D. The prescriber should base the starting dose of the newly prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?

Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?

Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between specific TIRF medicines has been established and is described in the Prescribing Information for which products?
Select one option.

A. Actiq to Abstral
B. Actiq to Fentora
C. Actiq to Subsys
D. All of the above

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Prescriber Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
8. I will provide a Medication Guide for the TIRF medicine I intend to prescribe to my patient or their caregiver and review it with them. If I convert my patient to a different TIRF medicine, the Medication Guide for the new TIRF medicine will be provided to, and reviewed with my patient or their caregiver.
9. I will complete and sign a TIRF REMS Access Patient-Prescriber Agreement (PPAF) with each new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.
11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.

Prescriber Name* (please print):_____

12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** _____ **DEA Number*** _____
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***
Site Name* _____ **Address*** _____ **City*** _____ **State*** _____ **ZIP*** _____ **Phone Number*** _____ **Fax Number*** _____ ***Required Fields**	**State License Number*** _____ **State Issued*** **DEA Number***

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Patient-Prescriber Agreement Form

For real-time processing of the Patient Prescriber Agreement Form go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax all pages to 1-866-822-1487.

As the prescriber of any TIRF medicine in this TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program, I acknowledge that:

1. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around the clock opioid therapy for their underlying persistent pain.
2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for one week or longer.
4. I have provided to, and reviewed with, my patient or their caregiver the Medication Guide for the TIRF medicine I intend to prescribe.
5. If I change my patient to a different TIRF medicine, I will provide the Medication Guide for the new TIRF medicine to my patient or my patient's caregiver, and I will review it with them.
6. I understand that if I change my patient to a different TIRF medicine, the initial dose of that TIRF medicine for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations.
7. I have counseled my patient or their caregiver about the risks, benefits, and appropriate use of the TIRF medicine including communication of the following safety messages:
   a. If you stop taking your around-the-clock pain medicine, you must stop taking your TIRF medicine.
   b. NEVER share your TIRF medicine.
   c. Giving a TIRF medicine to someone for whom it has not been prescribed can result in a fatal overdose.
   d. TIRF medicines can be fatal to a child; used and unused dosage units must be safely stored out of the reach of children living in or likely to visit the home and disposed of in accordance with the specific disposal instructions detailed in the product's Medication Guide.

Prescriber (*Required Fields):

Prescriber Signature* _____ **Date** _____
First Name* _____ **Last Name*** _____
DEA Number* _____ **National Provider Identifier (NPI)*** _____
Fax* _____

Prescriber Name* (please print):_____

As the patient being prescribed a TIRF medicine, or a legally authorized representative, I acknowledge that:

1. My prescriber has given me a copy of the Medication Guide for the TIRF medicine I have been prescribed, and has reviewed it with me.
2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines.
3. I understand that if I stop taking my around-the-clock opioid pain medicine for my constant pain, I must stop taking my TIRF medicine.
4. I understand how I should take this TIRF medicine, including how much I can take, and how often I can take it. If my prescriber prescribes a different TIRF medicine for me, I will ensure I understand how to take the new TIRF medicine.
5. I understand that any TIRF medicine can cause serious side effects, including life-threatening breathing problems which can lead to death, especially if I do not take my TIRF medicine exactly as my prescriber has directed me.
6. I agree to contact my prescriber if my TIRF medicine does not relieve my pain. I will not change the dose of my TIRF medicine myself or take it more often than my prescriber has directed.
7. I agree that I will never give my TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
8. I will store my TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.
9. I have been instructed on how to properly dispose of my partially used or unneeded TIRF medicine remaining from my prescription, and will dispose of my TIRF medicine properly as soon as I no longer need it.
10. I understand that selling or giving away my TIRF medicine is against the law.
11. I have asked my prescriber all the questions I have about my TIRF medicine. If I have any additional questions or concerns in the future about my treatment with my TIRF medicine, I will contact my prescriber.
12. I have reviewed the "Patient Privacy Notice for the TIRF REMS Access Program" below and I agree to its terms and conditions which allow my healthcare providers to share my health information, as defined in this document to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors for the limited purpose of managing the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program For the purpose of the TIRF REMS Access program, my name, address, telephone number and prescription information make up my "Health Information." My doctors, pharmacists, and healthcare providers may share my Health Information with the TIRF REMS Access program, and contractors that manage the TIRF REMS Access program. My Health Information will be kept in a secure database, and may only be used as stated below.

I allow the TIRF REMS Access program to receive, use, and share my Health Information in order to:

I. Enroll me in the TIRF REMS Access program and manage my participation (including contacting me) in the TIRF REMS Access program.

II. Provide me with educational information about the TIRF REMS Access program.

III. Contact my healthcare providers to collect my Health Information for the TIRF REMS Access program.

Prescriber Name* (please print):_____

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to evaluate the proper use of TIRF medicines and report to the FDA about the effectiveness of the TIRF REMS Access program.

I understand that I am not required to sign this written approval. However, if I do not sign, I will not be able to enroll in the TIRF REMS Access program and will not be able to receive TIRF medicines.

I understand that I may withdraw this written approval at any time by faxing a signed, written request to the TIRF REMS Access program at 1-866-822-1487. Upon receipt of this written request, the TIRF REMS Access program will notify my healthcare providers about my request. My healthcare providers will no longer be able to share my Health Information with the TIRF REMS Access program once they have received and processed that request. However, withdrawing this written approval will not affect the ability of the TIRF REMS Access program to use and share my Health Information that it has already received to the extent allowed by law. If I withdraw this written approval, I will no longer be able to participate in the TIRF REMS Access program and will no longer be able to receive TIRF medicines.

The sponsors of the TIRF REMS Access program agree to protect my information by using and sharing it only for the purposes described.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the list of currently approved TIRF products located on the TIRF REMS website at www.TIRFREMSaccess.com/TirfUI/ProductList.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Overview of Steps for the TIRF REMS Access Program for Patients

Step 1
Participating in the Program

- Your healthcare provider will talk with you about the best way to use your TIRF medicine, including the risks and how to store and dispose of it correctly. Your healthcare provider will also review written information about your TIRF medicine with you. This written information is called the Medication Guide. Your healthcare provider will give you a copy of the Medication Guide - **read and keep it.**
- Together you and your healthcare provider will complete and sign the TIRF REMS Access Patient-Prescriber Agreement Form. The form gives you important information you need to know and understand before taking a TIRF medicine.
- You will need to complete a new Patient-Prescriber Agreement Form every two (2) years. You will be notified by your healthcare provider in advance of the need to re-enroll.
- Your healthcare provider will submit a copy to the TIRF REMS Access program.
- Your healthcare provider will also give you a copy and keep a copy in your medical records.

Step 2
Getting a Prescription

- Once you have signed the Patient-Prescriber Agreement Form your healthcare provider will write you a prescription for your TIRF medicine.
- Your healthcare provider can help you find a participating pharmacy to have your prescription filled, because only pharmacies that are in the TIRF REMS Access program can dispense TIRF medicines. You can also find a participating pharmacy by calling the TIRF REMS Access program at 1**-866-822-1483**.

Step 3
Having your Prescription Filled

- The pharmacy will check to make sure that your healthcare provider is enrolled in the TIRF REMS Access program. Only then is the pharmacy allowed to dispense the TIRF medicine to you.
- You will be automatically enrolled in the TIRF REMS Access program when **y**ou receive your first prescription for a TIRF medicine.
- The pharmacy will remind you how to take, store and dispose of your TIRF medicine correctly.
- The pharmacy will also give you a copy of the Medication Guide. Read and keep the Medication Guide.

Additional Program Information

For more information about your TIRF medicine, you can find a copy of the Medication Guide at www.TIRFREMSaccess.com or you can call the TIRF REMS Access program at **1-866-822-1483**.

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs

What is a TIRF Medicine?
TIRF medicines are transmucosal immediate release fentanyl prescription medicines used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for pain. Click here to see a full list of TIRF medicines.

What is a REMS?
REMS stands for "Risk Evaluation and Mitigation Strategy." A Risk Evaluation and Mitigation Strategy (REMS) is a risk management program required by the FDA to ensure that the benefits of a drug outweigh the risks. FDA has determined that a REMS is necessary for all marketed TIRF medicines.

What are the goals of the TIRF REMS Access Program?
The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

What are the components of the TIRF REMS Access program?
Because of the risk for misuse, abuse, addiction, and overdose, TIRF medicines are available only through a restricted program called the TIRF REMS Access program.

An overview of the requirements for prescribers, patients, pharmacies, and distributors is included below:

- **Healthcare providers** who prescribe TIRF medicines for outpatient use must review the prescriber educational materials, enroll in the REMS program, and commit to comply with the REMS requirements.
- **Patients** who are prescribed TIRF medicines in an outpatient setting, must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement Form with their healthcare provider to receive TIRF medicines. These patients will be enrolled by the pharmacy at the time their first prescription is filled.
- **Outpatient pharmacies** that dispense TIRF medicines for outpatient use must enroll in the program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Inpatient pharmacies** that dispense TIRF medicines for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- **Wholesalers and distributors** that distribute TIRF medicines must enroll in the program and commit to distributing only to authorized enrolled pharmacies.

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

What type of Outpatient Pharmacy is my pharmacy?

There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions. The difference is in how these pharmacies enroll in the program.

Independent Outpatient Pharmacy: Retail, mail order or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in the TIRF REMS Access program as a single pharmacy location.

Chain Outpatient Pharmacy: Retail, mail or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program.

Closed System Outpatient Pharmacy: Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at 1-866-822-1483 to discuss enrollment.

How does an Independent Outpatient Pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Independent Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transactions.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on chain outpatient pharmacy enrollment below.)

How does a Chain Outpatient Pharmacy enroll in the TIRF REMS Access program?

An authorized chain outpatient pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain outpatient pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system, using established

telecommunication standards, and must run the standardized validation test transactions. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How does a Closed System Outpatient Pharmacy enroll in the TIRF REMS Access program?
If you believe you are a closed system outpatient pharmacy, call the TIRF REMS Access program call center at **1-866-822-1483** to discuss enrollment.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Independent outpatient pharmacies and chain outpatient pharmacies may re-enroll online or by fax. Closed system outpatient pharmacies may re-enroll by fax only.

For re-enrollment online, go to the "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

For re-enrollment by fax, review the TIRF REMS Access program Education Materials and submit a new TIRF REMS Access Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

Chain and Independent Outpatient Pharmacy CASH Claim FAQs

What is the definition of a TIRF REMS CASH Claim?
The definition of a TIRF REMS CASH Claim is any claim for a TIRF medicine that is not electronically transmitted to a Third Party Insurance BIN using the pharmacy management system and established telecommunication standards. This includes claims for patients without prescription coverage or any paper claims submitted to a program for payment.

Does a TIRF REMS CASH claim need to be submitted to the TIRF REMS Access Program?
Yes, all TIRF prescriptions, including CASH claims and other claims (i.e. workers comp), must be submitted to the TIRF REMS Access program to validate the enrollment status of the prescriber, patient and pharmacy prior to dispensing TIRF medicine to the patient.

How do I submit a TIRF REMS CASH claim to the TIRF REMS Access Program?
Prior to dispensing TIRF medicines, transmit using the REMS CASH BIN 014780,to submit a CASH claim to the TIRF REMS Access program.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website at www.TIRFREMSaccess.com, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

How long is my enrollment effective in TIRF REMS Access?

Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?

A list of participating pharmacies can be found on the TIRF REMS Access website (www.TIRFREMSaccess.com) homepage under the link "Pharmacy Lookup". You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You may re-enroll via your "Enrollment Activity" tab on the TIRF REMS Access program website (www.TIRFREMSaccess.com). The "Enrollment Activity" tab allows you to:

- Add to, update, or delete your registration information on file.
- Review the TIRF REMS Access Education Program.
- Take the TIRF REMS Access Knowledge Assessment.
- Submit your enrollment form by providing your attestation and signature.

Alternatively, you may also complete re-enrollment via fax by reviewing the TIRF REMS Access program Education Materials and submitting a new TIRF REMS Access Enrollment Form and Knowledge Assessment into the TIRF REMS Access program at 1-866-822-1487. All TIRF REMS Access Education Materials and Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

How long is my enrollment effective in TIRF REMS Access?
Your enrollment is effective for two (2) years. You will be required to re-enroll in the TIRF REMS Access program every two (2) years if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

You can complete re-enrollment via fax by submitting a new TIRF REMS Access Enrollment Form into the TIRF REMS Access program at 1-866-822-1487. TIRF REMS Access Enrollment Forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader or by calling the TIRF REMS Access call center at **1-866-822-1483**.

What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines are available only through the TIRF REMS Access program and they will comply with the program requirements.

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Healthcare Provider:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy.** The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

Prescriber Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- Patients that have already signed a Patient-Prescriber Agreement Form on file will not have to sign another form until their two year enrollment is due.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com including the Full Prescribing Information for each product covered in this program, and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Prescriber Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS **Access program beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs and you intend to prescribe any of these products for outpatient use you must enroll in the TIRF REMS program.

For inpatient administration (e.g. hospitals, in-patient hospices, and long-term care facilities that dispense for inpatient use) of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Prescriber Program Overview
- TIRF REMS Access Education Program
- Knowledge Assessment Form
- Prescriber Enrollment Form
- Frequently Asked Questions

You can also access the following patient materials at www.TIRFREMSaccess.com or order them by calling 1-866-822-1483:

- An Overview for Patients and Caregivers
- Patient-Prescriber Agreement Form
- Frequently Asked Questions
- Full Prescribing Information and Medication Guides for each TIRF medicine

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

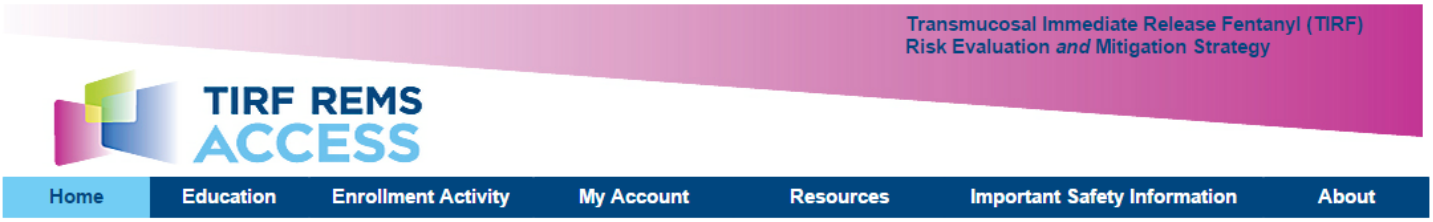
TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Home Page



Important Safety Information (ISI) is included on the bottom of the Home Page. To reduce the space and image distortion, ISI is not shown as part of Home Page in this document.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Independent Outpatient Pharmacies

To dispense TIRF medicines, your Independent Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Independent Outpatient Pharmacy?

For the purposes of this REMS, an independent outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail or institutional outpatient pharmacy having an authorized pharmacy representative that is responsible for ensuring enrollment and training of the pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location. Additionally, to qualify as an independent outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Options and Requirements for the TIRF REMS Access Program for Independent Outpatient Pharmacies

Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access Program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website and agreed to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Process (Section 2) for TIRF medicines in an independent outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment:

1. Select an individual to be your Authorized Independent Outpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Independent Outpatient Pharmacy Enrollment form.
5. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
6. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Independent Outpatient Authorized Pharmacist'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Independent Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and submit Independent Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Independent Outpatient Pharmacy Enrollment.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- Following completion of steps 1-4 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 6: Train Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 6 : Train Pharmacy Staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the pharmacy practice management system must populate the following fields in the pharmacy billing claim*:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name

    *Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Chain Outpatient Pharmacies

To dispense TIRF medicines, your Chain Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as a Chain Outpatient Pharmacy?

For the purposes of this REMS, a chain outpatient pharmacy is defined as an outpatient pharmacy such as a retail, mail order or institutional outpatient pharmacy having a chain headquarters that is responsible for ensuring enrollment and training of the pharmacy staff of all associated outpatient pharmacies. The chain headquarters will enroll multiple pharmacy locations (i.e.: chain stores) in the TIRF REMS Access program. Additionally, to qualify as a chain outpatient pharmacy, your pharmacy must use a pharmacy management system to electronically transmit the required validation and claim information to the TIRF REMS Access program using established telecommunication standards.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Inpatient Pharmacies” for more information.

Overview of the TIRF REMS Access Program for Chain Outpatient Pharmacies: Steps for Enrollment and Program Requirements

Chain Outpatient Pharmacy Education, Enrollment & Pharmacy Management Systems

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?

All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. If the authorized pharmacist or pharmacy representative logged onto the TIRF REMS Access program website, executed a TIRF REMS Access contract with their switch provider to agree to the shared program terms and conditions before September 12, 2012, your pharmacy is able to order and dispense all TIRF medications. If the authorized pharmacist or pharmacy representative has not agreed to the shared terms and conditions, your pharmacy will need to enroll in the TIRF REMS Access program (see how to enroll below).

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a chain outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Execute a TIRF REMS Access contract with your switch provider.
2. Select an individual to be your Authorized Chain Outpatient Pharmacy Representative.
3. Create an account and complete registration at www.TIRFREMSaccess.com
4. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
5. Complete and submit a Chain Outpatient Pharmacy Enrollment form
6. Enable the pharmacy management system to support communication with the TIRF REMS Access system.
7. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Execute a TIRF REMS Access contract with your switch provider

- Call the TIRF REMS Access program at **1-866-822-1483**.
- The TIRF REMS program will notify your switch provider and advise that a contract must be executed for participation in the program.

Your account executive will contact you directly and work with you to establish a contractual agreement.

Step 2: Select an individual to be your Authorized Chain Outpatient Pharmacy Representative

- Select an authorized chain outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration at the corporate level on behalf of your individual pharmacies.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt
- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Chain Outpatient Pharmacy – Authorized Chain Outpatient Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Chain Outpatient Pharmacy Registration page and select 'Submit' to continue

Step 4: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**.
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail).

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment', complete the Knowledge Assessment, and select 'Submit Assessment'
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 5: Complete and submit Chain Outpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Chain Outpatient Pharmacy Enrollment.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 6: Confirm the Pharmacy Management System supports communication with the TIRF REMS Access system

- A chain outpatient pharmacy is required to complete test transactions one time on behalf of all their stores. Following completion of steps 1-5 above, you will receive instruction on how to submit test transactions to the TIRF REMS Access program. Successful submission of the test transaction confirms the pharmacy management system supports communication with the TIRF REMS Access system.
- After successful completion of the test transactions you will receive enrollment confirmation.

Step 7: Train Pharmacy Staff

- Ensure that all chain outpatient pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain outpatient pharmacy in accordance to the chains' internal processes. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the Authorized Chain Outpatient Pharmacy Representative on the Chain Outpatient Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 7 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program prior to dispensing each TIRF prescription by submitting a pharmacy billing claim via the chain outpatient pharmacy practice management system. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation). Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the TIRF REMS Access program to confirm prescriber and patient enrollment the chain outpatient pharmacy practice management system must populate the following fields in the pharmacy billing claim*:

- Patient First Name,
- Patient Last Name,
- Patient Date of Birth,
- Patient ZIP / Postal Zone,
- Quantity Dispensed,
- Days Supply,
- Prescriber ID,
- Prescriber Last Name

*Use BIN 014780 for all cash and non-third party claims.

- If the prescriber or patient enrollment is not confirmed, or if any other rejection message is received that prevents the prescription from being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Step 3: Dispense TIRF Medication

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel Patient and Provide Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Closed System Outpatient Pharmacies

To dispense TIRF medicines, your Closed System Outpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment, while patients are on treatment, and to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a required Food and Drug Administration (FDA) restricted distribution program, because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your institution qualify as a Closed System Outpatient Pharmacy?

For the purposes of this REMS, a closed system outpatient pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system outpatient pharmacies.

NOTE: There are different requirements for outpatient pharmacies that support the process of electronically transmitting claim information, and for inpatient pharmacies that only dispense for inpatient use. Please refer to “An Overview for Chain Outpatient Pharmacies”, “An Overview for Independent Outpatient Pharmacies” or “An Overview for Inpatient Pharmacies” for more information. If you do not qualify as a closed system outpatient pharmacy, please refer to the requirements for the other type of pharmacies.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Dispensing Processes (Section 2) for TIRF medicines in a closed system outpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment Process

1. Confirm that your facility qualifies as a closed system outpatient pharmacy.
2. Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit a Closed System Outpatient Pharmacy Enrollment Form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Confirm your facility qualifies as a Closed System Outpatient Pharmacy

- Notify the TIRF REMS Access program by phone at **1-866-822-1483** or by email to information@TIRFREMSaccess.com that you are a closed system outpatient pharmacy.
- When your pharmacy is validated as a closed system outpatient pharmacy, a Closed System Outpatient Pharmacy Enrollment Form will be provided.

Step 2: Select an individual to be your Authorized Closed System Outpatient Pharmacy Representative

- Select an authorized closed system outpatient pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 3: Complete the TIRF REMS Access Education Program

- Review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- If Knowledge Assessment was completed on paper, Fax to **1-855-474-3062** or email the Knowledge Assessment to information@TIRFREMSaccess.com with enrollment form (see Step 4: Complete and submit enrollment form).

How do I complete the TIRF REMS Access Education Program online?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- 'Already enrolled via Fax and have an enrollment ID?' - Select No
- Create User ID and password and select the Create my Account button
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- In response to Question 2, select 'Pharmacy Staff'
- Review the content in the pop-up box and select 'Confirm' to continue

- Complete required fields in Pharmacy Staff details
- Select 'Other' from the dropdown list in the Chain Pharmacy name and populate the name of your closed system outpatient pharmacy organization in the 'Other' field and submit form
- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training
- Once you have completed the Education Program, select the 'Go To Knowledge Assessment' button and complete
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully

Step 4: Complete and Submit Enrollment Form

- Complete and return the Closed System Outpatient Pharmacy Enrollment Form by fax to **1-855-474-3062**. The authorized closed system outpatient pharmacy representative will receive an Enrollment Confirmation letter and instructions for enrolling dispensing locations within the closed system outpatient pharmacy by using a standard file template provided by the TIRF REMS Access program.
- If you did not complete the Education Program online then you need to submit the Knowledge Assessment form with the Enrollment form.
- Re-enroll every two (2) years**.** You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Step 5: Train Pharmacy Staff

- All closed system outpatient pharmacy staff involved in processing and dispensing of TIRF medications must be trained to dispense TIRF medicines in accordance with the TIRF REMS Access Education Program requirements available at www.TIRFREMSaccess.com.
- Ensure that this training is documented and retained by the closed system outpatient pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Section 2: Dispensing Process

Summary of Dispensing Process

1. Confirm pharmacy staff is trained.
2. Confirm patient and prescriber enrollment in TIRF REMS Access Program.
3. Dispense TIRF medication.
4. Counsel patient and provide medication guide.

Detailed Dispensing Process

Step 1: Confirm that the Pharmacy staff is trained

- Ensure all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to specifically dispense TIRF medicines in accordance with the TIRF REMS Access program requirements available at www.TIRFREMSaccess.com. (see Section 1, Step 5 : Train pharmacy staff).

Step 2: Confirm prescriber and patient enrollment:

Prior to dispensing each TIRF medicine prescription, confirm that the prescriber and patient are enrolled in the TIRF REMS Access program by contacting the TIRF REMS Access program by phone at **1-866-822-1483** or fax at **1-855-474-3062**. This includes third party insurance claims, cash claims and any other claims (i.e.: workers compensation).

- **To confirm enrollment confirmation by phone:**
  - Contact the TIRF REMS Access program at **1-866-822-1483** and select option **#2**.
  - Provide the following required data from the TIRF prescription to obtain an authorization to dispense:

Dispensing Pharmacy DEA	Patient Date of Birth	Rx Date of Service
Dispensing Pharmacy NPI	Patient First Name	Rx Number
Dispensing Pharmacy Phone #	Patient Last Name	Rx NDC
Dispensing Pharmacy Fax #	Patient Zip Code	Days Supply
Prescriber DEA or NPI	Prescriber Last Name	Quantity for Dispense

    - If validated, you will be supplied a *prescription authorization number* which indicates you can dispense TIRF medicine.
    - If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection.

- **To confirm enrollment confirmation by fax:**
  - Populate all of the required fields on the TIRF REMS Access Prescription Authorization Form and fax to **1-855-474-3062**. To obtain a TIRF REMS Access Prescription Authorization Form which may be reproduced to use continually, please email information@TIRFREMSaccess.com.

- If validated, you will be supplied a *prescription authorization number* via fax within one (1) business day which indicates you can dispense the TIRF medicine.
- If not validated, you will be provided a rejection reason and information regarding how to resolve the rejection using the phone number provided on the request.

Step 3: Dispensing

- Receive the *prescription authorization number* from the TIRF REMS Access program and then prepare, label and dispense the medication.

Step 4: Counsel patient and provide Medication Guide

- Counsel the patient on the appropriate use, safe storage, and the proper disposal procedures of TIRF medicines.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

To dispense TIRF medicines, your Inpatient Pharmacy must enroll in the TIRF REMS Access program.

What is the TIRF REMS Access Program?

The TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program is designed to ensure informed risk-benefit decisions before initiating treatment and, while patients are on treatment, to ensure appropriate use of TIRF medicines. TIRF medicines are available only through a restricted distribution program required by the Food and Drug Administration (FDA), because of the risk for misuse, abuse, addiction, overdose, and serious complications due to medication errors. A list of TIRF medicines available through the TIRF REMS Access program is located on the TIRF Products web page at www.TIRFREMSaccess.com/TirfUI/ProductList.

How does the TIRF REMS Access program work?

The TIRF REMS Access program requires pharmacies, prescribers, patients and wholesalers to enroll in the program in order to utilize TIRF medications. The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy prior to shipment of TIRF medicines. Pharmacies are required to verify the prescriber and the patient are enrolled in the TIRF REMS Access program before dispensing any TIRF medication.

Does your pharmacy qualify as an Inpatient Pharmacy?

For the purposes of this REMS, an inpatient pharmacy is defined as a pharmacy where the patient's care is coordinated on-site at a care facility and the pharmacy claims are submitted as a medical benefit.

Important Information about Outpatient Pharmacies within the Facility

Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

All enrollment activities can be completed at www.TIRFREMSaccess.com

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS Access Program?
All pharmacy enrollment information was transferred from the individual TIRF REMS to the TIRF REMS Access program on March 12, 2012. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.

You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

The following two sections provide detailed information on the Enrollment Process (Section 1) and the Implementation Processes (Section 2) for TIRF medicines in an inpatient pharmacy.

Section 1: Enrollment Process

Summary of Enrollment

1. Select an individual to be your Authorized Inpatient Pharmacy Representative.
2. Create an account and complete registration at www.TIRFREMSaccess.com.
3. Complete the TIRF REMS Access Education Program and Knowledge Assessment.
4. Complete and submit an Inpatient Pharmacy Enrollment form.
5. Train pharmacy staff.

Detailed Enrollment Process

Step 1: Select an individual to be your Authorized Chain Representative

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.

Step 2: Create an account and complete registration at www.TIRFREMSaccess.com

- Create an account at www.TIRFREMSaccess.com and then complete registration on behalf of your pharmacy.

How do I create an account and complete the TIRF REMS Access registration on-line?

- Select the Create Account button on the home page
- Complete the Create Account Information section
- Select 'No' if you have not submitted an enrollment form via fax at the 'Already enrolled via Fax and have an enrollment ID?' prompt.

- Create User ID and password and select 'Create My Account'
- Select 'Pharmacy' as the option to best describe you and select 'Continue'
- Select 'Inpatient Pharmacy – Authorized Pharmacy Representative'
- Review the content in the pop-up box and select 'Confirm' to continue
- Complete required fields on the Inpatient Pharmacy Registration page and select 'Submit' to continue

Step 3: Complete the TIRF REMS Access Education Program and Knowledge Assessment

How do I complete the TIRF REMS Access Education Program by fax?

- Review the TIRF REMS Access Education Program. A printable version of the TIRF REMS Access Education Program is available online at www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.
- Once you have reviewed the Education Program complete the Knowledge Assessment and submit by fax to **1-866-822-1487**
- The TIRF REMS Access program will notify you of the status of your Knowledge Assessment via your indicated preferred method of communication (fax or e-mail)

How do I complete the TIRF REMS Access Education Program online?

- Select the 'Start the TIRF REMS Access Education Program' to proceed to the training upon completion of registration
- Select 'Go To Knowledge Assessment' button and complete upon completion of the Education Program
- A Knowledge Assessment Confirmation Code will be provided once the assessment is completed successfully.

Step 4: Complete and submit Inpatient Pharmacy Enrollment

- To finalize enrollment in the TIRF REMS Access program complete Inpatient Pharmacy Enrollment
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

How do I complete the TIRF REMS Access Enrollment on-line?

- Upon successful completion of the TIRF REMS Access Education Program and Knowledge Assessment, you will be prompted to read the TIRF REMS Access attestation and enter your electronic signature, today's date, and check the attestation box before clicking 'Submit'.

NOTE: You are required to re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Section 2: Implementation Process

Summary of Implementation Process

1. Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements
2. Train Pharmacy Staff

Detailed Implementation Process

Step 1: Ensure appropriate patient selection and compliance with TIRF REMS Access program requirements

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Step 2: Train Pharmacy Staff

- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

Reporting Adverse Events and Monitoring

To report any adverse events including the misuse, abuse, addiction, or overdose of TIRF medication contact:

- TIRF REMS Access program at 1-866-822-1483 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

If you have any questions, need additional information, or need additional copies of any TIRF REMS Access documents, please visit www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Independent Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized independent outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.

Pharmacist Name* (please print):_____

12. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Please note: If you are a chain outpatient pharmacy, please complete the Chain Outpatient Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Independent Outpatient Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Independent Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

Pharmacist Name* (please print):_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor. In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Pharmacist Name* (please print):_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Outpatient Pharmacy Enrollment Form

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3, 4 and 5 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized chain outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without verifying through our pharmacy management system that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that ALL TIRF medicine prescriptions, regardless of the method of payment, must be processed through our pharmacy management system.
10. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.
15. I understand that differences in pharmacy software may affect automation capabilities for adjudicating prescriptions through the TIRF REMS Access program without an insurance claim (i.e.: cash claim). If insurance is not used, pharmacy staff must manually enter the REMS Cash BIN #014780 or the designated chain pharmacy cash bin in order for the transaction to be properly adjudicated through the TIRF REMS Access program.

Authorized Chain Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Chain Outpatient Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Outpatient Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

Chain ID*:_____

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

Pharmacy ("Pharmacy") agrees to the following requirements, with respect to the Transmucosal Immediate Release Fentanyl (TIRF) REMS program (the "Program"), sponsored by the Transmucosal REMS Industry Group (hereinafter "TRIG" or "Program Sponsor") and supported, under the direction of TRIG by McKesson Specialty Arizona Inc and its affiliates including NDCHealth Corporation d/b/a RelayHealth ("RelayHealth") and McKesson Canada, and any other pharmacy transaction switch system (collectively, "the Providers").

Pharmacy represents that (i) it shall perform its obligations under these terms and conditions in compliance with all applicable laws and regulations, (ii) Pharmacy's participation in the Program does not conflict with its obligations under any contracts or other arrangements with any third party, and (iii) Pharmacy is authorized to submit patient information to the Providers for purposes of verifying and tracking each patient's eligibility to participate in the Program and Pharmacy authorizes Providers and Program Sponsor and their respective designees and agents to use the submitted information for such purposes.

Pharmacy agrees to the following Program Requirements: (a) If applicable, enable Pharmacy's pharmacy practice management system to support the Program, including submission of required data fields and display of Program messages; (b) Respond appropriately to Program messages and alerts in order to comply with Program requirements, including contacting the call center when an exception process occurs; (c) Report all Program Drug dispensing activity for all transmucosal immediate release fentanyl Program Drug NDC #'s. This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request. Please reference the following link (www.TIRFREMSaccess.com/TirfUI/NDCList) for a detailed list of products (including their NDC numbers) available through the TIRF REMS Access program. This document is available on the Resources tab (for pharmacies and distributors) on the program website at www.TIRFREMSaccess.com.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

Pharmacy authorizes and directs the Providers to de-identify, in accordance with the Health Insurance Portability and Accountability Act of 1996, as amended, its historical and prospective prescriptions claims data submitted to the Providers and/or their affiliates in connection with or related to the Program on behalf of Pharmacy, and to use that de-identified data for purposes of (i) analyzing, identifying, designing and/or enabling a REMS service; (ii) developing communication documentation for such services for both Program Sponsors and Pharmacy; (iii) providing the Program Sponsors with reports and information (including any fees paid, which will be aggregated), for purposes of implementing, maintaining, supporting, monitoring or improving a Program, and (iv) any other purpose required by law. These reports may contain information aggregated by NCPDP number. Further, Pharmacy authorizes Providers to deliver all of the above enumerated data and reports otherwise to be delivered to Program Sponsor to the designee or agent of Program Sponsor.

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

Pharmacy acknowledges that the FDA or Program Sponsor may mandate modification, suspension or termination of a Program. The Providers reserve the right to modify, suspend or terminate any REMS service for any reason, without liability to Switch Systems.

Chain ID*:_____

EXCEPT FOR PROVIDER'S FRAUD OR INTENTIONAL MISCONDUCT ARISING OUT OF THE SERVICES OR THE PROGRAM, IN NO EVENT WILL THE PROGRAM SPONSOR OR PROVIDER BE LIABLE TO PHARMACY UNDER, IN CONNECTION WITH, OR RELATED TO THE PROGRAM OR THE SERVICES FOR ANY DIRECT, SPECIAL, INCIDENTAL, INDIRECT, OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS OR LOSS OF GOODWILL, WHETHER BASED ON BREACH OF CONTRACT, WARRANTY, TORT, PRODUCT LIABILITY, OR OTHERWISE, AND WHETHER OR NOT PROVIDERS OR PROGRAM SPONSOR HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

To the extent any of these terms and conditions conflict with any other written agreement between the parties with respect to the Program, the terms and conditions of such other written agreement shall prevail.

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Closed System Outpatient Pharmacy Enrollment Form

To enroll in TIRF REMS Access, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You may also scan the completed form and email to: information@TIRFREMSAccess.com. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized closed system outpatient pharmacy representative, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the risks and benefits associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that all pharmacy staff who participate in dispensing TIRF medicines are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. This training should be documented and is subject to audit.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product-specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand the importance of discussing the risks and benefits of TIRF medicines with patients and their caregivers, and in particular the importance of taking the drug as prescribed, not sharing with others, and proper disposal.
7. I understand that the product-specific Medication Guide must be given to the patient or their caregiver each time a TIRF medicine is dispensed.
8. I understand that a TIRF medicine will not be dispensed without obtaining a TIRF REMS Access prescription authorization number issued by the TIRF REMS Access program prior to dispensing the prescription. A TIRF REMS Access prescription authorization number verifies that the prescriber and pharmacy are enrolled and active, and that the patient has not been inactivated in the program.
9. I understand that all dispensing locations must be enrolled in the TIRF REMS Access program to dispense TIRF medicines.
10. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
11. I understand that our pharmacy will not sell, loan or transfer TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Closed System Chain ID*:_____

13. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient closed system pharmacies.

Authorized Closed System Outpatient Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System Outpatient Pharmacy Information:

Pharmacy Name* _____ **Closed System Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with your enrollment confirmation and instructions on how your pharmacy staff can complete the training process and how your closed system outpatient pharmacy dispensing locations may obtain a TIRF REMS Access Prescription Authorization.

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Closed System Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

Inpatient Pharmacy Enrollment Form (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)

For real-time processing of enrollment, please go to www.TIRFREMSaccess.com.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. Please note, you must review the TIRF REMS Access Education Program and successfully complete the Knowledge Assessment to complete enrollment. If you have not completed the Knowledge Assessment online, please include it with this enrollment form. You will receive enrollment confirmation via email or fax.

I understand that TIRF medicines are only available through the TIRF REMS (Risk Evaluation and Mitigation Strategy) Access program and that I must comply with the program requirements. In addition, as the designated authorized inpatient pharmacist, I acknowledge that:

1. I have reviewed the TIRF REMS Access Education Program, and I have completed the Knowledge Assessment. I understand the benefits and risks associated with TIRF medicines and the requirements of the TIRF REMS Access program for pharmacies.
2. I will ensure that our inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program.
3. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labeled product specific conversion recommendations (refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList. Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.
5. I understand that the initial starting dose for TIRF medicines for all patients is the lowest dose, unless individual product labels provide product-specific conversion recommendations, and I understand that patients must be titrated individually.
6. I understand that pharmacies within or associated with the healthcare facility that dispense to outpatients must be separately enrolled in and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients.
7. I understand that our inpatient pharmacy must not dispense TIRF medicines for outpatient use.
8. I understand that a prescriber who wants to discharge a patient with a TIRF medicine prescription, intended to be dispensed by an outpatient pharmacy, will be required to enroll in the TIRF REMS Access program.
9. I will establish, or oversee the establishment of, a system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
10. I understand that our pharmacy will not sell, loan or transfer any TIRF medicine inventory to any other pharmacy, institution, distributor, or prescriber.
11. I understand that TIRF medicines can only be obtained from wholesalers/distributors that are enrolled in the TIRF REMS Access program.
12. I understand that our pharmacy must re-enroll in the TIRF REMS Access program every two (2) years.
13. I understand that TIRF medicines are available only through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for inpatient pharmacies.

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent pain.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Outpatient Pharmacies

- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Outpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Inpatient pharmacies have different REMS requirements. Please see the TIRF REMS Access program - An Overview for Inpatient Pharmacies available at www.TIRFREMSaccess.com.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Attachment 2

Standardized validation test transaction required to validate pharmacy system enhancements

Participating pharmacies must demonstrate that their pharmacy management system can receive and display program reject codes and messages. The software certification process requires the pharmacy to submit several test transactions via their pharmacy management system.

Pharmacies will not be able to successfully process transactions for TIRF medicines through the pharmacy management system until these system changes have been implemented.

Test Transaction Flow

TEST #1 REQUIRED DATA FIELDS – PHARMACY SUBMITS THE REQUIRED DATA FIELDS:

° Submits a prescription billing request to RelayHealth BIN # 014780, PCN REMS with the following data fields populated;

- Patient First Name..... TIRFREMSTEST
- Patient Last Name..... Smithers
- Date of Birth..... 19841105
- Patient ZIP/Postal Zone..... 07921
- Drug Name..... TIRFPRODUCT 800 mcg – NDC # 49884-0462-55
- Quantity Dispensed..... 12
- Days Supply..... 4
- Prescriber ID..... BA1111119
- Prescriber Last Name..... REMSTEST

- Test #1 Response

° A Successful Expected Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: ***REMS* – This is certification test message # 1 for TIRF REMS. Resubmit this transaction with the following value in the in the Intermediary Authorization ID or Patient ID field – [NNNNNNNNNN]***

° Next Step – Proceed to Test #2
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and provide the vendor the field provided in the reject message, request the vendor to enable the submission of that field in your pharmacy management system. Once, this has been resolved Test 1 needs to be resubmitted.

TEST #2 RE-SUBMIT CLAIM WITH OVER-RIDE PROVIDED – PHARMACY RE-SUBMITS CLAIM WITH OVERRIDE PROVIDED FROM TEST #1.

° Receives and reviews the prescription billing request reject code and message for override value
° Inputs the identified code value provided in the reject message:
° Intermediary Authorization ID, or
° Patient ID
° Resubmits the prescription billing request.

• Test #2 Response
° A Successful Expected Response will look like this:
° Transaction Response Status..... "P" (Paid)
° Additional Message Information: ***REMS* – This is certification test message # 2 for TIRF REMS. Submit a reversal request for this prescription to complete TIRF REMS certification testing***

° Next Step – Proceed to Test #3
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "Will vary based upon missing/invalid required field"
° Additional Message Information: ***Missing/ Invalid [field]***

° Next Step – Call your software vendor and request the vendor enable the submission of either the Patient ID or Intermediary Authorization ID field in your pharmacy management system.

TEST #3 REVERSE CLAIM- PHARMACY SUBMITS

° Receives and reviews the prescription billing request and message
° Submits the prescription reversal request for the previously approved billing request.

• Test #3 Expected Response
° A Successful Expected Response will look like this:
° Transaction Response Status = "A" (Approved)
° Additional Message Information: ***REMS* – This is certification test message # 3 for TIRF REMS. TIRF REMS certification testing for NCPDP Telecommunication Standard is complete.***

° Next Step – Vendor Verification Test complete.
° An Unsuccessful Response will look like this:
° Transaction Response Status..... "R" (Rejected)
° Reject Code..... "NN"
° Additional Message Information: *"Invalid test transaction sequence"*

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Inpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program

This new shared program replaces the individual product REMS that were previously available. Any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program **beginning mm/dd/yyyy**. If you have not enrolled in one or more of these individual REMS programs, and if any of these products are prescribed and dispensed in your healthcare facility (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use), you must enroll your inpatient pharmacy in the shared TIRF REMS Access program.

For inpatient administration of these products, patient and prescriber enrollment in the TIRF REMS Access program is not required.

Inpatient Pharmacy Action:

Option 1: If you are already enrolled in at least one individual REMS program

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSAccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.

- The TIRF REMS Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483.**
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Option 2: If you do not have an existing enrollment in any individual REMS program

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between fentanyl products.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

TIRF medicines are opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain, unless otherwise indicated in the product label.

Patients considered opioid-tolerant are those who are regularly taking at least 60 mg oral morphine/day, or at least 25 micrograms transdermal fentanyl/hour, or at least 30 mg of oral oxycodone/day, or at least 8 mg oral hydromorphone/day, or at least 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

To help you understand the TIRF REMS Access program, the following program materials are available at www.TIRFREMSaccess.com or can be ordered by calling 1-866-822-1483:

- Overview for Inpatient Pharmacies
- TIRF REMS Access Education Program
- Knowledge Assessment
- Frequently Asked Questions
- Inpatient Pharmacy Enrollment Form
- Full Prescribing Information and Medication Guides for each TIRF medicine

Outpatient pharmacies within the facility providing dispensing services to discharged inpatients or outpatients have different REMS requirements. In order to dispense TIRF medicines to outpatients, a separate enrollment in the TIRF REMS Access program is required (see the TIRF REMS Access program - An Overview for Outpatient Pharmacies available at www.TIRFREMSaccess.com).

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Selected Important Safety Information

IMPORTANCE OF PROPER PATIENT SELECTION, DOSING, and POTENTIAL FOR ABUSE

TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. TIRF medicines can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing TIRF medicines in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Serious adverse events, including deaths, in patients treated with some oral transmucosal fentanyl medicines have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of a TIRF medicine for any other fentanyl medicine, including another TIRF medicine, may result in fatal overdose.

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

TIRF medicines are contraindicated in opioid non-tolerant patients and are contraindicated in the management of acute or postoperative pain, including headache/migraine and dental pain, or use in the emergency room. Please see the individual medicine prescribing information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with some TIRF medicines.

When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl medicine to a TIRF medicine, except for substitutions between a branded TIRF medicine and its generic equivalent. Patients beginning treatment with TIRF medicines must begin with titration from the lowest available dose for that specific medicine. Carefully consult the Initial Dosing Instructions in the TIRF medicine-specific Full Prescribing Information.

When dispensing, TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed that could cause a fatal overdose. Converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis, and must be titrated according to the labeled dosing instructions each time they begin use of a new TIRF medicine. The only exception is for substitution between a branded TIRF medicine and its specific generic equivalent.

Special care must be used when dosing TIRF medicines. Refer to the Full Prescribing Information for the individual TIRF medicine for guidance on the maximum number of doses that can be taken per breakthrough pain episode and the time that patients must wait before treating another episode of breakthrough pain with the TIRF medicine.

TIRF medicines are intended to be used only in the care of opioid-tolerant cancer patients and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children.

The concomitant use of TIRF medicines with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Adverse Reactions

The most commonly observed adverse reactions with TIRF medicines include typical opioid adverse reactions, such as nausea, vomiting, constipation, somnolence, dizziness, and headache. Refer to individual medicine prescribing information for all adverse reactions. Expect opioid side effects and manage them accordingly.

Please see the individual Full Prescribing Information for each TIRF medicine for all information including boxed warnings, and Medication Guide for important safety information for each TIRF medicine.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient. Patients should be counseled on the need to store TIRF medicines safely out of the reach of children and other persons for whom the medicine is not prescribed.

Provide your patient with a copy of the appropriate Medication Guide for the TIRF medicine you prescribe. Medication Guides will be provided to you by the manufacturers of individual TIRF medicines. If you require additional Medication Guides you can:

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at **1-866-822-1483**.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Wholesaler/Distributor:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

- Abstral® (fentanyl) sublingual tablets
- Actiq® (fentanyl citrate) oral transmucosal lozenge
- Fentora® (fentanyl citrate) buccal tablet
- Lazanda® (fentanyl) nasal spray
- Onsolis® (fentanyl buccal soluble film)
- Subsys™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared TIRF REMS Access program. If you have not enrolled in one or more of these individual REMS programs and you wish to purchase these products in order to fulfill orders from enrolled pharmacies, you must enroll in the TIRF REMS Access program.

Distributor Action:

Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

Option 2: If you <u>do not have an existing enrollment</u> in any individual REMS program

- Review and understand the requirements of the TIRF REMS Access program.
- Verify that relevant staff are trained on the TIRF REMS Access program requirements and procedures
- Complete the Distributor Enrollment Form. Forms are available at www.TIRFREMSaccess.com or by calling **1-866-822-1483**.
- By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

<u>Distributor Responsibilities in the TIRF REMS Access Program:</u>

Verification of TIRF REMS Access program Pharmacy Enrollment Prior to Distributing TIRF medicines

- Obtain the current list of enrolled pharmacies by:
  - Downloading (daily) a complete electronic registry of enrolled pharmacies from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete), or
  - Receiving (daily) a complete electronic registry, or
  - Accessing the website (www.TIRFREMSaccess.com) using a user ID and password, or
  - Calling the TIRF REMS Access program call center at **1-866-822-1483**.
- Ensure that pharmacies are enrolled in the TIRF REMS Access program before distributing TIRF medicines.
- If a pharmacy places an order for a TIRF medicine, but is not listed on the enrolled list for the TIRF REMS Access program, do not distribute TIRF medicines.

Provide periodic distribution data

- Provide weekly product activity data (i.e. EDI 867 transmission) to the TIRF REMS Access program including complete (unblinded/unblocked) information to validate compliance with the TIRF REMS Access program.

Please note that a manufacturer of products included in Attachment 1 cannot ship TIRF medicines to distributors who have not completed and signed the Distributor Enrollment Form. Refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1.

Adverse Event Reporting

Promptly report suspected adverse events including misuse, abuse, addiction and overdoses directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at 1-800-FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

To access the above information and to enroll in the TIRF REMS Access program, visit www.TIRFREMSaccess.com or call 1-866-822-1483 to have enrollment materials sent to you.

Sincerely,

TIRF REMS Access Industry Group

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

To enroll in TIRF REMS Access, complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the list of currently approved TIRF products located on the TIRF REMS Access website at www.TIRFREMSaccess.com/TirfUI/ProductList.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

If you have any questions or require additional information or further copies of any TIRF REMS Access documents, please visit either www.TIRFREMSaccess.com, or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Representative Name* (please print):_____

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LASHAUN WASHINGTON-BATTS
05/18/2017

CYNTHIA L LACIVITA
05/19/2017
Concur

September 18, 2017

REMS CORRESPONDENCE

Kathleen Uhl, M.D.
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

RE: Sequence # 0014
ANDA # 207338
Fentanyl Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent)

Dear Dr. Uhl:

Reference is made to Actavis Laboratories FL, Inc.'s (Actavis-FL)'s Abbreviated New Drug Application for Fentanyl Citrate Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent), ANDA # 207338, and to FDA's REMS information request email dated September 8, 2017 (**copy attached**). Actavis Laboratories FL, Inc. (an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA) is amending the ANDA to provide a complete response to the comments included in the letter. For ease of review, the Agency's comments are provided in bold face type, followed by Actavis' response.

In accordance with 21 CFR 314.96(d), Actavis hereby verifies that the information contained within this Amendment, dated September 18, 2017, does not require a recertification for a previously submitted patent certification.

Comments:
1. The TIRF REMS Industry Group (TRIG) uses a Drug Master File (DMF). Therefore, please submit a cover letter to your application referencing the approved TIRF REMS DMF as appropriate as soon as possible. Important: Please be sure to submit your cover letter as a "*REMS Correspondence*".

Response:
Actavis is currently a TRIG member and authorizes FDA to reference DMF No. 27320, sequence 0033 submitted on 08/29/2017, for the most recent, approved TIRF REMS and appended materials.

This supplement is an electronic submission organized in accordance with ICH-CTD format (eCTD). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface in accordance with Applicability Statement 2 (AS2) standards.

Should you have any questions or comments concerning this submission, please contact the undersigned at RegulatoryAffairsUS@actavis.com (*e-mail*), (954) 358-6125 (*telephone*), or 954-358-6350 (*fax*).

Sincerely,

Frida M. Navarro
Manager, Regulatory Affairs (for)
Janet Vaughn
Director, Regulatory Affairs

Nazmin Amir

From: Sarchet, Jennifer <Jennifer.Sarchet@fda.hhs.gov>
Sent: Friday, September 08, 2017 2:48 PM
To: Regulatory Affairs US
Cc: Dallas, Scott
Subject: ANDA 207338; TIRF; REMS; Information Request

Importance: High

Dear Ms. Vaughn,

In reference to ANDA 207338; TIRF; REMS: Please note that there has been a recent update to the approved TIRF REMS.

The TIRF REMS Industry Group (TRIG) uses a Drug Master File (DMF). Therefore, please submit a cover letter to your application referencing the approved TIRF REMS DMF as appropriate as soon as possible, but no later than 9/12/2017. Important: Please be sure to submit your cover letter as a "***REMS Correspondence***".

Please note you only need to submit a cover letter referencing the above. Please ***do not*** submit the entire REMS individually to your application.

I also kindly ask that you send me a courtesy e-mail to let me know that you have submitted the above to your application.

As a reminder, the single point of contact for the TRIG is Mr. Dinesh Anugu, Regulatory Affairs Associate. Mr. Anugu can be reached at danugu@insysrx.com or at 480-500-3193.

If you have any questions or concerns, please do not hesitate to contact me.

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs

CDER/FDA
240-402-4275 (office)

September 25, 2017

REMS CORRESPONDENCE

Kathleen Uhl, M.D.
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855-2773

RE: Sequence # 0015
ANDA # 207338
Fentanyl Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent)

Dear Dr. Uhl:

Reference is made to Actavis Laboratories FL, Inc.'s (Actavis-FL)'s Abbreviated New Drug Application for Fentanyl Sublingual Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.6 mg, and 0.8 mg (base equivalent), ANDA # 207338, and to FDA's REMS information request email dated September 25, 2017 (**copy attached**). Actavis Laboratories FL, Inc. (an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA) is amending the ANDA to provide a complete response to the comments included in the letter. For ease of review, the Agency's comments are provided in bold face type, followed by Actavis' response.

In accordance with 21 CFR 314.96(d), Actavis hereby verifies that the information contained within this Amendment, dated September 25, 2017, does not require a recertification for a previously submitted patent certification.

Comments:
1. In reference to ANDA 207338; TIRF; REMS and the below emails, if you have not already done so, please submit a Letter of Authorization (LOA) from the DMF holder confirming you have joined the TIRF Shared System REMS. I am unable to locate this in the application.

Response:
The Letter of Authorization to DMF No. 27320 (TIRF Access Program) is provided in **section 1.4.1**.

This supplement is an electronic submission organized in accordance with ICH-CTD format (eCTD). The submission has been verified virus-free and is being submitted through the FDA Electronic Submission Gateway (ESG) Web Interface in accordance with Applicability Statement 2 (AS2) standards.

Should you have any questions or comments concerning this submission, please contact the undersigned at RegulatoryAffairsUS@actavis.com (*e-mail*), (954) 358-6125 (*telephone*), or 954-358-6350 (*fax*).

Sincerely,

Frida M. Navarro
Manager, Regulatory Affairs (for)
Janet Vaughn
Director, Regulatory Affairs

accenture

Accenture LLP
1160 West Swedesford Road
Berwyn, PA 19312
www.accenture.com

Date: September 22, 2017

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

DMF#: 027320
Holder: McKesson Specialty Health (McKesson)
Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Letter of Authorization for: Not applicable because DMF does not cover multiple items.

McKesson hereby authorizes Teva Pharmaceuticals USA, Inc. to incorporate by reference information regarding the Transmucosal Immediate Release Fentanyl (TIRF) Access Program in DMF Number 027320 into any application filed by Teva Pharmaceuticals USA, Inc. We also authorize the FDA to review the aforementioned specific information in DMF Number 027320 when considering any application filed by Teva Pharmaceuticals USA, Inc.

The entire DMF can be referenced, which was submitted on August 20, 2013.

McKesson states that DMF Number 027320 is current and McKesson will comply with the statements made within it. McKesson will notify FDA through an amendment to DMF Number 027320 of any addition, change, or deletion of information in the DMF. McKesson will also notify in writing Teva Pharmaceuticals USA, Inc. that an addition, change, or deletion of information has been made to the DMF.

Sincerely,

For

Debra Hackett, Senior Project Manager, RegulatoryAffairs
U.S. Agent, Accenture, LLP
1160 West Swedesford Road, Building One
Berwyn, PA 19312
debra.hackett@accenture.com.

Frida Navarro-Iriarte

From: Sarchet, Jennifer <Jennifer.Sarchet@fda.hhs.gov>
Sent: Monday, September 25, 2017 12:56 PM
To: Regulatory Affairs US
Cc: Dallas, Scott
Subject: RE: ANDA 207338; TIRF; REMS; Information Request - Fentanyl Sublingual Tablets

Importance: High

Hello Ms. Navarro,

In reference to ANDA 207338; TIRF; REMS and the below emails, if you have not already done so, please submit a Letter of Authorization (LOA) from the DMF holder confirming you have joined the TIRF Shared System REMS. I am unable to locate this in the application. Once you have submitted the DMF LOA, please email me a courtesy notification.

If you have already done this, please let me know the date of the submission.

Please submit this as soon as possible as a "REMS Correspondence".

If you have any questions, please do not hesitate to contact me.

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

From: Regulatory Affairs US [mailto:RegulatoryAffairsUS@actavis.com]
Sent: Monday, September 18, 2017 5:12 PM
To: Sarchet, Jennifer
Cc: Dallas, Scott; Regulatory Affairs US
Subject: RE: ANDA 207338; TIRF; REMS; Information Request - Fentanyl Sublingual Tablets

Good afternoon Jennifer,
Please note that today, we submitted the requested REMS Correspondence, via the ESG Gateway.

Best regards,

Frida M. Navarro, Regulatory Affairs Manager
Direct: +1 954.358.6117
2945 West Corporate Lakes Blvd, Ste B, Weston, Florida 33331
frida.navarro-iriarte@actavis.com www.tevapharm.com

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Friday, September 08, 2017 2:48 PM
To: Regulatory Affairs US
Cc: Dallas, Scott
Subject: ANDA 207338; TIRF; REMS; Information Request
Importance: High

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The TIRF REMS Industry Group (TRIG) uses a Drug Master File (DMF). Therefore, please submit a cover letter to your application referencing the approved TIRF REMS DMF as appropriate as soon as possible, but no later than 9/12/2017. Important: Please be sure to submit your cover letter as a "***REMS Correspondence***".

Please note you only need to submit a cover letter referencing the above. Please ***do not*** submit the entire REMS individually to your application.

I also kindly ask that you send me a courtesy e-mail to let me know that you have submitted the above to your application.

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If you have any questions or concerns, please do not hesitate to contact me.

Thank you,
Jennifer

Jennifer Sarchet, MSHA, BSN, RN
CDR, U.S. Public Health Service Corps
REMS, Office of Bioequivalence
Office of Generic Drugs
CDER/FDA
240-402-4275 (office)

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Addendum to Risk Evaluation and Mitigation Strategy Review

Date:	September 25, 2017
Reviewer:	LaShaun Washington-Batts, Pharm.D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Selena Ready, Pharm.D. DRISK
Division Director:	Cynthia LaCivita, Pharm.D. DRISK
Drug Name:	fentanyl citrate
Therapeutic Class:	Opioid Analgesic
Dosage and Route:	100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg tablets
Application Type/Number:	ANDA 207338
Applicant/Sponsor:	Actavis Laboratories FL, Inc.
OSE RCM #:	2016-1238
DMF #	027320

1 INTRODUCTION

This review is an addendum to risk evaluation and mitigation strategy (REMS) Review by the Division of Risk Management (DRISK), dated May 18, 2017, evaluating the REMS for fentanyl citrate, abbreviated new drug application (ANDA) 207338, submitted by Actavis Laboratories FL, Inc. (Applicant) on June 19, 2014 and amended on October 13, 2015 and September 18, 2017. The Applicant is a member of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Industry Group (TRIG) and will market their product under the shared system TIRF REMS.

2 DISCUSSION AND CONCLUSION

In the May 18, 2017 REMS Review, DRISK evaluated the proposed REMS for fentanyl citrate, ANDA 207338, and recommended approval. Since that time, a TIRF REMS modification was approved by the Agency on September 7, 2017. The REMS modification was required to conform to safety labeling changes (SLC) approved on December 16, 2016 that address the addition of language related to the risks of misuse, abuse, addiction, overdose, death, and neonatal opioid withdrawal syndrome (NOWS), serotonin syndrome with concomitant use of serotonergic drugs, adrenal insufficiency, androgen deficiency, and risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants to the Prescribing Information.

On September 18, 2017, the Applicant submitted an amendment to their application with a cover letter referencing the TIRF REMS and Supporting Document approved on September 7, 2017, which is located in the TIRF REMS drug master file #27320 (DMF #27320). Therefore, the proposed REMS for fentanyl citrate, ANDA 207338, is acceptable.

3 RECOMMENDATIONS

DRISK recommends approval of the proposed REMS for fentanyl citrate, ANDA 207338, submitted by the Applicant on September 18, 2017 and as appended to this addendum provided that the OGD Division of Labeling determines the Medication Guide is adequate prior to the approval of the application.

Upon approval, the list of approved products will be updated on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

If a class wide TIRF REMS modification is approved between the date of this addendum and action being taken on this application, this REMS addendum will no longer be applicable and the REMS should be considered deficient.

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/s/

LASHAUN WASHINGTON-BATTS
09/25/2017

CYNTHIA L LACIVITA
09/25/2017
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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Addendum to Risk Evaluation and Mitigation Strategy Review

Date:	November 17, 2017
Reviewer:	LaShaun Washington-Batts, Pharm.D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Selena Ready, Pharm.D. DRISK
Division Director:	Cynthia LaCivita, Pharm.D. DRISK
Drug Name:	fentanyl citrate
Therapeutic Class:	Opioid Analgesic
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1 INTRODUCTION

This review is an addendum to risk evaluation and mitigation strategy (REMS) Reviews by the Division of Risk Management (DRISK), dated September 25, 2017, evaluating the REMS for fentanyl citrate, abbreviated new drug application (ANDA) 207338, submitted by Actavis Laboratories FL, Inc. (Applicant) on June 19, 2014 and amended on October 13, 2015 and September 18, 2017. The Applicant is a member of the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Industry Group (TRIG) and will market their product under the shared system TIRF REMS.

2 DISCUSSION AND CONCLUSION

In the REMS Review dated September 25, 2017, DRISK evaluated the proposed REMS for fentanyl citrate, ANDA 207338, and recommended approval based upon the submission of a cover letter dated September 18, 2017, which cross-referenced the TIRF REMS approved on September 7, 2017 located in the TIRF REMS Drug Master File (DMF) #27320.

Upon further review of the application, at the time of the DRISK Review, there was no Letter of Authorization on file from the DMF holder (McKesson) giving authorization to the Applicant to cross-reference the TIRF REMS in the DMF as a proposed REMS for ANDA 207338.

On September 25, 2017, the Applicant submitted the Letter of Authorization from the DMF holder and therefore, the cover letter dated September 18, 2017 cross-referencing the most recently approved TIRF REMS in the DMF is sufficient for the proposed REMS for ANDA 207338.

3 RECOMMENDATIONS

DRISK recommends approval of the proposed REMS for fentanyl citrate, ANDA 207338, submitted by the Applicant on September 18, 2017, which cross-references the most recently approved TIRF REMS in the DMF.

Upon approval, the list of approved products will be updated on FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) website, available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

If a class wide TIRF REMS modification is approved between the date of this addendum and action being taken on this application, this REMS addendum will no longer be applicable and the REMS should be considered deficient.

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/s/

LASHAUN WASHINGTON-BATTS
11/17/2017

CYNTHIA L LACIVITA
11/17/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 207338

ANDA APPROVAL

Actavis Laboratories FL, Inc.
2945 West Corporate Lakes Blvd., Suite B
Weston, FL 33331
Attention: Janet Vaughn
Senior Director of Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on June 19, 2014, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Fentanyl Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg.

Reference is also made to the complete response letter issued by this office on July 28, 2016, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Fentanyl Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Abstral Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, of Sentynl Therapeutics Inc. (Sentynl).

The RLD upon which you have based your ANDA, Sentynl's Abstral Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,759,059 (the '059 patent)	September 24, 2019
6,761,910 (the '910 patent)	September 24, 2019
7,910,132 (the '132 patent)	September 24, 2019

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Fentanyl Sublingual Tablets, 100 mcg,

200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, under this ANDA. You have notified the Agency that Actavis Laboratories FL, Inc. (Actavis) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that litigation was initiated within the statutory 45-day period against Actavis for infringement of the '059, '910 and '132 patents in the United States District Court for the District of New Jersey [Orexo AB v. Actavis Laboratories FL, Inc., Andrx Corporation, Actavis, Inc., and Actavis Pharma, Inc., Civil Action No. 3:15-cv-00826(PGS-DEA)]. You have also notified the Agency that this case was dismissed.

With respect to 180-day generic drug exclusivity, we note that Actavis was the first ANDA applicant for Fentanyl Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, to submit a substantially complete ANDA with a paragraph IV certification. Therefore, with this approval, Actavis may be eligible for 180 days of generic drug exclusivity for Fentanyl Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg. This exclusivity, which is provided for under 505(j)(5)(B)(iv) of the FD&C Act, would begin to run from the date of the commercial marketing identified in section 505(j)(5)(B)(iv). The Agency notes that Actavis failed to obtain tentative approval of this ANDA within 30 months after the date of which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the FD&C Act (forfeiture of exclusivity for failure to obtain tentative approval). The Agency is not, however, making a formal determination at this time of Actavis' eligibility for 180-day generic drug exclusivity. It will do so only if a subsequent paragraph IV applicant becomes eligible for full approval (a) within 180 days after Actavis begins commercial marketing of Fentanyl Sublingual Tablets, 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg and 800 mcg, or (b) at any time prior to the expiration of the '059, '910 and '132 patents if Actavis has not begun commercial marketing. Please submit correspondence to this ANDA notifying the Agency within 30 days of the date of the first commercial marketing of this drug product or the RLD. If you do not notify the Agency within 30 days, the date of first commercial marketing will be deemed to be the date of the drug product's approval. See 21 CFR 314.107(c)(2).

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our REMS notification letter dated January 20, 2015. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your final proposed REMS, referenced in Drug Master File 027320 is approved. The REMS is posted to the FDA REMS website, available at http://www.fda.gov/rems. The REMS consists of a Medication Guide, ETASU, and an implementation system.

Your REMS must be fully operational before you introduce Fentanyl Sublingual Tablets into interstate commerce.

The Transmucosal Immediate – Release Fentanyl (TIRF) REMS uses a shared system for the ETASU and the REMS assessments. This shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 207338 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 207338/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 207338/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 207338/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 207338

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Office of Generic Drugs should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Office of Generic Drugs in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, Pharm.D.
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Sarah Kurtz

Digitally signed by Sarah Kurtz
Date: 11/17/2017 03:40:56PM
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