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February 8, 2012

Bob Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia
Products (DAAP), HFD-170
5901-B Ammendale Road
Beltsville, MD 20704-1266

NDA 21-947; Sequence No. 0013
FENTORA®
(fentanyl citrate) buccal tablet CII

Proposed REMS Modification

Dear Dr. Rappaport:

Reference is made to NDA 21-947 for FENTORA® (fentanyl citrate) buccal tablet.

The FENTORA REMS was approved on 28 December 2011 as part of the single, shared REMS system developed for the transmucosal immediate-release fentanyl (TIRF) class of products. The REMS system has not been implemented yet and at this time, no data are available to generate an assessment report.

The purpose of this submission is to provide a proposed REMS modification to this single-shared system which includes the addition of a recently approved TIRF product, the NDC code for conducting the pharmacy test transaction was updated in the Outpatient Pharmacy letter, as well as additional changes to ensure consistency throughout the REMS documents.

This modification provides only changes made to the REMS. No changes have been made to the full prescribing information for FENTORA.

This submission is provided in virus-free eCTD format. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at (610) 883-5670.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6337 or e-mail me at sfranks@cephalon.com. In my absence, please contact Christine Kampf at (610) 727-6189 or via email at christine.kampf@tevapharm.com

Sincerely,

Susan Franks
Senior Director
Regulatory Affairs

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FENTORA safely and effectively. See full prescribing information for FENTORA.

FENTORA® (fentanyl citrate) buccal tablet, CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, FENTORA 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to FENTORA. (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)**
- **FENTORA 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2011
Warnings and Precautions, TIRF REMS Access Program (5.11)	12/2011

----------INDICATIONS AND USAGE----------

FENTORA is an opioid agonist indicated 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. (1)
Limitations of Use:
FENTORA 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 FENTORA. (1)
- Initial dose of FENTORA: 100 mcg. (2.1)
- Initiate titration using multiples of 100 mcg FENTORA tablet. Limit patient access to only one strength of FENTORA at any one time. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single FENTORA tablet. (2 1)
- No more than two doses can be taken per breakthrough pain episode. (2.1)
- Wait at least 4 hours before treating another episode of breakthrough pain with FENTORA. (2.1)
- Place entire tablet in buccal cavity; tablet is not to be split, sucked, chewed or swallowed. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl or components of FENTORA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate FENTORA 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cephalon, Inc., at 1-800-896-5855 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 FENTORA with caution to patients with hepatic or renal impairment. (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 FENTORA, including following use in opioid non-tolerant patients and improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

FENTORA 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 FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of FENTORA 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 FENTORA. *[see Dosage and Administration* (2.1)]

- When dispensing, do not substitute a FENTORA prescription for other fentanyl products.

ABUSE POTENTIAL

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA 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, FENTORA is available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

FENTORA is indicated 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. 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/hr of transdermal fentanyl, 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 while taking FENTORA.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, FENTORA is contraindicated in the management of acute or postoperative pain.

FENTORA is 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.

Limitations of Use:

As a part of the TIRF REMS Access program, FENTORA may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]*. For inpatient administration of FENTORA (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe FENTORA 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 FENTORA *[see Warnings and Precautions (5.11)]*.

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

2.1 Initial Dose

FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

Patients on Actiq

The initial dose of FENTORA is **always** 100 mcg with the only exception being patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1). The doses of FENTORA in this table are starting doses and not intended to represent equianalgesic doses to Actiq. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial FENTORA Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*****From this initial dose, titrate patient to effective dose.

b. For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength.

All Other Patients
The initial dose of FENTORA is 100 mcg.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of FENTORA for any episode of breakthrough pain.
b. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA.

2.2 Dose Titration

a. From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of FENTORA over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted.
b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg FENTORA tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of FENTORA for any breakthrough pain episode. During titration, one **dose** of FENTORA may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).
d. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA. To reduce the risk of overdose during titration, patients should have only one strength of FENTORA tablets available at any time.
e. Patients should be strongly encouraged to use all of their FENTORA tablets of one strength prior to being prescribed the next strength. If this is not practical, unused FENTORA should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened FENTORA tablets remaining from a prescription as soon as they are no longer needed.

2.3 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use **only ONE** FENTORA tablet of the appropriate strength per breakthrough pain episode.
b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode.
c. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA.
d. Dosage adjustment of FENTORA may be required in some patients. Generally, the FENTORA 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.
e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.

2.4 Administration of FENTORA

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer FENTORA.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire FENTORA tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). **Patients should not split the tablet.**

The FENTORA tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

The FENTORA tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the FENTORA tablet remain, they may be swallowed with a glass of water.

It is recommended that patients alternate sides of the mouth when administering subsequent doses of FENTORA.

3 DOSAGE FORMS AND STRENGTHS

FENTORA tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*.

4 CONTRAINDICATIONS

FENTORA is contraindicated in opioid non-tolerant patients.

FENTORA 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.

FENTORA is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

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 FENTORA. 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

FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and FENTORA are not equivalent on a microgram per microgram basis. FENTORA is NOT a generic version of Actiq. **All patients should be titrated from the 100 mcg dose.**

The initial dose of FENTORA should be 100 mcg. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a FENTORA prescription for an Actiq prescription under any circumstances. FENTORA and

Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of FENTORA for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1), and Medication Guide for specific patient instructions.]*

5.4 Additive CNS Depressant Effects

The concomitant use of FENTORA 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., hypoventilation, 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 FENTORA 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 FENTORA of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate FENTORA with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of FENTORA may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer FENTORA 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to FENTORA reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients.

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use FENTORA with caution in patients with bradyarrhythmias.

5.10 MAO Inhibitors

FENTORA 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.

5.11 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)]*, FENTORA 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 FENTORA, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe FENTORA 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 FENTORA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense FENTORA must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute FENTORA 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 FENTORA has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The most commonly observed adverse events seen with FENTORA are typical of opioid side effects. Opioid side effects should be expected and managed accordingly.

The clinical trials of FENTORA were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

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.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received FENTORA for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of FENTORA therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of FENTORA. There was no evidence of excess toxicity in this subset of patients.

The duration of exposure to FENTORA varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving FENTORA. Events are classified by system organ class.

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy
Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when FENTORA is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of FENTORA with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving FENTORA who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]*. The concomitant use of FENTORA with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of FENTORA. Patients receiving FENTORA who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased FENTORA activity and the dose of FENTORA should be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women. FENTORA 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 characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal 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 FENTORA.

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 FENTORA for analgesia 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 FENTORA 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 FENTORA.

8.4 Pediatric Use

The safety and efficacy of FENTORA have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of FENTORA, 69 (23%) were 65 years of age and older.

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating FENTORA 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 FENTORA 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 patients with cancer 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.

8.8 Race

The pharmacokinetic effects of race with the use of FENTORA have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse and Addiction

Handle FENTORA appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

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, since 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. FENTORA should be prescribed with caution to patients who have a higher risk of substance abuse, including patients with bipolar disorder and/or schizophrenia.

Patients with chronic pain may be at a higher risk for suicide.

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 non-medical purposes, often in combination with other psychoactive substances. Since FENTORA tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation 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 Physical Dependence and Withdrawal

The administration of FENTORA should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with cancer and chronic 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 FENTORA 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 hypoventilation *[see Clinical Pharmacology (12.2)]*.

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the FENTORA tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 FENTORA 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 hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of FENTORA, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

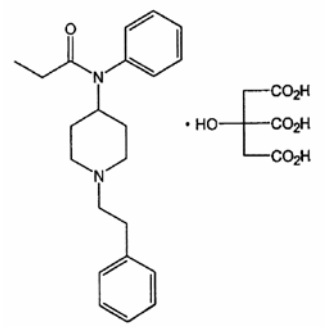
11 DESCRIPTION

FENTORA (fentanyl buccal tablet) is a potent opioid analgesic, intended for buccal mucosal administration.

FENTORA is designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

FENTORA employs the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

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 FENTORA should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*.

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 another oral transmucosal fentanyl citrate (Actiq). 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) and Overdosage (10).

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of FENTORA increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption

Following buccal administration of FENTORA, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of FENTORA is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of FENTORA and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with FENTORA) (Table 4).

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving FENTORA or Actiq

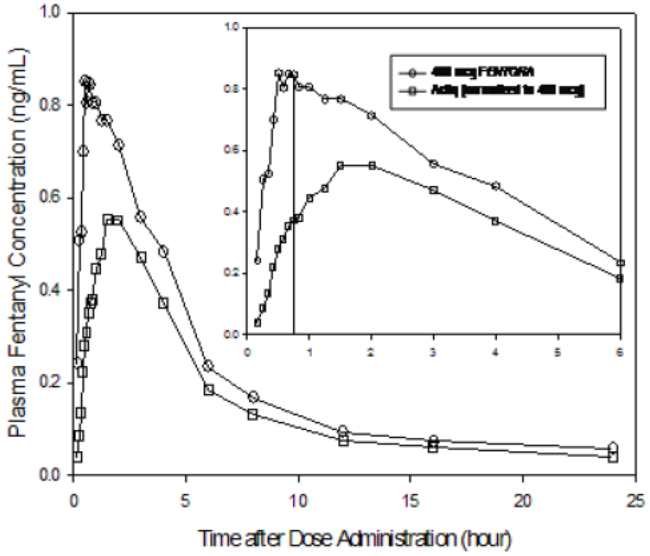
Pharmacokinetic Parameter (mean)	FENTORA 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10 5%
Fraction Absorbed Transmucosally	48% ± 31 8%	22% ± 17 3%
T_{max} (minute)**	46 8 (20-240)	90 8 (35-240)
C_{max} (ng/mL)	1 02 ± 0 42	0 63 ± 0 21
$AUC_{0\text{-}tmax}$ (ng·hr/mL)	0 40 ± 0 18	0 14 ± 0 05
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6 48 ± 2 98	4 79 ± 1 96

* Based on venous blood samples
** Data for T_{max} presented as median (range)
*** Actiq (OTFC) data was dose adjusted (800 mcg to 400 mcg)

Similarly, in another bioavailability study exposure following administration of FENTORA was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl were substantially greater with FENTORA compared to Actiq (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for FENTORA.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of FENTORA and Actiq in Healthy Subjects



Actiq data was dose adjusted (800 mcg to 400 mcg).

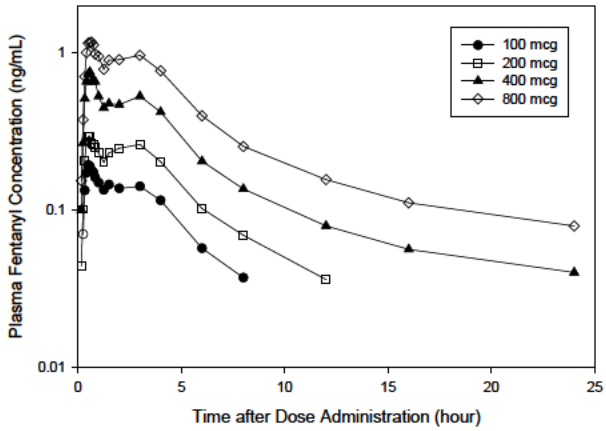
Mean pharmacokinetic parameters are presented in Table 5. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0 25 ± 0 14	0 40 ± 0 18	0 97 ± 0 53	1 59 ± 0 90
T_{max} minute** (range)	45 0 (25 0 - 181 0)	40 0 (20 0 - 180 0)	35 0 (20 0 - 180 0)	40 0 (25 0 - 180 0)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	0 98 ± 0 37	2 11 ± 1 13	4 72 ± 1 95	9 05 ± 3 72
$AUC_{0\text{-}tmax}$ (ng·hr/mL)	0 09 ± 0 06	0 13 ± 0 09	0 34 ± 0 23	0 52 ± 0 38
T1/2, hr**	2 63 (1 47 - 13 57)	4 43 (1 85 - 20 76)	11 09 (4 63 - 20 59)	11 70 (4 63 - 28 63)

* Based on venous sampling
** Data for T_{max} presented as median (range)

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of FENTORA was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6.

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng·hr/mL)	$AUC_{0\text{-}8}$ (ng·hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Metabolism

The metabolic pathways following buccal administration of FENTORA have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Elimination

Disposition of fentanyl following buccal administration of FENTORA has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Gender

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

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. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl impairs fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for FENTORA.

14 CLINICAL STUDIES

The efficacy of FENTORA was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of FENTORA. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of FENTORA and 3 being placebo. Patients used one tablet of study drug (either FENTORA or Placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

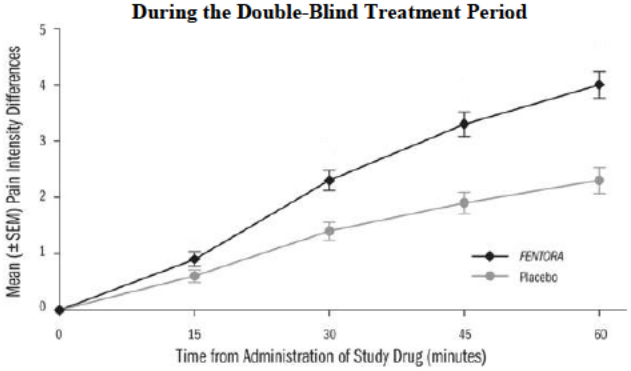
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 7. The median dose was 400 mcg.

Table 7. Successful Dose of FENTORA Following Initial Titration

FENTORA Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for FENTORA-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

FENTORA is supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in FENTORA can be fatal to a child. **Patients and their caregivers must be instructed to keep FENTORA out of the reach of children.** *[see Boxed Warning - WARNING RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL, Overdosage (10), and Patient/Caregiver Instructions (17.1)]*

Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)

Protect FENTORA from freezing and moisture. Do not use if the blister package has been tampered with.

16.2 Disposal of FENTORA

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed. Information is available in the *Patient Counseling Information (17.2)* and in the *Medication Guide*. If additional assistance is required, call Cephalon, Inc., at 1-800-896-5855.

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush FENTORA blister packages or cartons down the toilet. If you need additional assistance with disposal of FENTORA, call Cephalon, Inc., at 1-800-896-5855.

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with [C2], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 63459-541-28
200 mcg	2	Orange	NDC 63459-542-28
400 mcg	4	Sage green	NDC 63459-544-28
600 mcg	6	Magenta (pink)	NDC 63459-546-28
800 mcg	8	Yellow	NDC 63459-548-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide).*

17.1 Patient/Caregiver Instructions

- Before initiating treatment with FENTORA, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time FENTORA is dispensed because new information may be available.
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive FENTORA.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding FENTORA or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the FENTORA Medication Guide with every patient before initiating treatment with FENTORA.
  - Advise the patient that FENTORA 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 FENTORA.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of FENTORA.
  - 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, especially small children, exposed to FENTORA are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep FENTORA tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3) and Medication Guide for specific patient instructions.]*
- Instruct patients not to take FENTORA 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 FENTORA 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 FENTORA.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF FENTORA USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of FENTORA for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with FENTORA.
- Instruct patients NOT to share FENTORA and that sharing FENTORA with anyone else could result in the other individual's death due to overdose.
- Make patients aware that FENTORA contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in FENTORA, fentanyl, is a drug that some people abuse. FENTORA 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.
- Instruct patients not to open the blister until ready to use FENTORA and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.
- Instruct patients that FENTORA tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking FENTORA.
- Instruct patients to use FENTORA exactly as prescribed by their doctor and not to take FENTORA more often than prescribed.
- Caution patients that FENTORA 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 FENTORA of these dangers and counsel them accordingly.
- Warn patients to not combine FENTORA 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 FENTORA, they should ask their doctor about the effects that FENTORA (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 Disposal of Unopened FENTORA Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush the FENTORA blister packages or cartons down the toilet.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of FENTORA are provided in the FENTORA *Medication Guide*. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Cephalon toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

MEDICATION GUIDE

FENTORA® (fen-tor-a) CII
(fentanyl citrate) buccal tablet
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use FENTORA 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 FENTORA in a safe place away from children.

Get emergency help right away if:

- **a child takes FENTORA. FENTORA can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed FENTORA uses it**
- **an adult who is not already taking opioids around-the-clock, uses FENTORA.**

These are medical emergencies that can cause death. If possible, try to remove FENTORA from the mouth.

Read this Medication Guide completely before you start using FENTORA, 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 FENTORA?

FENTORA can cause life-threatening breathing problems which can lead to death.

1. **Do not use FENTORA 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 FENTORA. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use FENTORA exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of FENTORA for each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain with FENTORA. **See the Medication Guide section "How should I use FENTORA?" and the Patient Instructions for Use at the end of this Medication Guide for detailed information about how to use FENTORA the right way.**
4. **Do not switch from FENTORA to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of FENTORA is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of FENTORA that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use FENTORA 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 FENTORA to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   FENTORA 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 FENTORA in a safe place** to protect it from being stolen. FENTORA can be a target for people who abuse (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
7. FENTORA 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 FENTORA, you must:
   - talk to your healthcare provider

- understand the benefits and risks of FENTORA
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form.

What is FENTORA?

- FENTORA is a prescription medicine that contains the medicine fentanyl.
- FENTORA is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- FENTORA 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 FENTORA if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using FENTORA.
- FENTORA is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if FENTORA is safe and effective in children under 18 years of age.

Who should not use FENTORA?

Do not use FENTORA:

- **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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in FENTORA. See the end of this Medication Guide for a complete list of ingredients in FENTORA.

What should I tell my healthcare provider before using FENTORA?

Before using FENTORA, 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. FENTORA may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. FENTORA passes into your breast milk. It can cause serious harm to your baby. You should not take FENTORA 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 FENTORA. Sometimes, the doses of certain medicines and FENTORA need to be changed if used together.

- **Do not take any medicine while using FENTORA 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 FENTORA.**
- 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 FENTORA?

Before you can begin to use FENTORA:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- FENTORA 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 FENTORA prescription filled.

Using FENTORA:

- **Use FENTORA exactly as prescribed. Do not use FENTORA 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 FENTORA the right way.**
- **Do not split, suck, chew, or swallow FENTORA tablets. You will get less relief for your breakthrough cancer pain.**
- **Use FENTORA tablets whole.**
- Wait 30 minutes after using FENTORA. If there is any of the FENTORA 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 FENTORA for each episode of breakthrough cancer pain.
  - Use **1** dose of FENTORA for an episode of breakthrough cancer pain.
  - If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of FENTORA, you can use **only 1** more dose of FENTORA as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of FENTORA, call your healthcare provider for instructions. **Do not use another dose of FENTORA at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with FENTORA.
  - If you only need to take 1 dose of FENTORA for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of FENTORA for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using FENTORA.
- Talk to your healthcare provider if your dose of FENTORA does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of FENTORA 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 much FENTORA 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 FENTORA?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how FENTORA affects you. FENTORA can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using FENTORA.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of FENTORA?

FENTORA 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 FENTORA?**"
   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 much FENTORA 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 FENTORA 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 FENTORA 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 or the inside of your cheek).** Tell your healthcare provider if this is a problem for you.

The most common side effects of FENTORA 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 FENTORA 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 FENTORA.

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 FENTORA. 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 FENTORA?

- **Always keep FENTORA in a safe place away from children and from anyone for whom it has not been prescribed**. Protect FENTORA from theft.
- Store FENTORA at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze FENTORA.
- Keep FENTORA in the original blister unit. Do not remove FENTORA from its blister packaging for storage in a temporary container, such as a pill box.
- Keep FENTORA dry.

How should I dispose of unused FENTORA tablets when they are no longer needed?

- Dispose of any unused FENTORA tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the FENTORA packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of FENTORA, call Cephalon, Inc., at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

General information about FENTORA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use FENTORA only for the purpose for which it was prescribed**. **Do not give FENTORA to other people, even if they have the same symptoms you have.** FENTORA can harm other people and even cause death. Sharing FENTORA is against the law.

This Medication Guide summarizes the most important information about FENTORA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about FENTORA 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 in FENTORA?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient Instructions for Use

Before you use FENTORA, 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 FENTORA the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use FENTORA.

When you get an episode of breakthrough cancer pain, use the dose of FENTORA prescribed by your healthcare provider as follows:

- FENTORA comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your FENTORA tablets will be printed in the boxed area shown as **XXX mcg** (See Figure 1).

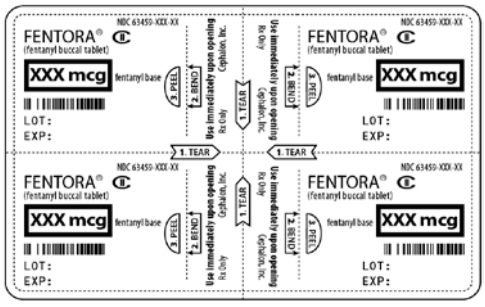


Figure 1

- Peel back foil on blister unit to expose tablet (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, FENTORA tablet must be used right away.
- Do not split the FENTORA tablet. **Use FENTORA tablets whole**.
- Place a FENTORA tablet in your mouth above a rear molar tooth between the upper cheek and gum. **Leave the tablet in place until it dissolves.** A FENTORA tablet generally takes between 14 to 25 minutes to dissolve (See Figure 3).

Figure 3

- After 30 minutes, if there is any FENTORA left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use FENTORA in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do. Do not split the tablet.
- **Do not split, suck, chew or swallow FENTORA tablets.** You will get less relief for your breakthrough cancer pain.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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FENTORA is a trademark of Cephalon, Inc. or its affiliates.

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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
SUBSYS™ (fentanyl sublingual spray)	Insys Therapeutics Inc.	100 mcg 200 mcg 400 mcg 600 mcg 800 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

[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.

<u>Outpatient Pharmacies</u>

- 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.

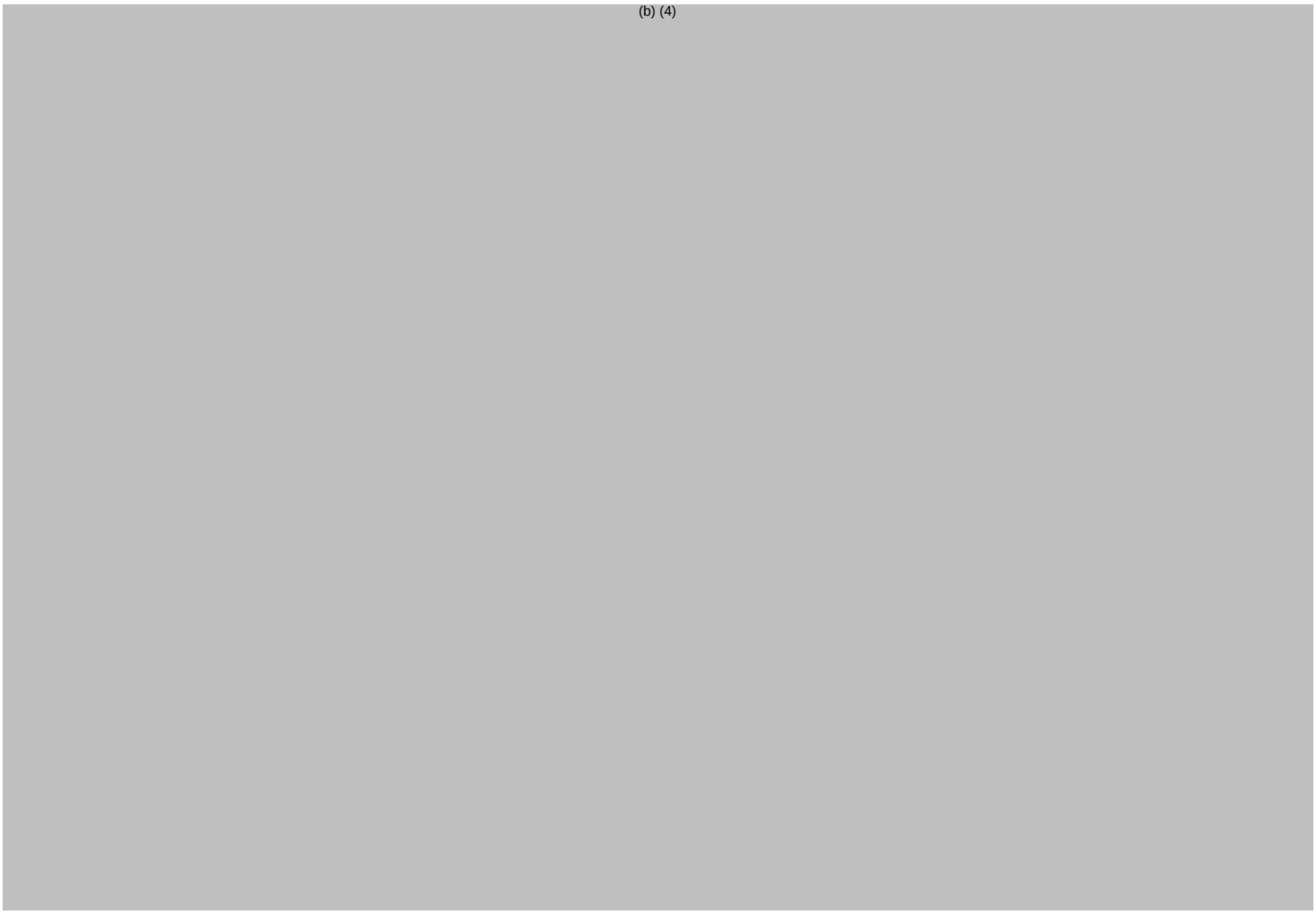
The call center specialists' responsibilities will include, but are not limited to, the following:

- 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

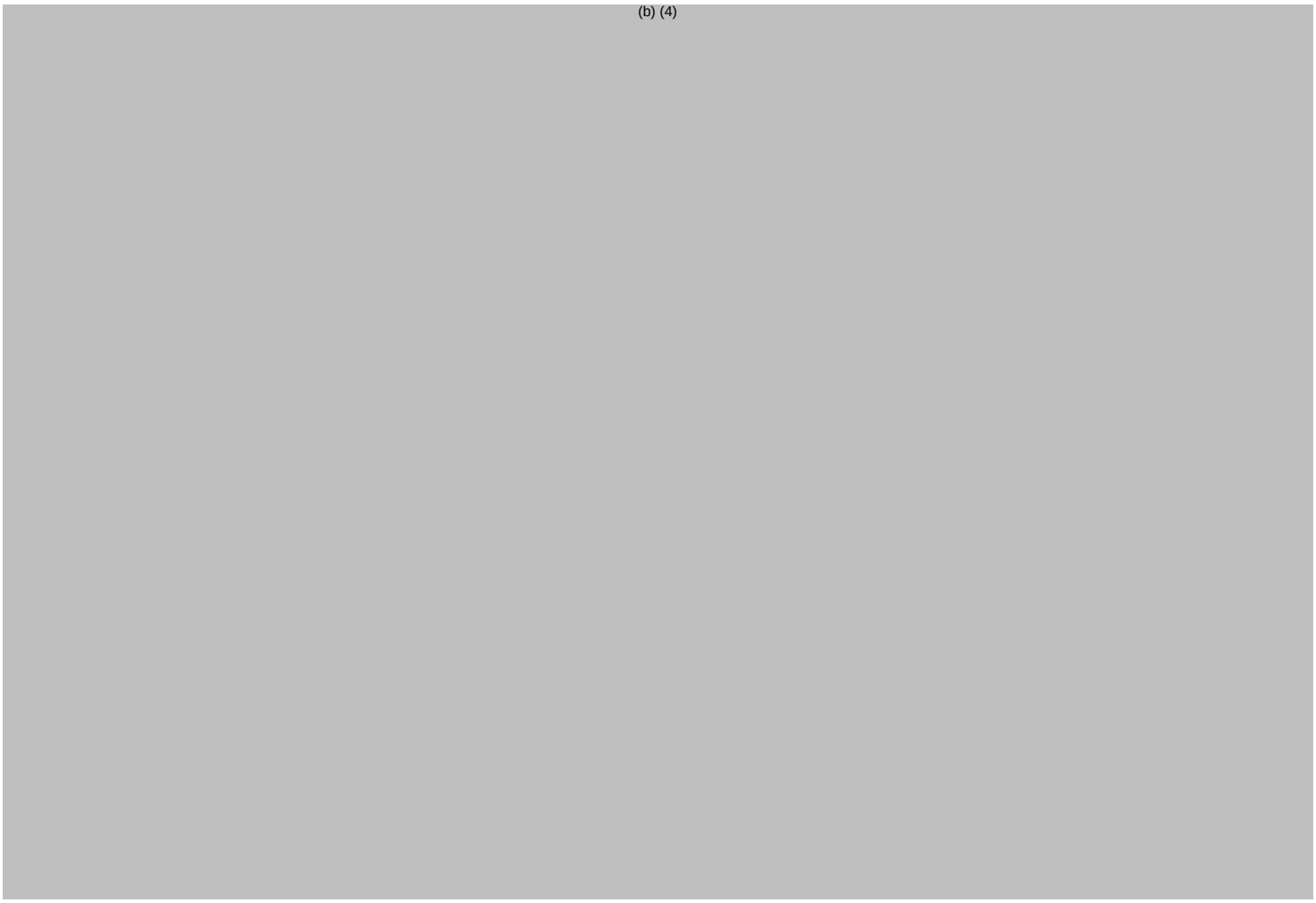
The following metrics will be tabulated for every reporting period to assess program outreach efforts:

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



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 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)
- SUBSYS™ (fentanyl sublingual spray)
- Approved generic equivalents of these products are also covered under this program.

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947/S-015
Communication Type:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	Compton/3-9-12
Clearance History:	Stradley 6/1 Racoosin/ 6/4 SRT/SWAT/5-14-12
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

Version: DARRTS 11/15/11

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

NDA 021947/S-015

SUPPLEMENT APPROVAL

Cephalon, Inc
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Sr. Regulatory Associate

Dear Ms. Kampf:

Please refer to your Supplemental New Drug Application (sNDA) dated February 8, 2012, received February 9, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl buccal tablets).

We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated February 8, 2012.

This supplemental new drug application proposes modifications to the approved REMS for FENTORA, 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.

CONTENT OF LABELING

The label approved on December 28, 2011, as part of supplement S-013, is attached for your convenience.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for FENTORA was originally approved on July 20, 2011. The REMS was modified on December 28, 2011, as part of the approval of the TIRF REMS single-shared system. 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 consist of edits to the Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray), and minor editorial changes. Additionally, the TIRF REMS Access Program “go-live” placeholder date has been updated with the actual "go-live" date of March 12, 2012.

Your proposed modified REMS, submitted on February 8, 2012, and appended to this letter, is approved.

The TIRF REMS Access program includes the following products:

NDA 020747	Actiq (fentanyl citrate) oral transmucosl 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 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.

The timetable for submission of assessments of the REMS is amended to correspond with the TIRF REMS Access Program timetable for submission of assessments approved on December 28, 2011. The first assessment is due June 28, 2012, and the second assessment is due December 28, 2012, and assessments are due annually thereafter.

There are no changes to the REMS assessment plan described in our December 28, 2011, letter.

We remind you that assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in this approved REMS, you must submit a REMS assessment and may propose a modification to the approved

REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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:

NDA 021947
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021947
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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 NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FENTORA safely and effectively. See full prescribing information for FENTORA.

FENTORA® (fentanyl citrate) buccal tablet, CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL
See full prescribing information for complete boxed warning.
- **Due to the risk of fatal respiratory depression, FENTORA 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to FENTORA. (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)**
- **FENTORA 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2011
Warnings and Precautions, TIRF REMS Access Program (5.11)	12/2011

----------INDICATIONS AND USAGE----------

FENTORA is an opioid agonist indicated 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. (1)
Limitations of Use:
FENTORA 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 FENTORA. (1)
- Initial dose of FENTORA: 100 mcg. (2.1)
- Initiate titration using multiples of 100 mcg FENTORA tablet. Limit patient access to only one strength of FENTORA at any one time. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single FENTORA tablet. (2 1)
- No more than two doses can be taken per breakthrough pain episode. (2.1)
- Wait at least 4 hours before treating another episode of breakthrough pain with FENTORA. (2.1)
- Place entire tablet in buccal cavity; tablet is not to be split, sucked, chewed or swallowed. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl or components of FENTORA. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate FENTORA 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cephalon, Inc., at 1-800-896-5855 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 FENTORA with caution to patients with hepatic or renal impairment. (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 FENTORA, including following use in opioid non-tolerant patients and improper dosing. The substitution of FENTORA for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, FENTORA is contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

FENTORA 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 FENTORA with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of FENTORA 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 FENTORA. *[see Dosage and Administration* (2.1)]

- When dispensing, do not substitute a FENTORA prescription for other fentanyl products.

ABUSE POTENTIAL

FENTORA contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. FENTORA can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing FENTORA 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, FENTORA is available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

FENTORA is indicated 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. 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/hr of transdermal fentanyl, 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 while taking FENTORA.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, FENTORA is contraindicated in the management of acute or postoperative pain.

FENTORA is 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.

Limitations of Use:

As a part of the TIRF REMS Access program, FENTORA may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]*. For inpatient administration of FENTORA (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe FENTORA 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 FENTORA *[see Warnings and Precautions (5.11)]*.

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

2.1 Initial Dose

FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

Patients on Actiq

The initial dose of FENTORA is **always** 100 mcg with the only exception being patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1). The doses of FENTORA in this table are starting doses and not intended to represent equianalgesic doses to Actiq. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial FENTORA Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*****From this initial dose, titrate patient to effective dose.

b. For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength.

All Other Patients
The initial dose of FENTORA is 100 mcg.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of FENTORA for any episode of breakthrough pain.
b. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA.

2.2 Dose Titration

a. From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of FENTORA over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted.
b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg FENTORA tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of FENTORA for any breakthrough pain episode. During titration, one **dose** of FENTORA may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).
d. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA. To reduce the risk of overdose during titration, patients should have only one strength of FENTORA tablets available at any time.
e. Patients should be strongly encouraged to use all of their FENTORA tablets of one strength prior to being prescribed the next strength. If this is not practical, unused FENTORA should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened FENTORA tablets remaining from a prescription as soon as they are no longer needed.

2.3 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use **only ONE** FENTORA tablet of the appropriate strength per breakthrough pain episode.
b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode.
c. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with FENTORA.
d. Dosage adjustment of FENTORA may be required in some patients. Generally, the FENTORA 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.
e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.

2.4 Administration of FENTORA

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer FENTORA.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire FENTORA tablet in the buccal cavity (above a rear molar, between the upper cheek and gum). **Patients should not split the tablet.**

The FENTORA tablet should not be sucked, chewed or swallowed, as this will result in lower plasma concentrations than when taken as directed.

The FENTORA tablet should be left between the cheek and gum until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the FENTORA tablet remain, they may be swallowed with a glass of water.

It is recommended that patients alternate sides of the mouth when administering subsequent doses of FENTORA.

3 DOSAGE FORMS AND STRENGTHS

FENTORA tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*.

4 CONTRAINDICATIONS

FENTORA is contraindicated in opioid non-tolerant patients.

FENTORA 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.

FENTORA is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

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 FENTORA. 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

FENTORA is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and FENTORA are not equivalent on a microgram per microgram basis. FENTORA is NOT a generic version of Actiq. **All patients should be titrated from the 100 mcg dose.**

The initial dose of FENTORA should be 100 mcg. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a FENTORA prescription for an Actiq prescription under any circumstances. FENTORA and

Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of FENTORA compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of FENTORA for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that FENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1), and Medication Guide for specific patient instructions.]*

5.4 Additive CNS Depressant Effects

The concomitant use of FENTORA 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., hypoventilation, 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 FENTORA 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 FENTORA of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate FENTORA with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of FENTORA may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer FENTORA 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to FENTORA reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients.

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use FENTORA with caution in patients with bradyarrhythmias.

5.10 MAO Inhibitors

FENTORA 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.

5.11 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)]*, FENTORA 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 FENTORA, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe FENTORA 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 FENTORA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense FENTORA must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute FENTORA 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 FENTORA has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The most commonly observed adverse events seen with FENTORA are typical of opioid side effects. Opioid side effects should be expected and managed accordingly.

The clinical trials of FENTORA were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

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.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received FENTORA for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of FENTORA therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of FENTORA. There was no evidence of excess toxicity in this subset of patients.

The duration of exposure to FENTORA varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving FENTORA. Events are classified by system organ class.

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy
Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when FENTORA is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of FENTORA with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving FENTORA who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]*. The concomitant use of FENTORA with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of FENTORA. Patients receiving FENTORA who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased FENTORA activity and the dose of FENTORA should be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women. FENTORA 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 characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal 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 FENTORA.

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 FENTORA for analgesia 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 FENTORA 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 FENTORA.

8.4 Pediatric Use

The safety and efficacy of FENTORA have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of FENTORA, 69 (23%) were 65 years of age and older.

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating FENTORA 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 FENTORA 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 patients with cancer 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.

8.8 Race

The pharmacokinetic effects of race with the use of FENTORA have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse and Addiction

Handle FENTORA appropriately to minimize the risk of diversion, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law.

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, since 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. FENTORA should be prescribed with caution to patients who have a higher risk of substance abuse, including patients with bipolar disorder and/or schizophrenia.

Patients with chronic pain may be at a higher risk for suicide.

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 non-medical purposes, often in combination with other psychoactive substances. Since FENTORA tablets may be diverted for non-medical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation 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 Physical Dependence and Withdrawal

The administration of FENTORA should be guided by the response of the patient. Physical dependence, per se, is not ordinarily a concern when one is treating a patient with cancer and chronic 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 FENTORA 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 hypoventilation *[see Clinical Pharmacology (12.2)]*.

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the FENTORA tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 FENTORA 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 hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of FENTORA, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

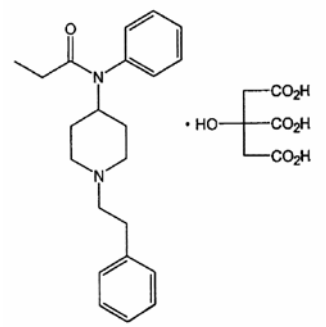
11 DESCRIPTION

FENTORA (fentanyl buccal tablet) is a potent opioid analgesic, intended for buccal mucosal administration.

FENTORA is designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

FENTORA employs the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

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 FENTORA should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*.

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 another oral transmucosal fentanyl citrate (Actiq). 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) and Overdosage (10).

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of FENTORA increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption

Following buccal administration of FENTORA, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of FENTORA is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of FENTORA and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with FENTORA) (Table 4).

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving FENTORA or Actiq

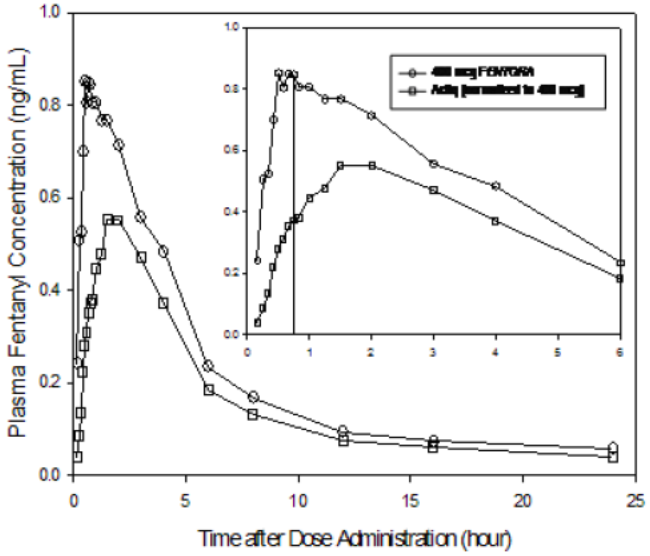
Pharmacokinetic Parameter (mean)	FENTORA 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10 5%
Fraction Absorbed Transmucosally	48% ± 31 8%	22% ± 17 3%
T_{max} (minute)**	46 8 (20-240)	90 8 (35-240)
C_{max} (ng/mL)	1 02 ± 0 42	0 63 ± 0 21
$AUC_{0\text{-}tmax}$ (ng·hr/mL)	0 40 ± 0 18	0 14 ± 0 05
$AUC_{0\text{-}inf}$ (ng·hr/mL)	6 48 ± 2 98	4 79 ± 1 96

* Based on venous blood samples
** Data for T_{max} presented as median (range)
*** Actiq (OTFC) data was dose adjusted (800 mcg to 400 mcg)

Similarly, in another bioavailability study exposure following administration of FENTORA was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl were substantially greater with FENTORA compared to Actiq (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for FENTORA.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of FENTORA and Actiq in Healthy Subjects



Actiq data was dose adjusted (800 mcg to 400 mcg).

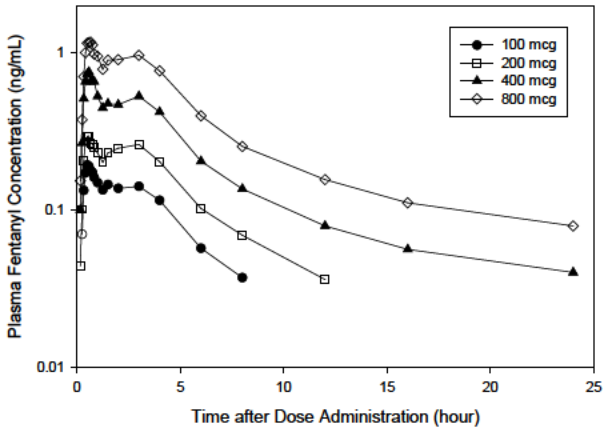
Mean pharmacokinetic parameters are presented in Table 5. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0 25 ± 0 14	0 40 ± 0 18	0 97 ± 0 53	1 59 ± 0 90
T_{max} minute** (range)	45 0 (25 0 - 181 0)	40 0 (20 0 - 180 0)	35 0 (20 0 - 180 0)	40 0 (25 0 - 180 0)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	0 98 ± 0 37	2 11 ± 1 13	4 72 ± 1 95	9 05 ± 3 72
$AUC_{0\text{-}tmax}$ (ng·hr/mL)	0 09 ± 0 06	0 13 ± 0 09	0 34 ± 0 23	0 52 ± 0 38
T1/2, hr**	2 63 (1 47 - 13 57)	4 43 (1 85 - 20 76)	11 09 (4 63 - 20 59)	11 70 (4 63 - 28 63)

* Based on venous sampling
** Data for T_{max} presented as median (range)

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of FENTORA was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6.

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng·hr/mL)	$AUC_{0\text{-}8}$ (ng·hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Metabolism

The metabolic pathways following buccal administration of FENTORA have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Elimination

Disposition of fentanyl following buccal administration of FENTORA has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Gender

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

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. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl impairs fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for FENTORA.

14 CLINICAL STUDIES

The efficacy of FENTORA was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of FENTORA. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of FENTORA and 3 being placebo. Patients used one tablet of study drug (either FENTORA or Placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

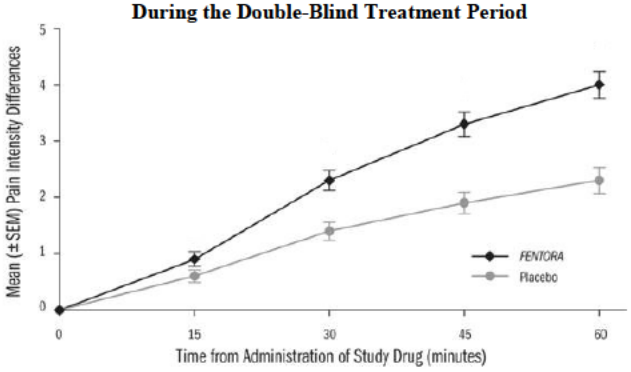
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 7. The median dose was 400 mcg.

Table 7. Successful Dose of FENTORA Following Initial Titration

FENTORA Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for FENTORA-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

FENTORA is supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in FENTORA can be fatal to a child. **Patients and their caregivers must be instructed to keep FENTORA out of the reach of children.** *[see Boxed Warning - WARNING RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL, Overdosage (10), and Patient/Caregiver Instructions (17.1)]*

Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)

Protect FENTORA from freezing and moisture. Do not use if the blister package has been tampered with.

16.2 Disposal of FENTORA

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed. Information is available in the *Patient Counseling Information (17.2)* and in the *Medication Guide*. If additional assistance is required, call Cephalon, Inc., at 1-800-896-5855.

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush FENTORA blister packages or cartons down the toilet. If you need additional assistance with disposal of FENTORA, call Cephalon, Inc., at 1-800-896-5855.

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with [C2], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 63459-541-28
200 mcg	2	Orange	NDC 63459-542-28
400 mcg	4	Sage green	NDC 63459-544-28
600 mcg	6	Magenta (pink)	NDC 63459-546-28
800 mcg	8	Yellow	NDC 63459-548-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (*Medication Guide).*

17.1 Patient/Caregiver Instructions

- Before initiating treatment with FENTORA, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time FENTORA is dispensed because new information may be available.
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive FENTORA.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding FENTORA or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the FENTORA Medication Guide with every patient before initiating treatment with FENTORA.
  - Advise the patient that FENTORA 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 FENTORA.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of FENTORA.
  - 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, especially small children, exposed to FENTORA are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep FENTORA tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1), Warnings and Precautions (5.3) and Medication Guide for specific patient instructions.]*
- Instruct patients not to take FENTORA 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 FENTORA 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 FENTORA.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF FENTORA USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of FENTORA for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with FENTORA.
- Instruct patients NOT to share FENTORA and that sharing FENTORA with anyone else could result in the other individual's death due to overdose.
- Make patients aware that FENTORA contains fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in FENTORA, fentanyl, is a drug that some people abuse. FENTORA 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.
- Instruct patients not to open the blister until ready to use FENTORA and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.
- Instruct patients that FENTORA tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking FENTORA.
- Instruct patients to use FENTORA exactly as prescribed by their doctor and not to take FENTORA more often than prescribed.
- Caution patients that FENTORA 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 FENTORA of these dangers and counsel them accordingly.
- Warn patients to not combine FENTORA 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 FENTORA, they should ask their doctor about the effects that FENTORA (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 Disposal of Unopened FENTORA Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused FENTORA, remove FENTORA tablets from blister packages and flush down the toilet. Do not flush the FENTORA blister packages or cartons down the toilet.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of FENTORA are provided in the FENTORA *Medication Guide*. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Cephalon toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

MEDICATION GUIDE

FENTORA® (fen-tor-a) CII
(fentanyl citrate) buccal tablet
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use FENTORA 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 FENTORA in a safe place away from children.

Get emergency help right away if:

- **a child takes FENTORA. FENTORA can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed FENTORA uses it**
- **an adult who is not already taking opioids around-the-clock, uses FENTORA.**

These are medical emergencies that can cause death. If possible, try to remove FENTORA from the mouth.

Read this Medication Guide completely before you start using FENTORA, 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 FENTORA?

FENTORA can cause life-threatening breathing problems which can lead to death.

1. **Do not use FENTORA 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 FENTORA. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use FENTORA exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of FENTORA for each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain with FENTORA. **See the Medication Guide section "How should I use FENTORA?" and the Patient Instructions for Use at the end of this Medication Guide for detailed information about how to use FENTORA the right way.**
4. **Do not switch from FENTORA to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of FENTORA is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of FENTORA that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use FENTORA 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 FENTORA to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   FENTORA 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 FENTORA in a safe place** to protect it from being stolen. FENTORA can be a target for people who abuse (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
7. FENTORA 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 FENTORA, you must:
   - talk to your healthcare provider

- understand the benefits and risks of FENTORA
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form.

What is FENTORA?

- FENTORA is a prescription medicine that contains the medicine fentanyl.
- FENTORA is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- FENTORA 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 FENTORA if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using FENTORA.
- FENTORA is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if FENTORA is safe and effective in children under 18 years of age.

Who should not use FENTORA?

Do not use FENTORA:

- **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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in FENTORA. See the end of this Medication Guide for a complete list of ingredients in FENTORA.

What should I tell my healthcare provider before using FENTORA?

Before using FENTORA, 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. FENTORA may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. FENTORA passes into your breast milk. It can cause serious harm to your baby. You should not take FENTORA 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 FENTORA. Sometimes, the doses of certain medicines and FENTORA need to be changed if used together.

- **Do not take any medicine while using FENTORA 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 FENTORA.**
- 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 FENTORA?

Before you can begin to use FENTORA:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- FENTORA 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 FENTORA prescription filled.

Using FENTORA:

- **Use FENTORA exactly as prescribed. Do not use FENTORA 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 FENTORA the right way.**
- **Do not split, suck, chew, or swallow FENTORA tablets. You will get less relief for your breakthrough cancer pain.**
- **Use FENTORA tablets whole.**
- Wait 30 minutes after using FENTORA. If there is any of the FENTORA 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 FENTORA for each episode of breakthrough cancer pain.
  - Use **1** dose of FENTORA for an episode of breakthrough cancer pain.
  - If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of FENTORA, you can use **only 1** more dose of FENTORA as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of FENTORA, call your healthcare provider for instructions. **Do not use another dose of FENTORA at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with FENTORA.
  - If you only need to take 1 dose of FENTORA for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of FENTORA for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using FENTORA.
- Talk to your healthcare provider if your dose of FENTORA does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of FENTORA 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 much FENTORA 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 FENTORA?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how FENTORA affects you. FENTORA can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using FENTORA.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of FENTORA?

FENTORA 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 FENTORA?**"
   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 much FENTORA 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 FENTORA 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 FENTORA 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 or the inside of your cheek).** Tell your healthcare provider if this is a problem for you.

The most common side effects of FENTORA 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 FENTORA 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 FENTORA.

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 FENTORA. 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 FENTORA?

- **Always keep FENTORA in a safe place away from children and from anyone for whom it has not been prescribed**. Protect FENTORA from theft.
- Store FENTORA at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze FENTORA.
- Keep FENTORA in the original blister unit. Do not remove FENTORA from its blister packaging for storage in a temporary container, such as a pill box.
- Keep FENTORA dry.

How should I dispose of unused FENTORA tablets when they are no longer needed?

- Dispose of any unused FENTORA tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the FENTORA packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of FENTORA, call Cephalon, Inc., at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

General information about FENTORA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use FENTORA only for the purpose for which it was prescribed**. **Do not give FENTORA to other people, even if they have the same symptoms you have.** FENTORA can harm other people and even cause death. Sharing FENTORA is against the law.

This Medication Guide summarizes the most important information about FENTORA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about FENTORA 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 in FENTORA?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient Instructions for Use

Before you use FENTORA, 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 FENTORA the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use FENTORA.

When you get an episode of breakthrough cancer pain, use the dose of FENTORA prescribed by your healthcare provider as follows:

- FENTORA comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your FENTORA tablets will be printed in the boxed area shown as **XXX mcg** (See Figure 1).

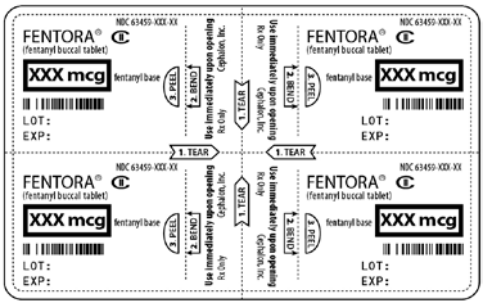


Figure 1

- Peel back foil on blister unit to expose tablet (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, FENTORA tablet must be used right away.
- Do not split the FENTORA tablet. **Use FENTORA tablets whole**.
- Place a FENTORA tablet in your mouth above a rear molar tooth between the upper cheek and gum. **Leave the tablet in place until it dissolves.** A FENTORA tablet generally takes between 14 to 25 minutes to dissolve (See Figure 3).

Figure 3

- After 30 minutes, if there is any FENTORA left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use FENTORA in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do. Do not split the tablet.
- **Do not split, suck, chew or swallow FENTORA tablets.** You will get less relief for your breakthrough cancer pain.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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FENTORA is a trademark of Cephalon, Inc. or its affiliates.

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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* 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.
5. 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 **outpatient pharmacies** or through the call center **for closed system pharmacies**.
7. 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.
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 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
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 03/12/2012,** 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.

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.

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
- 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.

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 ABSTRA_ 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 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 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.
Subsys™ ˛fentan˛l˛ sublingual spray	Always 100 mcg.	If the breakthrough ˛ ain e˛ isode 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 ade ˛uate anal˛esia is achieved usin˛ a sin˛le 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 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* _____
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

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
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):_____

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" 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:

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

II. 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. 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 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.

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 03/12/2012**, 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 03/12/2012**, 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.

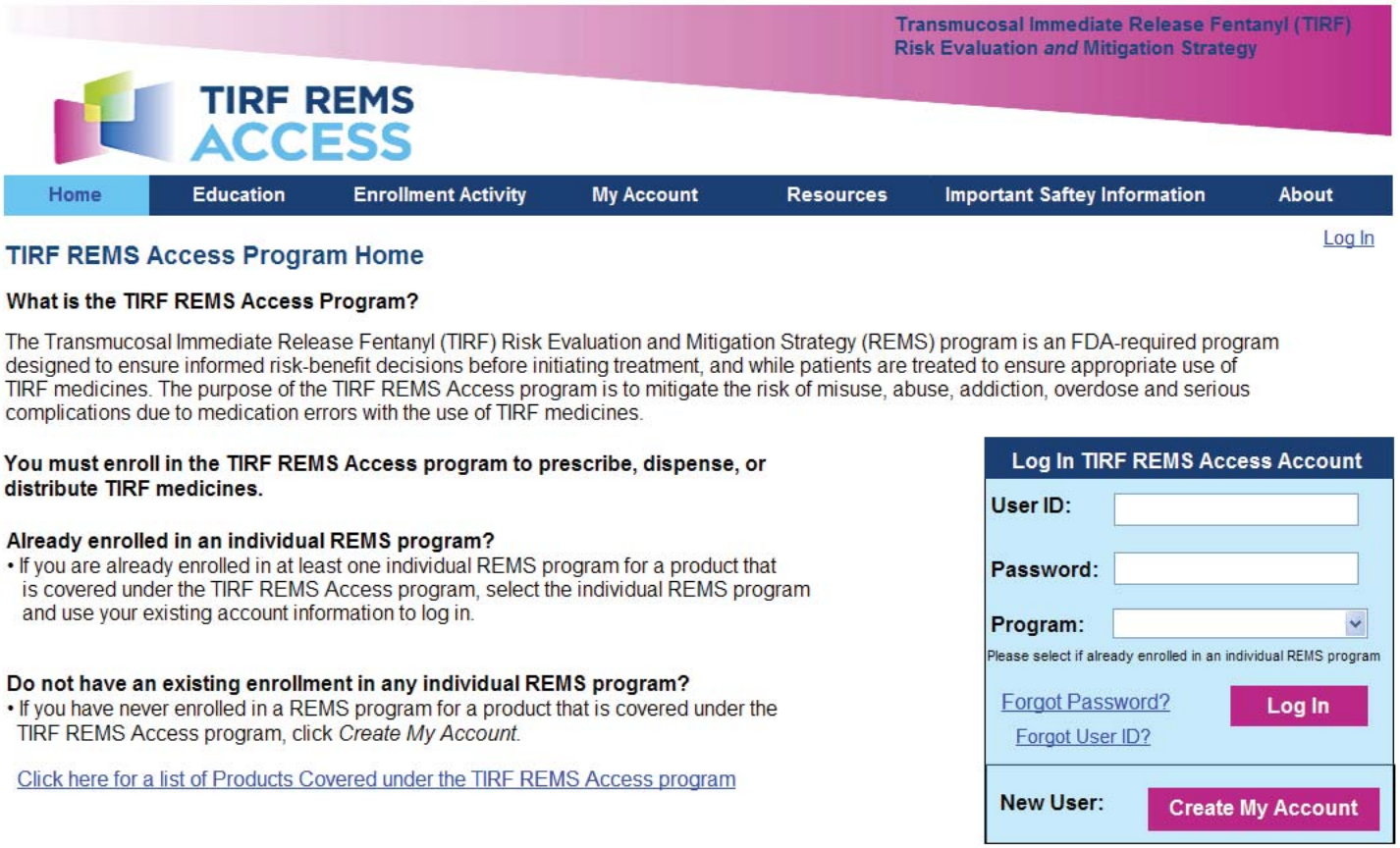
What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines 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



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 03/12/2012.** 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 03/12/2012**. 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.

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 03/12/2012**, 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

- 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
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 03/12/2012**, 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

- 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
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 03/12/2012** 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

- 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
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, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-30, 20482-002-30, 20482-004-30, 20482-006-30, 20482-008-30, 20482-012-30, 20482-016-30,
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 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[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
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, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-30, 20482-002-30, 20482-004-30, 20482-006-30, 20482-008-30, 20482-012-30, 20482-016-30,
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 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 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
Closed System Pharmacy Enrollment Form

To submit this form via fax, 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. 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 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 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 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.
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.

Closed System Chain ID*:_____

Authorized Closed System Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System 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 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 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

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):_____

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):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

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 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 03/12/2012**. 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 03/12/2012**, 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 – [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 03/12/2012**. 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 03/12/2012**. 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 03/12/2012**. 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 03/12/2012**, 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

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):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

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

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.

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/s/

JUDITH A RACOOSIN
06/05/2012

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 020747 NDA 021947
Communication Type:	Correspondence
Communication Group:	NDA Information Request/Advice
Communication Name:	General Advice Letter
Communication ID:	COR-NDAIR-10
Drafted by:	Nancy Dickinson/6-29-12
Reviewed by and dates	
Clearance History:	Compton/6-29-12 Won/6-29-12 Stradley/6/29/12 Racoosin/ 6/29/12
Finalized:	
Filename:	
Use Statement:	Use to send general advice to the applicant that is not necessarily related to a pending application.
Notes:	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 can administer an exercise enforcement discretion letter regarding a sponsor's compliance with specific required elements of REMS during their transition to full operation of the REMS. FDA administered 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 must be met during the transition to full operation of the TIRF REMS. A second enforcement discretion letter to the TIRF REMS sponsors sent on March 12, 2012 stated that all integrated health systems must be enrolled in the TIRF REMS Access Program on June 30, 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

NDA 021947
NDA 020747

REMS COMMUNICATION

Cephalon, Inc
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Sr. Regulatory Associate

Dear Ms. Kampf:

This letter is in reference to 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
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanyl) 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).

The enforcement discretion letter dated March 20, 2012, stated that all integrated healthcare systems must be enrolled in the TIRF REMS Access Program by June 30, 2012. FDA approved a modification of the TIRF REMS on June 5, 2012, to include a closed system pharmacy enrollment form that would enable integrated healthcare systems (closed systems) to enroll in the REMS and meet the enrollment deadline.

In May 2012, FDA learned that Department of Defense (DoD) medical logistics units (MLUs), located within military medical centers, were not able to enroll in the TIRF REMS as inpatient pharmacies. DoD MLUs are facilities located on bases that provide the initial supply of

medicines, including TIRF medicines, to Special Operations units prior to mission deployments. There is currently no mechanism for enrolling these units in the TIRF REMS Access Program as they are not considered to be inpatient, outpatient, or closed system pharmacies. Therefore, FDA is concerned that the TIRF REMS Access Program may stop distributors from shipping to these units because they will not be enrolled in the REMS by June 30, 2012. Because of their unique role and the fact that these units dispense medication to be used solely on the battlefield, FDA has determined that TIRF medications can continue to be distributed to these DoD MLUs, which do not operate as pharmacies, without enrolling them in the REMS. DoD will provide a list of the MLUs to the TIRF REMS Access Program so that distributors will know who they are and that they can receive TIRF medicines.

If you have any questions, Kimberly Compton R.Ph., Sr. Regulatory Health Project Manager, at (301) 796-1191.

Sincerely yours,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

JUDITH A RACOOSIN
06/29/2012

From:	Liberatore, Mark
To:	Willene Brondum (wbrondum@insysrx.com)
Cc:	Lehrfeld, Kimberly; Mehta, Reema; Liberatore, Mark; Jenkins, Darrell
Subject:	PPAF
Date:	Monday, October 29, 2012 9:45:17 AM

Dear Willy,

FDA acknowledges the TRIG's concerns regarding physicians who have expressed dissatisfaction that they cannot use their medical judgment to enroll certain patients in the TIRF REMS Access Program because those patients are not opioid tolerant as required by the REMS.

In your email from September 18, 2012 you stated the TRIG believes "the aim of the TIRF REMS Access program is to educate and thereby enable safe use of TIRF medicines without being unduly burdensome on patient access to the drug." FDA disagrees with this statement. The purpose of the TIRF REMS Access Program, as is stated in the REMS Goals, is to mitigate the risk of "overdose and serious complications due to medication errors by prescribing and dispensing TIRF medications only to appropriate patients, which includes use only in opioid-tolerant patients." Furthermore, TIRF medications are contraindicated in non-opioid tolerant patients.

FDA is in agreement with scheduling a teleconference to discuss this issue. In particular, we would like to discuss how the TRIG proposes to address this situation while continuing to meet the goals of the TIRF REMS Access Program. I will look to schedule this teleconference in the near future.

Regards,

-Mark

MARK LIBERATORE, PHARM. D.
LT, UNITED STATES PUBLIC HEALTH SERVICE
SAFETY REGULATORY PROJECT MANAGER
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
10903 NEW HAMPSHIRE AVENUE
SILVER SPRING, MARYLAND 20993
BUILDING 22, ROOM 4487
MARK.LIBERATORE@FDA.HHS.GOV
301-796-2221

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/s/

MARK A LIBERATORE
10/29/2012

From: Liberatore, Mark
To: Servello, Diane L
Cc: Jenkins, Darrell; wbrondum@insysrx.com; Liberatore, Mark
Subject: RE: Pre-testing of KAB Survey questions
Date: Thursday, August 01, 2013 10:30:27 AM

Hello Diane,

Please see the response to your May 29 email regarding protocols for KAB surveys:

We acknowledge that you provided the survey methodology and instruments to assess the patients/caregivers', prescribers', and pharmacists' understanding of the key risk messages and safe use conditions of TIRF medicines. We offer the following comments and recommendations for the proposed survey protocols. Please modify the survey protocols accordingly before the launch of the second wave of surveys.

For the Prescriber Survey:

- *Revise the statement on page 11 of the proposed survey protocol of "Participants will be informed that prescribers from these states are not eligible to participate and physicians who practice in these states will not receive compensation for their participation." to "Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation."*
- *Base the study analysis for representativeness of prescribers on at least prescribers' medical specialty, medical degree, and geography.*

For the Patient Survey:

- *Move the link (page 19) of "How to learn more about transmucosal immediate release fentanyl medicines" from the online survey preamble to after respondents complete the survey because the link quoted above may include information that educates or influences a respondent's ability to answer subsequent survey questions.*
- *Add one question to ask which specific TIRF medicine has the patient taken after Question #3. For example, "Please specify which TIRF medicine that you or the person you take care of have filled within the last 3 months. (select from a drop-down list of TIRF medicines)(select all that apply)".*

For All Survey Protocols

- *Include in analyses all eligible surveys that are completed.*
- *Make a conclusion in your assessment submission about whether or not the REMS is meeting the REMS goals, and what changes, if any, you propose.*
- *Do not submit your methodology and instruments again prior to the assessment submission. Submit all methodology and instruments utilized with your assessments with track changes to mark any deviations made from the proposed survey protocols and survey instruments.*

Please let me know if you have any questions.
Kind regards,
-Mark

Mark Liberatore, Pharm.D.
Lieutenant Commander, US Public Health Service

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 4487
Silver Spring, MD 20993

301.796.2221
mark.liberatore@fda.hhs.gov

From: Servello, Diane L [mailto:Diane.Servello@covidien.com]
Sent: Wednesday, May 29, 2013 3:01 PM
To: Liberatore, Mark
Cc: Jenkins, Darrell; wbrondum@insysrx.com
Subject: RE: Pre-testing of KAB Survey questions

Mark:

As communicated in the e-mails below, the TRIG has revised our protocols for KAB surveys to incorporate the results from pre-testing conducted to determine the reasons for the poor performance on several key risk message questions from our last survey. The revised protocols are enclosed as follows:

1. Patient/Caregiver KAB protocol.
2. Pharmacist KAB protocol.
3. Prescriber KAB protocol.

In order to allow enough time to conduct the KAB surveys and provide results in our next assessment report, the TRIG needs the Agency's comments on these protocols within a 60 day

timeframe. In your e-mail below, you confirmed that the Agency will target August 3, 2013 to provide any feedback to the TRIG regarding the protocols.

Thank you for your assistance in expediting the review of these protocols. We look forward to receiving your comments.

Best regards,
Diane

Diane Servello
Sr. Director, Regulatory Affairs - API/Specialty Generics/Regulatory Operations
Mallinckrodt (a Covidien Company)
675 McDonnell Blvd.
Hazelwood, MO 63042 USA

Office: 314-654-3320
Mobile: 256-714-3694
Fax: 314-654-6496
e-mail: diane.servello@covidien.com

From: Liberatore, Mark [mailto:Mark.Liberatore@fda.hhs.gov]
Sent: Monday, April 22, 2013 12:03 PM
To: Servello, Diane L
Cc: Jenkins, Darrell; wbrondum@insysrx.com; Kopper, Nathan; Liberatore, Mark
Subject: RE: Pre-testing of KAB Survey questions

Diane,

The team agrees with the dates outlined below. We will expect the KAB protocol by June 3rd, and will target August 3rd for reply to what the TRIG sends to the Agency.

Regards,
-Mark

From: Liberatore, Mark
Sent: Monday, April 22, 2013 8:31 AM
To: 'Servello, Diane L'
Cc: Jenkins, Darrell; wbrondum@insysrx.com; Kopper, Nathan
Subject: RE: Pre-testing of KAB Survey questions

Diane,

I forwarded the email below to the team. I will make you aware of any feedback as it

becomes available.

Regards,
-Mark

From: Servello, Diane L [mailto:Diane.Servello@covidien.com]
Sent: Friday, April 19, 2013 4:52 PM
To: Liberatore, Mark
Cc: Jenkins, Darrell; wbrondum@insysrx.com; Kopper, Nathan
Subject: Pre-testing of KAB Survey questions

Dear Mark:

I refer to your 3/15/2013 e-mail providing questions to the TRIG regarding our 12 month Assessment report. In the section pertaining to our KAB survey, the Agency recommended that pre-testing be conducted on questions related to the key risk messages prior to our next survey to determine the reasons for the poor performance on these questions. We are currently making arrangements to conduct the pre-testing. According to the current timeline, we expect to have a revised KAB survey protocol which incorporates the modifications from the pre-testing ready for submission to the Agency by the week of June 3rd. In order to allow enough time to conduct the KAB survey and provide results in our next assessment report, we would need the Agency's comments within a 60 day timeframe. The TRIG has opted to conduct the survey in September 2013, even if we have not received the Agency's comments by that time, so that the results of the KAB survey will be available for inclusion with our assessment report that is due in December 2013.

Please let me know if you have any comments or questions.

Best regards,
Diane

Diane Servello
Sr. Director, Regulatory Affairs - API/Specialty Generics/Regulatory Operations
Mallinckrodt (a Covidien Company)
675 McDonnell Blvd.
Hazelwood, MO 63042 USA

Office: 314-654-3320
Mobile: 256-714-3694
Fax: 314-654-6496
e-mail: diane.servello@covidien.com

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/s/

MARK A LIBERATORE
08/22/2013

Memorandum to File

Subject: Single Shared System Vendor Question

On August 21, 2013, this email was sent to the TRIG point of contact. The following chart represents the reply sent by the TRIG on August 30, 2013.

From:	Liberatore, Mark
To:	Servello, Diane L (Diane.Servello@mallinckrodt.com)
Cc:	Jarral, Vaishali; Jenkins, Darrell; Liberatore, Mark
Subject:	SSS REMS Vendor Question
Date:	Wednesday, August 21, 2013 1:56:41 PM

Hi Diane,

Please see the following inquiry from the team. This is unrelated to Mod 2 or DMF discussions:

> FDA is updating our records regarding the vendors and sub-vendors responsible for implementing the various aspects of the shared system REMS. Please include such vendors as; project management vendors, fulfillment vendors, survey vendors, call center vendors, database vendors, educational vendors, or any other vendors that support the shared system REMS.

Please provide a spreadsheet listing the following information for each vendor:

> Contact information (name and phone number), physical address where the work for the REMS is performed, description of the vendor's function.

Please provide this information to me, when able.

If you have any questions, please let me know.

Thank you for your assistance.

Kind regards,

-Mark

Mark Liberatore, Pharm.D.

Lieutenant Commander, US Public Health Service

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 4487

Silver Spring, MD 20993

301.796.2221

mark.liberatore@fda.hhs.gov

TIRF REMS Access Vendor List

Name	Type	Contact Person	Physical Address	Description of Function
McKesson Specialty Health	REMS Administrator & Submission Agent	Doug Lawrence 480-663-4109	4343 N Scottsdale Road, Suite 150 Scottsdale, AZ 85251	McKesson Specialty Health (MSH) is responsible for the administration of the TIRF REMS Access call center, website and REMS database. MSH also acts as the TIRF REMS Submission Agent.
RelayHealth	Affiliate of McKesson Specialty Health	Dave Gallagher 404-728-2132	1564 Northeast Expressway Atlanta, GA 30329-2010	RelayHealth is responsible for pharmacy network channel development. RelayHealth is also responsible for processing pharmacy claims through the REMS edits to provide authorization prior to pharmacy dispensing.
United BioSource Corporation	KAB Survey Administrator and Assessment Reporting	Annette Stemhagen 215-591-2887	920 Harvest Drive, Suite 200 Blue Bell, PA 19422	United BioSource Corporation is responsible for administration of TIRF REMS Access KAB survey and preparation of REMS Assessment reports.
Accenture	eCTD Consultant	Matt Francis 610-535-6500 X 5665	585 East Swedesford Road Wayne, PA 19087	Accenture acts as the REMS Submission Holder for TIRF REMS Access and is responsible for REMS Submission via DMF.
(b) (4)	Branding Agency	(b) (4)		(b) (4) is responsible for arranging approved TIRF REMS Access program material in branded format for stakeholder use.

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

/s/

MARK A LIBERATORE
09/03/2013

Cephalon, Inc.
41 Moores Road
PO Box 4011
Frazer, PA 19355
Phone 610-344-0200
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September 26, 2012

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20704-1266

NDA 21-947; Sequence No. 0023
FENTORA® (fentanyl citrate) buccal tablet, CII

TIRF REMS Modification #2

Dear Dr. Rappaport:

Reference is made to NDA 21-947 for FENTORA® (fentanyl citrate) buccal tablet.

Reference is also made to the email communication from Mark Liberatore, Sr. Regulatory Manager for the Office of Surveillance and Epidemiology (OSE), to the TRIG single point of contact Willene Brondum (Insys Therapeutics, Inc.) on June 28, 2012. By way of this email, FDA provided the TRIG an overview of the revisions required to appropriately address the participation of closed system pharmacies in the TIRF REMS Access program. As requested in Mr. Liberatore's email, the TRIG provided, via email, the requested modified REMS documents in track changes on July 24, 2012. On September 17, 2012, FDA requested that each TRIG sponsor submit the track change documents that encompass "Modification 2" to their respective applications.

The purpose of this submission is to provide Modification 2 to the TIRF REMS Access program materials. This modification includes only those documents that required revisions to incorporate the closed system pharmacies and are provided in track changes. In addition, it is noted that 7 of these track change versions replace the previously approved versions in the eCTD backbone. The revised documents are as follows:

- Chain Pharmacy Enrollment Form
- Education Program
- FAQ
- Outpatient Pharmacy Enrollment Form
- Outpatient Pharmacy Letter
- REMS
- TIRF Supporting Document

One new REMS document was created as a result of this Modification; this document is the Closed System Pharmacy Overview.

This modification provides only changes made to the REMS. No changes have been made to the full prescribing information for FENTORA.

This submission is provided in virus-free eCTD format. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6189 or via email at christine.kampf@tevapharm.com. In my absence, please contact Susan Franks at (610) 727-6337 or via email at susan.franks@tevapharm.com

Sincerely,

Christine M. Kampf
Manager, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

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

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.)

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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.

Responses to FDA Modification 2 General Comments to TIRF REMS Assess Program
04Mar2013

1. **Submit the form which will be used by Closed System Outpatient Pharmacies to validate prescriptions by completing and faxing to the TIRF REMS Access Program.**

   We have attached to this email the TIRF REMS Access Prescription Authorization Request form used by closed system outpatient pharmacies to validate prescriptions via fax.

2. **Submit the script used by TIRF REMS Access program call center staff when validating prescriptions for Closed System Outpatient Pharmacies.**

   The call center agents adhere to a work instruction when validating prescriptions for closed system outpatient pharmacies. The process is outlined below:

   1.) REMS agent requests the closed system pharmacy NPI number or DEA number used to register in the TIRF REMS Access program.
   2.) REMS agent uses the number provided to search for the pharmacy in the TIRF REMS Access database and confirms they are a closed system outpatient pharmacy.
   3.) If confirmed, the REMS agent collects the following information:

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

   4.) This information is used to validate the prescription with the TIRF REMS Access program using the same REMS edits and business rules in the claim adjudication process as used for chain outpatient and independent outpatient pharmacies.
   - If validated, the system will provide the REMS Agent an *Authorization Number* which is provided to the closed system caller
   - If not validated, a rejection reason and information regarding how to resolve the rejection is provided to the closed system caller for follow-up or trouble-shooting

3. **What are the call center hours of operation?**

   Monday – Friday: 8am - 8pm ET

4. **Is validation of a Closed System Outpatient Pharmacy's TIRF prescription possible on weekends or on weekdays when the call center is not operational?**

   No, validation of closed system prescriptions can only be obtained during TIRF REMS Access program call center hours of operation of Monday – Friday, 8am-8pm ET.

   Have there been any complaints from Closed System Outpatient Pharmacies due to them not being able to dispense TIRF prescriptions when the call center is not operational?

No complaints have been received since the implementation of the closed system outpatient pharmacy solution.

5. **Currently Closed System Outpatient Pharmacies can only validate TIRF prescriptions via phone or fax. Are there plans to provide these pharmacies with an online interface for performing the validation?**

   The current prescription authorization volume and absence of complaints does not warrant a change to the current process. Therefore we are not pursuing an online solution at this time. We will continue to monitor and assess the need for an alternate solution as appropriate.

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

/s/

MARK A LIBERATORE
03/20/2013

1. **Provide a rationale for revising the existing text "fatal overdose" to "fatal respiratory depression" as proposed by the TRIG to the Patient Prescriber Agreement Form, Prescriber attestation #2.**

   "2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal ~~overdose~~ respiratory depression can occur at any dose."

   RESPONSE: Fatal respiratory depression is consistent with the label/ boxed warning for all TIRF medicines.

2. **The revised definitions for outpatient pharmacies as proposed by the TRIG have been updated to align with industry standards to prevent confusion. Provide a response to the following:**

   2a. How is the term "generally", which is included in the definitions for chain outpatient pharmacies and independent outpatient pharmacies, used to determine the appropriate category designation?

   RESPONSE: There is no industry standard number of stores for chain vs. independent pharmacies. The definitions allow for flexibility of pharmacies to define their pharmacy type for managing the enrollment process in the TIRF REMS Access program.

   2b. Chain outpatient pharmacy: How many pharmacies with less than 10 stores under the same ownership has the TRIG enrolled as a chain pharmacy? Describe what criteria was used to enroll these pharmacies as a chain outpatient pharmacy.

   RESPONSE: There are four (4) chain outpatient pharmacy headquarters with less than 10 sub-stores enrolled in the TIRF REMS Access program. The pharmacies are enrolled as chain outpatient pharmacies due to their request to have a single authorized pharmacy representative responsible for managing enrollment and training for all stores.

   2c. Independent outpatient pharmacy: How many pharmacies with more than 10 stores under the same ownership has the TRIG enrolled as an independent pharmacy? Describe what criteria was used to enroll these pharmacies as an independent outpatient pharmacy.

   RESPONSE: There are three (3) independent outpatient pharmacies with more than 10 stores enrolled in the TIRF REMS Access program. The pharmacies are enrolled as independent outpatient pharmacies due to their request to have an authorized pharmacy representative from each store responsible for managing enrollment and training of each individual store.

3. **From the website prototype (pages 124 & 136), it appears both chain outpatient pharmacies and independent outpatient pharmacies can enroll pharmacy locations and maintain a list of multiple stores in their pharmacy profile. Provide a rationale for the following:**

   3d. Any differences between the lists managed for independent outpatient pharmacies as compared to chain outpatient pharmacies

   RESPONSE: The difference is the concept of enrollment. The chain outpatient pharmacy headquarters authorized pharmacy representative can add store locations and mark them as trained on the pharmacy dashboard as appropriate. Each independent outpatient pharmacy must individually enroll and complete test transactions at the store level, regardless if the authorized pharmacist is the same across multiple stores.

Chain outpatient pharmacy headquarters manages the training status of each individual store for which they have taken responsibility whereas the authorized pharmacist for the independent outpatient pharmacy has the ability to manage the enrollment process (enrollment form, training, knowledge assessment, test transactions) for other independent pharmacies for which they are the authorized pharmacist.

3e. Why are separate enrollment forms for chain and independent outpatient pharmacies necessary if both entities can enroll multiple pharmacy locations?

RESPONSE: The forms identify the pharmacy type for enrollment purposes. They differ in that the chain enrollment form allows enrollment for multiple pharmacy store locations under one chain enrollment. The independent outpatient pharmacy enrollment form only allows one store to be enrolled per form. Both enrollment forms contain the same 14 acknowledgement statements and Terms and Conditions.

4. Provide a summary of the process for stakeholder enrollment (pharmacy, prescriber) via fax. The summary should include a flowchart of the process and a description of each step within the process. Additionally, provide a response to the following:

RESPONSE: Refer to prescriber, independent outpatient pharmacy, chain outpatient pharmacy, inpatient pharmacy and closed system outpatient pharmacy fax enrollment flows in the Appendix beginning on page 4.

4f. Have incomplete prescriber enrollments resulted from a prescriber's ability to sign the enrollment form before completing the Education Program and Knowledge Assessment? If so, how many?

RESPONSE: Enrollment is not deemed as complete until all enrollment requirements are met. A total of 567 prescribers submitted a signed TIRF REMS Access enrollment form prior to completing the Knowledge Assessment. 485 (85.5%) of these prescribers are currently enrolled in the TIRF REMS Access program. The TIRF REMS Access database tracks the completion of each step and upon processing, immediately notifies the stakeholder of ALL outstanding requirements (i.e.; missing signature, missing address, knowledge assessment) via the incomplete correspondence letter.

4g. If the knowledge assessment authorization number is not searchable within the TIRF REMS Access database, how is the TRIG able to identify which stakeholders have completed the assessment online after receipt of an enrollment form?

RESPONSE: In clarification, although the Knowledge Assessment code is searchable, current TIRF REMS Access Call Center work instructions were created based on best practices and ease of database navigation. Upon receipt of a faxed enrollment form, the TIRF REMS Access Call Center Agent conducts a search of the TIRF REMS Access database to locate the stakeholder record. Fields used to search the TIRF REMS Access database include: name, city, state, zip code, phone number, fax number and stakeholder identifiers (DEA, NPI, state license number, NCPDP, Medicaid ID, chain ID, enrollment ID). Once the stakeholder has been identified in the TIRF REMS database, the Knowledge Assessment code will be visible if the Knowledge Assessment has been completed.

4h. Once the enrollment form is received and a stakeholder is notified of the need to complete the assessment, how does the TRIG track if it is completed?

RESPONSE: The TIRF REMS Access database programmatically tracks the lifecycle of the enrollment from submission to completion regardless if the stakeholder completes the Knowledge Assessment via fax or web. The stakeholder is not enrolled until all steps are completed.

4i. The comment provided by the TRIG indicated that "…it is not required for the KA to be completed prior to the receipt of the enrollment form" is contradictory to the first attestation statement on the enrollment form which states "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…" Provide further clarification by what was meant by the TRIG's comment.

RESPONSE: To clarify TRIGs comment, stakeholders are not enrolled until all steps of the enrollment process are completed, including the Knowledge Assessment (KA). If the enrollment form is received prior to the KA, it will be processed but the stakeholder enrollment will be incomplete until a complete KA is received.

5. Patient attestation on the Patient Prescriber Agreement Form

5a. The patient attestation on the Patient Prescriber Agreement Form was revised by the TRIG. Provide a rationale for the revision to the attestation statement.

RESPONSE: TRIG's rationale for this proposed change was an attempt to adapt the following language from the TIRF Medication Guides to the language of the PPAF.

"Do not use [TIRF] 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."

5b. The Agency proposes the following revisions to Attestation #2 and inclusion of the deleted attestation as attestation #3.

"2. I understand that TIRF medicines should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. ~~opioid pain medications. I understand that before I can take any TIRF medicine, I must be opioid tolerant.~~ If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines. ~~whether I am opioid tolerant~~."

"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.~~ 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."

RESPONSE: TRIG agrees with the Agency's recommendation. The PPAF has been updated. A redlined and clean version of the revised PPAF is attached in the FDA Inquiry to Modification 2 Response email sent to the FDA on May 6, 2013.

APPENDIX – TIRF REMS Access Process Flows

TIRF REMS Access – Prescriber - Fax Enrollment Process Flow

Prescriber

TIRF REMS Access Call Center

(b) (4)

TIRF REMS Access - Chain Outpatient Pharmacy - Fax Enrollment Process Flow

TIRF REMS Access - Independent Outpatient Pharmacy - Fax Enrollment Process Flow

Independent Pharmacy (Authorized Pharmacy Representative)	(b) (4)
TIRF REMS Access Call Center	

TIRF REMS Access - Inpatient Pharmacy - Fax Enrollment Process Flow

Inpatient Pharmacy (Authorized Pharmacy Representative)	(b) (4)
TIRF REMS Access Call Center	

TIRF REMS Access – Closed System Outpatient Pharmacy - Enrollment Process Flow

	(b) (4)
Closed System Pharmacy (Authorized Pharmacy Representative)	
TIRF REMS Access Program	

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/s/

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05/07/2013

Branded Pharmaceutical Products R&D

October 17, 2013

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947, Sequence No. 0037
FENTORA® (fentanyl buccal tablet), CII

NDA 020747, Sequence No. 0031
ACTIQ® (fentanyl citrate) oral transmucosal lozenge, CII

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT
REMS MODIFICATION #2

Dear Dr. Rappaport:

Reference is made to NDA 021947 for FENTORA® (fentanyl buccal tablet) and NDA 020747 for ACTIQ® (fentanyl citrate) oral transmucosal lozenge.

Further reference is made to Teva's Prior Approval Supplement (PAS) for a Single Shared REMS for Transmucosal Immediate-Release Fentanyl (TIRF) products approved on December 28, 2012. Reference is also made to the PAS submitted on September 26, 2012 (NDA 021947, Sequence No. 0023 and NDA 020747, Sequence No. 0021) for a Proposed REMS Modification 2.

On September 11, 2013, a Letter of Authorization (LOA) for DMF 027320 was submitted to the above referenced applications (NDA 021947, Sequence No. 0036 and NDA 020747, Sequence No. 0029). As instructed by FDA, DMF 027320 houses the shared TIRF REMS in one centralized location 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 of DMF 027320, submitted on September 23, 2013 for the final documentation pertaining to REMS Modification 2.

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.786.7051| www.tevapharm-na.com

This Amendment provides the current Medication Guide for ACTIQ (and its authorized generic) and FENTORA to their respective applications. No changes have been made to either Medication Guide as a result of Modification 2 to the TIRF REMS Access Program.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at 610-786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6189 or via email at christine.kampf@tevapharm.com.

Sincerely,

Christine M. Kampf
Manager, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947/S-017
CommunicationType:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	KC/4-29-13, updated 8-28-13 based on OCC cleared "template" of 7-10-13, and again 11-4 and 5-13
Clearance History by:	Sullivan—finalized 11/5/13 Won 5-10-13 Lehrfeld 5/7/13 Mehta 5/7/13 SRT 7/19/13 and 11/4/13 Racoosin 5/14/13
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 04/11/2013

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

NDA 021947/S-017

SUPPLEMENT APPROVAL

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Christine M. Kampf
Sr. Regulatory Associate

Dear Ms. Kampf:

Please refer to your Supplemental New Drug Application (sNDA) dated September 26, 2012, received September 26, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl buccal tablets).

We acknowledge receipt of your amendment dated October 17, 2013, and your risk evaluation and mitigation strategy (REMS) assessment dated December 20, 2012.

This supplemental new drug application provides for modifications to the approved REMS for FENTORA (fentanyl buccal tablets), 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 FENTORA (fentanyl buccal tablets) was originally approved on July 20, 2011. The REMS was last modified on June 5, 2012. 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 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 September 26, 2012, jointly amended on September 24, 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.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 5, 2012.

There are no changes to the REMS assessment plan described in our December 28, 2011, letter.

In addition to the assessments submitted according to the timetable included in this approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021947 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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:

NDA 021947
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021947: NEW INDICATION OF USE
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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 NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, M.D., M.P.H.
Deputy Director for Safety
Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation II
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.

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):_____

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*** _____ ***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):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

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):_____

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 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,

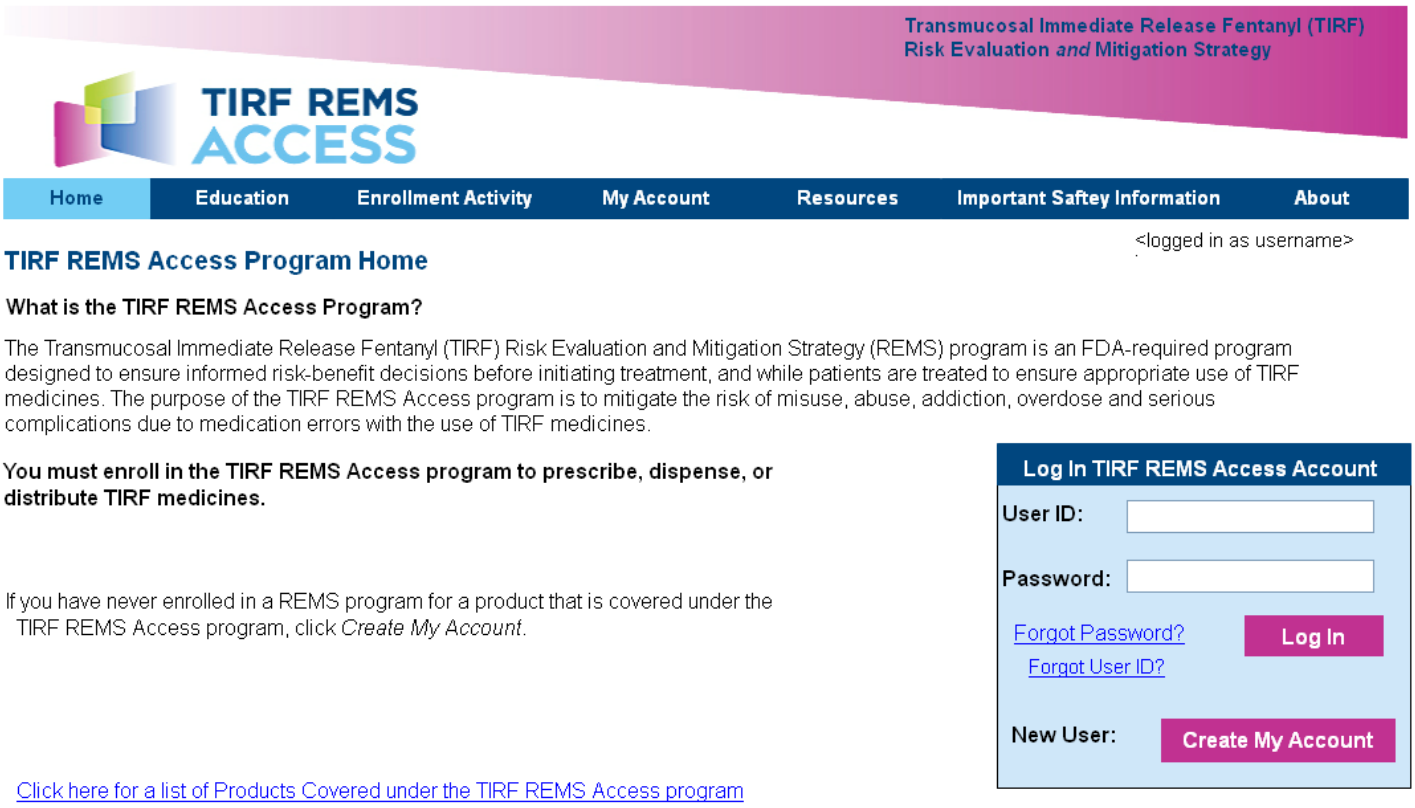
TIRF REMS Access Industry Group

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

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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

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):_____

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):_____

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List of TIRF Medicines Available Only through the TIRF REMS Access Program

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- 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 <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
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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.

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
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- 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.

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
- 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

- 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.

MEDICATION GUIDE

FENTORA® (fen-tor-a) CII
(fentanyl citrate) buccal tablet
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use FENTORA 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 FENTORA in a safe place away from children.

Get emergency help right away if:

- **a child takes FENTORA. FENTORA can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed FENTORA uses it**
- **an adult who is not already taking opioids around-the-clock, uses FENTORA.**

These are medical emergencies that can cause death. If possible, try to remove FENTORA from the mouth.

Read this Medication Guide completely before you start using FENTORA, 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 FENTORA?

FENTORA can cause life-threatening breathing problems which can lead to death.

1. **Do not use FENTORA 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 FENTORA. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use FENTORA exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of FENTORA for each episode of breakthrough cancer pain.
   - You must wait at least 4 hours before treating a new episode of breakthrough pain with FENTORA. **See the Medication Guide section "How should I use FENTORA?" and the Patient Instructions for Use at the end of this Medication Guide for detailed information about how to use FENTORA the right way.**
4. **Do not switch from FENTORA to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of FENTORA is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of FENTORA that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use FENTORA 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 FENTORA to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   FENTORA 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 FENTORA in a safe place** to protect it from being stolen. FENTORA can be a target for people who abuse (narcotic) medicines or street drugs.
   - **Selling or giving away this medicine is against the law.**
7. FENTORA 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 FENTORA, you must:
   - talk to your healthcare provider

- understand the benefits and risks of FENTORA
- agree to all of the instructions
- sign the Patient-Prescriber Agreement form.

What is FENTORA?

- FENTORA is a prescription medicine that contains the medicine fentanyl.
- FENTORA is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain.
- FENTORA 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 FENTORA if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using FENTORA.
- FENTORA is only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if FENTORA is safe and effective in children under 18 years of age.

Who should not use FENTORA?

Do not use FENTORA:

- **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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in FENTORA. See the end of this Medication Guide for a complete list of ingredients in FENTORA.

What should I tell my healthcare provider before using FENTORA?

Before using FENTORA, 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. FENTORA may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. FENTORA passes into your breast milk. It can cause serious harm to your baby. You should not take FENTORA 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 FENTORA. Sometimes, the doses of certain medicines and FENTORA need to be changed if used together.

- **Do not take any medicine while using FENTORA 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 FENTORA.**
- 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 FENTORA?

Before you can begin to use FENTORA:

- Your healthcare provider will explain the TIRF REMS Access program to you.
- You will sign the TIRF REMS Access program Patient-Prescriber Agreement form.
- FENTORA 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 FENTORA prescription filled.

Using FENTORA:

- **Use FENTORA exactly as prescribed. Do not use FENTORA 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 FENTORA the right way.**
- **Do not split, suck, chew, or swallow FENTORA tablets. You will get less relief for your breakthrough cancer pain.**
- **Use FENTORA tablets whole.**
- Wait 30 minutes after using FENTORA. If there is any of the FENTORA 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 FENTORA for each episode of breakthrough cancer pain.
  - Use **1** dose of FENTORA for an episode of breakthrough cancer pain.
  - If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of FENTORA, you can use **only 1** more dose of FENTORA as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of FENTORA, call your healthcare provider for instructions. **Do not use another dose of FENTORA at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with FENTORA.
  - If you only need to take 1 dose of FENTORA for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of FENTORA for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of FENTORA for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using FENTORA.
- Talk to your healthcare provider if your dose of FENTORA does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of FENTORA 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 much FENTORA 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 FENTORA?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how FENTORA affects you. FENTORA can make you sleepy. Ask your healthcare provider when it is okay to do these activities.
- **Do not drink alcohol while using FENTORA.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of FENTORA?

FENTORA 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 FENTORA?**"
   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 much FENTORA 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 FENTORA 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 FENTORA 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 or the inside of your cheek).** Tell your healthcare provider if this is a problem for you.

The most common side effects of FENTORA 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 FENTORA 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 FENTORA.

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 FENTORA. 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 FENTORA?

- **Always keep FENTORA in a safe place away from children and from anyone for whom it has not been prescribed**. Protect FENTORA from theft.
- Store FENTORA at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze FENTORA.
- Keep FENTORA in the original blister unit. Do not remove FENTORA from its blister packaging for storage in a temporary container, such as a pill box.
- Keep FENTORA dry.

How should I dispose of unused FENTORA tablets when they are no longer needed?

- Dispose of any unused FENTORA tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the FENTORA packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of FENTORA, call Cephalon, Inc., at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

General information about FENTORA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use FENTORA only for the purpose for which it was prescribed**. **Do not give FENTORA to other people, even if they have the same symptoms you have.** FENTORA can harm other people and even cause death. Sharing FENTORA is against the law.

This Medication Guide summarizes the most important information about FENTORA. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about FENTORA 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 in FENTORA?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient Instructions for Use

Before you use FENTORA, 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 FENTORA the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use FENTORA.

When you get an episode of breakthrough cancer pain, use the dose of FENTORA prescribed by your healthcare provider as follows:

- FENTORA comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your FENTORA tablets will be printed in the boxed area shown as **XXX mcg** (See Figure 1).

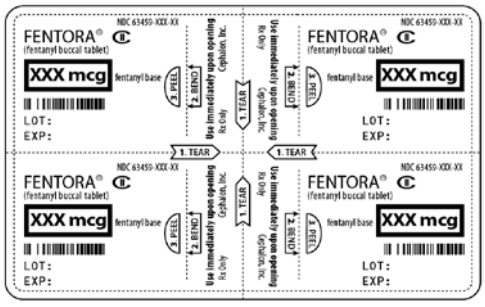


Figure 1

- Peel back foil on blister unit to expose tablet (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, FENTORA tablet must be used right away.
- Do not split the FENTORA tablet. **Use FENTORA tablets whole**.
- Place a FENTORA tablet in your mouth above a rear molar tooth between the upper cheek and gum. **Leave the tablet in place until it dissolves.** A FENTORA tablet generally takes between 14 to 25 minutes to dissolve (See Figure 3).

Figure 3

- After 30 minutes, if there is any FENTORA left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use FENTORA in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do. Do not split the tablet.
- **Do not split, suck, chew or swallow FENTORA tablets.** You will get less relief for your breakthrough cancer pain.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:
Cephalon, Inc.
Frazer, PA 19355

Revised December 2011

FENTORA is a trademark of Cephalon, Inc. or its affiliates.

FENT-007
FENTMG-006

Printed in USA

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

/s/

JUDITH A RACOOSIN
11/07/2013

Branded Pharmaceutical Products R&D

May 21, 2013

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research Division of Anesthesia,
Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947, Sequence No. 0031
FENTORA® (fentanyl buccal tablet), CII

PRIOR APPROVAL SUPPLEMENT – EXPEDITED REVIEW REQUESTED
REMS MODIFICATION

Dear Dr. Rappaport:

Reference is made to the New Drug Application (NDA 021947) for the use of FENTORA (fentanyl buccal tablet) 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 purpose of this supplement is to allow for the commercialization of an authorized generic of FENTORA, Fentanyl Buccal Tablets. The formulation remains unchanged from the reference drug FENTORA; however because FENTORA is covered by a class-wide REMS program, the TIRF REMS Access program, the submission requirements to allow for the commericialization of a generic FENTORA differ from 21 CFR 314.70 (d), requiring the authorized generic for FENTORA to be submitted as a Prior Approval Supplement. Teva considers the proposed revisions to provide for an authorized generic to not be substantive in nature and given the unique submission requirements to provide for an authorized generic covered by a REMS program, we respectfully request expedited review for this Prior Approval Supplement.

This supplement provides for changes to the full Prescribing Information, Medication Guide and Carton/Container labels replacing the brand name "FENTORA" with "Fentanyl Buccal Tablets" and providing associated NDCs, a change to the Company name and Contact Information was also applied. Additionally, revisions have been made to the currently approved REMS to support inclusion of the generic equivalent of FENTORA.

The REMS materials provided for this authorized generic are exactly the same as the current TIRF REMS Access Program materials, approved on 05 June 2012, with the following exceptions, all of which relate to the name of the product and/or its assigned NDC:

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.783.6311 | www.tevapharm-na.com

- Outpatient Pharmacy Enrollment Form: Pages 3 and 6
- Chain Pharmacy Enrollment Form: Pages 4 and 7
- Education Program: Slide 18
- Supporting Document: Page 4
- Website: Reference is made to a telephone conversation with Sr. Regulatory Project Manager for the Division of Anesthesia, Analgesia and Addiction Products (DAAAP), Ms. Kimberly Compton, on 17 May 2013. During this call, Ms. Kimberly Compton confirmed FDA's agreement to receive only a marked up copy of the website. As such, provided is a copy of the website in tracked changes through call-out boxes and red text. A summary of the location of these revisions as well as the modification made is provided below:

Table 1: Summary of TIRF REMS Website Prototype Changes

PDF Page #	Section	Modification
18	Outpatient Pharmacy Enrollment Transition – Terms and Conditions	Add new NDCs
67	Education Program – Page 13	Add "and generic equivalents" for FENTORA Product description
110	TIRF REMS Access Program Terms and Conditions	Add new NDCs
121	TIRF REMS Access Program Terms and Conditions	
139	Prescriber Request Materials	Add functionality and option to order Medication Guide(s) for generic Fentanyl Buccal Tablets
142	Inpatient Pharmacy Request Materials	
149	Outpatient Pharmacy Request Materials	
154	Distributor Request Materials	
161	Chain Pharmacy Request Materials	
163	Resources for Prescribers	Add Medication Guide PDF link Add Prescribing Information PDF link
164	Resources for Patients	
165	Resources for Pharmacies	
166	Resources for Distributors	
171	Attachment 1	Add product information

Where changes were required to the REMS materials red-line and clean copies of the REMS materials are included, with the exception of the website as noted above. All changes to REMS materials have been made to the currently approved version of the TIRF REMS Access Program, approved by FDA on 05 June 2012.

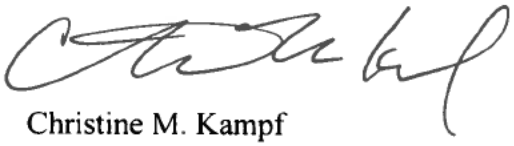
Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

Additionally, because FENTORA, and any generic equivalents, are covered by a class-wide REMS program, Teva does not intend to implement these changes (when approved) until the authorized generic, covered by this supplement, is marketed. As such, Teva respectfully requests that no changes to the REMS material, specific to FENTORA and its authorized generic, are posted until the authorized generic is marketed.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client and Service Pack No. 10.5.1997, antivirus engine No. 9.700.1001, virus pattern No. 9.605.00 with a release date of 5/21/13 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6189 or via email at christine.kampf@tevapharm.com.

Sincerely,



Christine M. Kampf
Manager, Regulatory Affairs

Teva Branded Pharmaceutical Products R&D, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use fentanyl buccal tablets safely and effectively. See full prescribing information for fentanyl buccal tablets.

Fentanyl Buccal Tablets, CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL
See full prescribing information for complete boxed warning.
- **Due to the risk of fatal respiratory depression, fentanyl buccal tablets are 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to fentanyl buccal tablets. (2.1, 5.2)**
- **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)**
- **Fentanyl buccal tablets are 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Maintenance Dosing (2.3) 02/2013
Dosage and Administration, Administration of Fentanyl Buccal Tablets (2.4) 02/2013
Dosage and Administration, Discontinuation of Fentanyl Buccal Tablets (2.5) 02/2013

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets are an opioid agonist indicated 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. (1)
Limitations of Use:
Fentanyl buccal tablets 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 fentanyl buccal tablets. (1)
- Initial dose of fentanyl buccal tablets: 100 mcg. (2.1)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablet. Limit patient access to only one strength of fentanyl buccal tablets at any one time. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablet. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.1)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets. (2.1)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl or components of fentanyl buccal tablets. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Fentanyl buccal tablets is not bioequivalent to other fentanyl products. Do not convert from other fentanyl products on a mcg per mcg basis. (5.2)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate fentanyl buccal tablets 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 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----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Administer fentanyl buccal tablets with caution to patients with hepatic or renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2013

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 fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Fentanyl buccal tablets must be kept out of reach of children. *[see Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of fentanyl buccal tablets with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets 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 fentanyl buccal tablets. *[see Dosage and Administration (2.1)]*

- When dispensing, do not substitute a fentanyl buccal tablets prescription for other fentanyl products.

ABUSE POTENTIAL

Fentanyl buccal tablets contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Fentanyl buccal tablets can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing fentanyl buccal tablets 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, fentanyl buccal tablets are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets are indicated 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. 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/hr of transdermal fentanyl, 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 while taking fentanyl buccal tablets.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain.

Fentanyl buccal tablets 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.

Limitations of Use:

As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]*. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets *[see Warnings and Precautions (5.11)]*.

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

2.1 Initial Dose

Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

Patients on Actiq

The initial dose of fentanyl buccal tablets is **always** 100 mcg with the only exception being patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1). The doses of fentanyl buccal tablets in this table are starting doses and not intended to represent equianalgesic doses to Actiq. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial Fentanyl Buccal Tablets Dose*

200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*From this initial dose, titrate patient to effective dose.

b. For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablet and should proceed using multiples of this tablet strength.

All Other Patients

The initial dose of fentanyl buccal tablets is 100 mcg.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any episode of breakthrough pain.
b. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets.

2.2 Dose Titration

a. From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablets over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted.
b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg fentanyl buccal tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode. During titration, one **dose** of fentanyl buccal tablets may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).
d. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets. To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal tablets available at any time.
e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.3 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use **only ONE** fentanyl buccal tablet of the appropriate strength per breakthrough pain episode.
b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode.
c. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets.
d. Dosage adjustment of fentanyl buccal tablets may be required in some patients.
   Generally, the fentanyl buccal tablets 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.
e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.
f. Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue.)

2.4 Administration of Fentanyl Buccal Tablets

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer fentanyl buccal tablets.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. **Patients should not split the tablet.**

The fentanyl buccal tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.

The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.

It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets in the buccal cavity.

2.5 Discontinuation of Fentanyl Buccal Tablets

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

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*.

4 CONTRAINDICATIONS

Fentanyl buccal tablets are contraindicated in opioid non-tolerant patients.

Fentanyl buccal tablets are 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.

Fentanyl buccal tablets are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in fentanyl buccal tablets. 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

Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and fentanyl buccal tablets are not equivalent on a microgram per microgram basis. Fentanyl buccal tablets are NOT a generic version of Actiq. **All patients should be titrated from the 100 mcg dose.**

The initial dose of fentanyl buccal tablets should be 100 mcg. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a fentanyl buccal tablets prescription for an Actiq prescription under any circumstances. Fentanyl buccal tablets and Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of fentanyl buccal tablets for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that fentanyl buccal tablets contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1)]*

5.4 Additive CNS Depressant Effects

The concomitant use of fentanyl buccal tablets 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., hypoventilation, 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 fentanyl buccal tablets 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 fentanyl buccal tablets of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate fentanyl buccal tablets with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of fentanyl buccal tablets may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer fentanyl buccal tablets 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to fentanyl buccal tablets reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients.

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use fentanyl buccal tablets with caution in patients with bradyarrhythmias.

5.10 MAO Inhibitors

Fentanyl buccal tablets are 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.

5.11 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)]*, fentanyl buccal tablets 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 fentanyl buccal tablets, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense fentanyl buccal tablets must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute fentanyl buccal tablets 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

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.

The safety of fentanyl buccal tablets has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The most commonly observed adverse events seen with fentanyl buccal tablets are typical of opioid side effects. Opioid side effects should be expected and managed accordingly.

The clinical trials of fentanyl buccal tablets were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tablets for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tablets therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.

Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.

Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets. There was no evidence of excess toxicity in this subset of patients.

The duration of exposure to fentanyl buccal tablets varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets. Events are classified by system organ class.

Adverse Events (≥1%)

Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration

General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain

Hepatobiliary Disorders: Jaundice

Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess

Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture

Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count

Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake

Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain

Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy

Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness

Renal and Urinary Disorders: Renal Failure

Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing

Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat

Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when fentanyl buccal tablets is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of fentanyl buccal tablets with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl buccal tablets who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]*. The concomitant use of fentanyl buccal tablets with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl buccal tablets. Patients receiving fentanyl buccal tablets who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased fentanyl buccal tablets activity and the dose of fentanyl buccal tablets should be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women. fentanyl buccal tablets 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 characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal 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 fentanyl buccal tablets.

Fentanyl (25, 50 or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100 or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses ≥100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

Published studies concur with the conducted studies regarding the lack of teratogenic potential for fentanyl. One literature report showed that administration of fentanyl (10, 100, or 500 mcg/kg) to pregnant rats from GD 7-21, via implanted microosmotic minipumps, was not teratogenic (the high dose was approximately 6-times the single human dose of 800 mcg per pain episode on a mg/m^2 basis). Another report showed that intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant rats from GD 6-18 was embryotoxic in the 30 mcg/kg group, but was not teratogenic. Conversion

to human equivalent doses indicates this is within the range of the human recommended dosing for fentanyl buccal tablets.

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100 and 400 mcg/kg). Maternal toxicity was noted at doses ≥100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at ≥100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, do not use fentanyl buccal tablets for analgesia 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 fentanyl buccal tablets 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 fentanyl buccal tablets.

8.4 Pediatric Use

The safety and efficacy of fentanyl buccal tablets have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older.

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablets 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 fentanyl buccal tablets 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 patients with cancer 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.

8.8 Race

The pharmacokinetic effects of race with the use of fentanyl buccal tablets have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl buccal tablets contain fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to other opioids including hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated abuse of a prescription drug and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, and sometimes tolerance and/or physical dependence.

Abuse and addiction are separate and distinct from physical dependence and tolerance (see section 9 3). Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Abuse of fentanyl buccal tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of fentanyl buccal tablets with alcohol and other substances.

Fentanyl buccal tablets, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy.

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use. Withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug constitute evidence of physical dependence. 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). Clinically significant physical dependence may not occur until after several days to weeks of continued opioid usage.

Fentanyl buccal tablets should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If fentanyl buccal tablets are abruptly discontinued, or the dosage is rapidly reduced, in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea; increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of fentanyl buccal tablets 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 hypoventilation *[see Clinical Pharmacology (12.2)]*.

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the fentanyl buccal tablets tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 fentanyl buccal tablets 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

hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of fentanyl buccal tablets, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

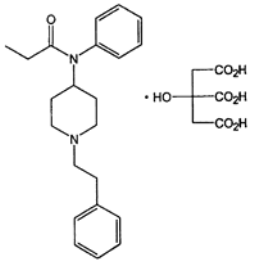
11 DESCRIPTION

Fentanyl buccal tablets are a potent opioid analgesic, intended for buccal mucosal administration.

Fentanyl buccal tablets are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

Fentanyl buccal tablets employ the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an 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 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 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 fentanyl buccal tablets should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*.

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 another oral transmucosal fentanyl citrate (Actiq). 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, Contraindications (4), Warnings and Precautions (5.2) and Overdosage (10).

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of fentanyl buccal tablets increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption

Following buccal administration of fentanyl buccal tablets, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of fentanyl buccal tablets is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is

swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets) (Table 4).

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or Actiq

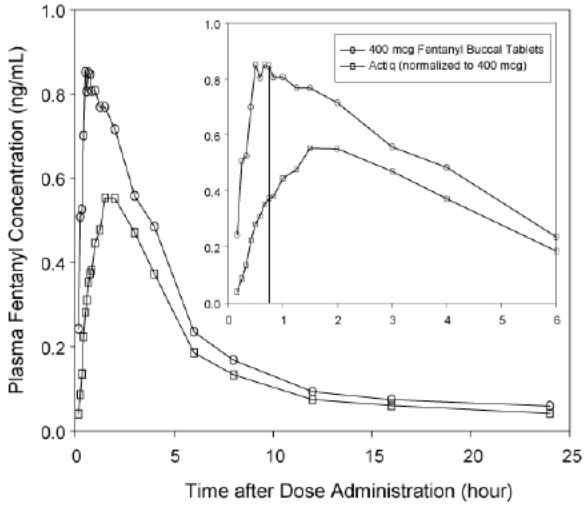
Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
***Actiq data was dose adjusted (800 mcg to 400 mcg).

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl were substantially greater with fentanyl buccal tablets compared to Actiq (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablets.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and Actiq in Healthy Subjects



Actiq data were dose adjusted (800 mcg to 400 mcg)

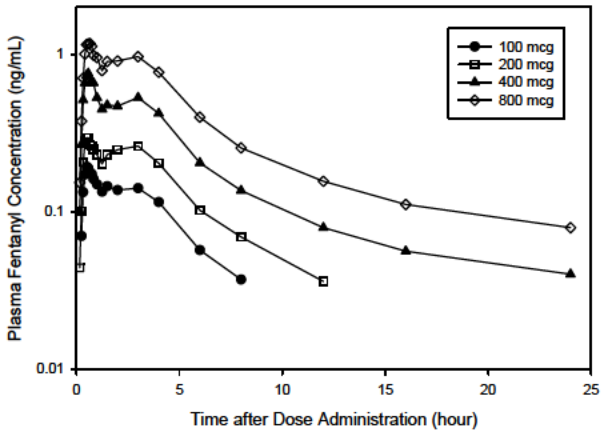
Mean pharmacokinetic parameters are presented in Table 5. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90
T_{max}, minute** (range)	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
T1/2, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6.

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng·hr/mL)	$AUC_{0\text{-}8}$ (ng·hr/mL)
Mucositis	1 25 ± 0 78	25 0 (15 - 45)	0 21 ± 0 16	2 33 ± 0 93
No mucositis	1 24 ± 0 77	22 5 (10 - 121)	0 25 ± 0 24	1 86 ± 0 86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement.

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both

albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Metabolism

The metabolic pathways following buccal administration of fentanyl buccal tablets have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Elimination

Disposition of fentanyl following buccal administration of fentanyl buccal tablets has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Gender

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2.3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In mice, at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis

Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 8.6-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets and 3 being placebo. Patients used one tablet of study drug (either fentanyl buccal tablets or placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

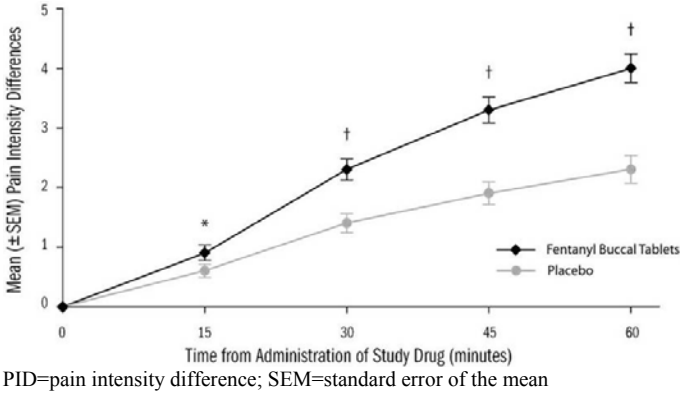
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 7. The median dose was 400 mcg.

Table 7. Successful Dose of Fentanyl Buccal Tablets Following Initial Titration

Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets -treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Fentanyl buccal tablets are supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in fentanyl buccal tablets can be fatal to a child. **Patients and their caregivers must be instructed to keep fentanyl buccal tablets out of the reach of children.** *[see Boxed Warning, Overdosage (10), and Patient Counseling Information (17.1)]*

Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)

Protect fentanyl buccal tablets from freezing and moisture. Do not use if the blister package has been tampered with.

16.2 Disposal of Fentanyl Buccal Tablets

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed *[see Patient Counseling Information (17.2)]*. If additional assistance is required, call Teva Pharmaceuticals at 1-800-896-5855.

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855.

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with ©2, and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 0093-1150-28
200 mcg	2	Orange	NDC0093-1151-28
400 mcg	4	Sage green	NDC 0093-1153-28
600 mcg	6	Magenta (pink)	NDC 0093-1154-28
800 mcg	8	Yellow	NDC 0093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient/Caregiver Instructions

- Before initiating treatment with fentanyl buccal tablets, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time fentanyl buccal tablets are dispensed because new information may be available.
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the fentanyl buccal tablets Medication Guide with every patient before initiating treatment with fentanyl buccal tablets.
  - Advise the patient that fentanyl buccal tablets are 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 fentanyl buccal tablets.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets.
  - 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, especially small children, exposed to fentanyl buccal tablets are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep fentanyl buccal tablets tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1) and Warnings and Precautions (5.3)]*
- Instruct patients not to take fentanyl buccal tablets 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 fentanyl buccal tablets are 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 fentanyl buccal tablets.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.
- Instruct patients NOT to share fentanyl buccal tablets and that sharing fentanyl buccal tablets with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablets contain fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in fentanyl buccal tablets, fentanyl, is a drug that some people abuse. Fentanyl buccal tablets 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.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.
- Instruct patients that fentanyl buccal tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets.
- Instruct patients to use fentanyl buccal tablets exactly as prescribed by their doctor and not to take fentanyl buccal tablets more often than prescribed.
- Caution patients that fentanyl buccal tablets 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 fentanyl buccal tablets of these dangers and counsel them accordingly.
- Warn patients to not combine fentanyl buccal tablets 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 fentanyl buccal tablets, they should ask their doctor about the effects that fentanyl buccal tablets (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 Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush the fentanyl buccal tablets blister packages or cartons down the toilet.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

FBT-002

Manufactured For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

Iss. 4/2013

MEDICATION GUIDE

Fentanyl 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 they are 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

- 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 buccal tablets pass into your breast milk. They 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 the fentanyl buccal tablet. 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 much 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 much fentanyl buccal tablets 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 1-800-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, 59°F to 86°F (15° C to 30°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 tablets packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855 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, sodium bicarbonate, sodium carbonate, citric acid, 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 FENTORA tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as

  XXX mcg (See Figure 1).

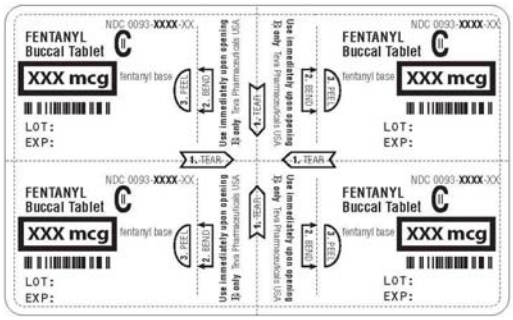


Figure 1

- Peel back foil on blister unit to expose tablet (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:
  - 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.

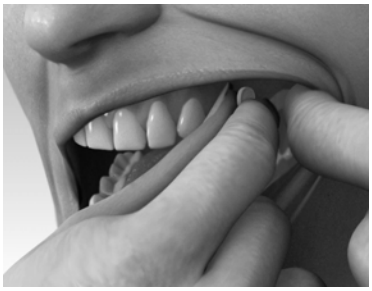


Figure 3

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).

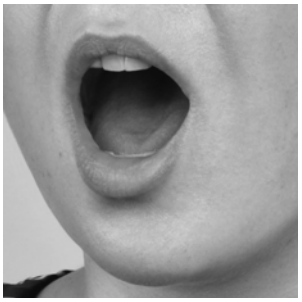


Figure 4a

Figure 4b

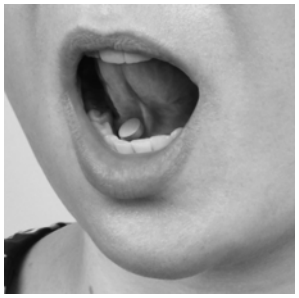


Figure 4c

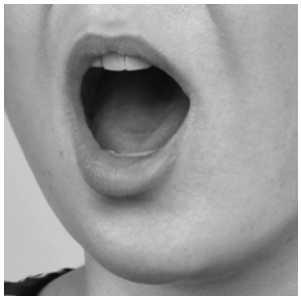


Figure 4d

- **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 For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

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FBTMG-002

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ~~FENTORA~~ fentanyl buccal tablets safely and effectively. See full prescribing information for ~~FENTORA~~fentanyl buccal tablets.

~~FENTORA®~~ (~~f~~Fentanyl ~~b~~Buccal ~~t~~Tablets), CII

Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, ~~FENTORA~~ fentanyl buccal tablets ~~is~~are 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to fentanyl buccal tablets~~FENTORA~~. (2.1, 5.2)**
- **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)**
- **Fentanyl buccal tablets~~FENTORA~~ ~~is~~are 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Maintenance Dosing (2.3) 02/2013
Dosage and Administration, Administration of ~~FENTORA~~ Fentanyl Buccal Tablets (2.4) 02/2013
Dosage and Administration, Discontinuation of ~~FENTORA~~ Fentanyl Buccal Tablets (2.5) 02/2013

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are an opioid agonist indicated 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 (1)
Limitations of Use:
Fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ (1)
- Initial dose of fentanyl buccal tablets~~FENTORA~~: 100 mcg (2.1)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablet~~FENTORA tablet~~ Limit patient access to only one strength of fentanyl buccal tablets~~FENTORA~~ at any one time (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablet~~FENTORA tablet~~ (2.1)
- No more than two doses can be taken per breakthrough pain episode (2.1)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~ (2.1)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain (4)
- Intolerance or hypersensitivity to fentanyl or components of fentanyl buccal tablets~~FENTORA~~ (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur Monitor patients accordingly (5.1)
- Fentanyl buccal tablets~~FENTORA~~ is not bioequivalent to other fentanyl products Do not convert from other fentanyl products on a mcg per mcg basis (5.2)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation Consider dosage adjustments if warranted (5.4)
- Titrate fentanyl buccal tablets~~FENTORA~~ 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding (5.8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 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----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Administer fentanyl buccal tablets~~FENTORA~~ with caution to patients with hepatic or renal impairment (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: ~~02~~1/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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* Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with ~~FENTORA~~fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. The substitution of fentanyl buccal tablets~~FENTORA~~ for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, fentanyl buccal tablets~~FENTORA~~ ~~is~~ are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Fentanyl buccal tablets~~FENTORA~~ must be kept out of reach of children. *[see Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of fentanyl buccal tablets~~FENTORA~~ with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~. *[see Dosage and Administration (2.1)]*

- When dispensing, do not substitute a fentanyl buccal tablets~~FENTORA~~ prescription for other fentanyl products.

ABUSE POTENTIAL

Fentanyl buccal tablets~~FENTORA~~ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Fentanyl buccal tablets~~FENTORA~~ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing fentanyl buccal tablets~~FENTORA~~ 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, fentanyl buccal tablets~~FENTORA~~ ~~is~~are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are indicated 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 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/hr of transdermal fentanyl, 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 while taking fentanyl buccal tablets~~FENTORA~~.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids For this reason, fentanyl buccal tablets~~FENTORA~~ ~~is~~are contraindicated in the management of acute or postoperative pain

Fentanyl buccal tablets~~FENTORA~~ ~~is~~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

Limitations of Use:

As a part of the TIRF REMS Access program, fentanyl buccal tablets~~FENTORA~~ may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]* For inpatient administration of fentanyl buccal tablets~~FENTORA~~ (e g , hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ *[see Warnings and Precautions (5.11)]*

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose

2.1 Initial Dose

~~FENTORA~~ Fentanyl buccal tablets ~~is~~are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

Patients on Actiq

The initial dose of fentanyl buccal tablets~~FENTORA~~ is always 100 mcg with the only exception being patients already using Actiq

a For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1) The doses of fentanyl buccal tablets~~FENTORA~~ in this table are

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starting doses and not intended to represent equianalgesic doses to Actiq Patients must be instructed to stop the use of Actiq and dispose of any remaining units

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial ~~FENTORA~~ Fentanyl Buccal Tablets Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*From this initial dose, titrate patient to effective dose

b For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablet~~FENTORA tablet~~ and should proceed using multiples of this tablet strength

All Other Patients

The initial dose of fentanyl buccal tablets~~FENTORA~~ is 100 mcg

Repeat Dosing

a In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode Thus patients should take a maximum of two doses of fentanyl buccal tablets~~FENTORA~~ for any episode of breakthrough pain

b Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~

2.2 Dose Titration

a From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects Patients should record their use of fentanyl buccal tablets~~FENTORA~~ over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted

b Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets) Titrate using multiples of the 200 mcg fentanyl buccal ~~FENTORA~~ tablet for doses above 400 mcg (600 mcg and 800 mcg) Note: Do not use more than 4 tablets simultaneously

c In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode Thus patients should take a maximum of two doses of fentanyl buccal tablets~~FENTORA~~ for any breakthrough pain episode During titration, one **dose** of fentanyl buccal tablets~~FENTORA~~ may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg)

d Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~ To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal ~~FENTORA~~ tablets available at any time

e Patients should be strongly encouraged to use all of their fentanyl buccal tablets~~FENTORA tablets~~ of one strength prior to being prescribed the next strength If this is not practical, unused fentanyl buccal tablets~~FENTORA~~ should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened fentanyl buccal ~~FENTORA~~ tablets remaining from a prescription as soon as they are no longer needed

2.3 Maintenance Dosing

a Once titrated to an effective dose, patients should generally use **only ONE** fentanyl buccal ~~FENTORA~~ tablet of the appropriate strength per breakthrough pain episode

b On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode

c Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~

d Dosage adjustment of fentanyl buccal tablets~~FENTORA~~ may be required in some patients
Generally, the fentanyl buccal tablets~~FENTORA~~ 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

e If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated

f Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue)

2.4 Administration of ~~FENTORA~~Fentanyl Buccal Tablets

Opening the Blister Package:

1 Instruct patients not to open the blister until ready to administer fentanyl buccal tablets~~FENTORA~~

2 Separate a single blister unit from the blister card by bending and tearing apart at the perforations

3 Bend the blister unit along the line where indicated

4 Peel back the blister backing to expose the tablet **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**

5 Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire fentanyl buccal ~~FENTORA~~ tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal ~~FENTORA~~ tablet under the tongue **Patients should not split the tablet.**

The fentanyl buccal ~~FENTORA~~ tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed

The fentanyl buccal ~~FENTORA~~ tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes

After 30 minutes, if remnants from the fentanyl buccal ~~FENTORA~~ tablet remain, they may be swallowed with a glass of water

It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets~~FENTORA~~ in the buccal cavity

2.5 Discontinuation of ~~FENTORA~~Fentanyl Buccal Tablets

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

Fentanyl buccal ~~FENTORA~~ tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*

4 CONTRAINDICATIONS

Fentanyl buccal tablets~~FENTORA is~~are contraindicated in opioid non-tolerant patients

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are 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

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl

5 WARNINGS AND PRECAUTIONS

See Boxed Warning

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in fentanyl buccal tabletsFENTORA 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

FENTORA Fentanyl buccal tablets isare not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and fentanyl buccal tabletsFENTORA are not equivalent on a microgram per microgram basis Fentanyl buccal tabletsFENTORA isare NOT a generic version of Actiq **All patients should be titrated from the 100 mcg dose.**

The initial dose of fentanyl buccal tabletsFENTORA should be 100 mcg Titrate each patient individually to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a fentanyl buccal tabletsFENTORA prescription for an Actiq prescription under any circumstances. Fentanyl buccal tabletsFENTORA and Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tabletsFENTORA compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl **As a result of these differences, the substitution of the same dose of fentanyl buccal tabletsFENTORA for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that fentanyl buccal tabletsFENTORA contains a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children *[see How Supplied/Storage and Handling (16.1)]*

5.4 Additive CNS Depressant Effects

The concomitant use of fentanyl buccal tabletsFENTORA 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 , hypoventilation, 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 fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA of these dangers and counsel them accordingly

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate fentanyl buccal tabletsFENTORA with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression In such patients, even normal therapeutic doses of fentanyl buccal tabletsFENTORA may further decrease respiratory drive to the point of respiratory failure

5.7 Head Injuries and Increased Intracranial Pressure

Administer fentanyl buccal tabletsFENTORA 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to fentanyl buccal tabletsFENTORA reported application site reactions These reactions ranged from paresthesia to ulceration and bleeding Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%) Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia Therefore, use fentanyl buccal tabletsFENTORA with caution in patients with bradyarrhythmias

5.10 MAO Inhibitors

Fentanyl buccal tabletsFENTORA is are 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

5.11 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)]*, fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA, patient and prescriber enrollment is not required

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement
- Pharmacies that dispense fentanyl buccal tabletsFENTORA must enroll in the program and agree to comply with the REMS requirements
- Wholesalers and distributors that distribute fentanyl buccal tabletsFENTORA 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

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

The safety of fentanyl buccal tabletsFENTORA has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain The average duration of therapy was 76 days with some patients being treated for over 12 months

The most commonly observed adverse events seen with fentanyl buccal tabletsFENTORA are typical of opioid side effects Opioid side effects should be expected and managed accordingly

The clinical trials of fentanyl buccal tabletsFENTORA were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tabletsFENTORA for breakthrough pain along with a concomitant opioid for persistent pain There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tabletsFENTORA therapy or cancer-related symptoms

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies

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Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets~~FENTORA~~ There was no evidence of excess toxicity in this subset of patients

The duration of exposure to fentanyl buccal tablets~~FENTORA~~ varied greatly, and included open-label and double-blind studies The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets~~FENTORA~~ Events are classified by system organ class

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy
Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when fentanyl buccal tablets~~FENTORA~~ is given concurrently with agents that affect CYP3A4 activity

The concomitant use of fentanyl buccal tablets~~FENTORA~~ with CYP3A4 inhibitors (e g , indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression Patients receiving fentanyl buccal tablets~~FENTORA~~ who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]* The concomitant use of fentanyl buccal tablets~~FENTORA~~ with CYP3A4 inducers (e g , barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl buccal tablets~~FENTORA~~ Patients receiving fentanyl buccal tablets~~FENTORA~~ who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased fentanyl buccal tablets~~FENTORA~~ activity and the dose of fentanyl buccal tablets~~FENTORA~~ should be adjusted accordingly

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women fentanyl buccal tablets~~FENTORA~~ 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 characteristic of neonatal abstinence syndrome in newborn infants Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl

Fentanyl is embryocidal 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 fentanyl buccal tabletsFENTORA

Fentanyl (25, 50 or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17) Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1 4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison) Fentanyl (50, 100 or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18) Maternal toxicity was noted at doses ≥100 mcg/kg No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7 5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison)

Published studies concur with the conducted studies regarding the lack of teratogenic potential for fentanyl One literature report showed that administration of fentanyl (10, 100, or 500 mcg/kg) to pregnant rats from GD 7-21, via implanted microosmotic minipumps, was not teratogenic (the high dose was approximately 6-times the single human dose of 800 mcg per pain episode on a mg/m^2 basis) Another report showed that intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant rats from GD 6-18 was embryotoxic in the 30 mcg/kg group, but was not teratogenic Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for fentanyl buccal tabletsFENTORA

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100 and 400 mcg/kg) Maternal toxicity was noted at doses ≥100 mcg/kg A reduction in pup growth and delayed attainment of developmental indices were observed at ≥100 mcg/kg No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group Pups from this group also had significantly reduced body weights throughout the lactation period The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, do not use fentanyl buccal tabletsFENTORA for analgesia 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 fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA

8.4 Pediatric Use

The safety and efficacy of fentanyl buccal tabletsFENTORA have not been established in pediatric patients below the age of 18 years

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of fentanyl buccal tabletsFENTORA, 69 (23%) were 65 years of age and older

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain Therefore, caution should be exercised in individually titrating fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA 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 patients with cancer 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

8.8 Race

The pharmacokinetic effects of race with the use of fentanyl buccal tabletsFENTORA have not been systematically evaluated In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U S subjects

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl buccal tabletsFENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to other opioids including hydromorphone, methadone, morphine, oxycodone, and oxymorphone Fentanyl can be abused and is subject to misuse and criminal diversion

9.2 Abuse

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated abuse of a prescription drug and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, and sometimes tolerance and/or physical dependence

Abuse and addiction are separate and distinct from physical dependence and tolerance (see section 9 3) Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts In addition, abuse of opioids can occur in the absence of true addiction

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs

Abuse of fentanyl buccal tabletsFENTORA poses a risk of overdose and death This risk is increased with concurrent abuse of fentanyl buccal tabletsFENTORA with alcohol and other substances

Fentanyl buccal tabletsFENTORA, like other opioids, may be diverted for non-medical use Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors) Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use Withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug constitute evidence of physical dependence 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) Clinically significant physical dependence may not occur until after several days to weeks of continued opioid usage

Fentanyl buccal tabletsFENTORA should not be abruptly discontinued *[see Dosage and Administration (2.5)]* If fentanyl buccal tabletsFENTORA isare abruptly discontinued, or the dosage is rapidly reduced, in a physically-dependent patient, an abstinence syndrome may occur Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea; increased blood pressure, respiratory rate, or heart rate

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1)]*

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of fentanyl buccal tabletsFENTORA 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 hypoventilation *[see Clinical Pharmacology (12.2)]*

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the fentanyl buccal tabletsFENTORA tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 fentanyl buccal tabletsFENTORA 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 hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled

Although muscle rigidity interfering with respiration has not been seen following the use of fentanyl buccal tabletsFENTORA, this is possible with fentanyl and other opioids If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent

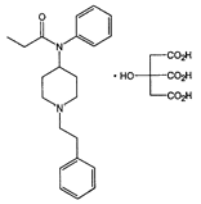
11 DESCRIPTION

FENTORA (fFentanyl buccal tablets) isare a potent opioid analgesic, intended for buccal mucosal administration

Fentanyl buccal tabletsFENTORA isare designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa

Fentanyl buccal tabletsFENTORA employs the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa

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:



All tablet strengths are expressed as the amount of fentanyl free base, e g , the 100 microgram strength tablet contains 100 micrograms of fentanyl free base

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an 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 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 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 fentanyl buccal tabletsFENTORA should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*

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 another oral transmucosal fentanyl citrate (Actiq) 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, Contraindications (4), Warnings and Precautions (5.2) and Overdosage (10)

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics Systemic exposure to fentanyl following administration of fentanyl buccal tablets~~FENTORA~~ increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range

Absorption

Following buccal administration of fentanyl buccal tablets~~FENTORA~~, fentanyl is readily absorbed with an absolute bioavailability of 65% The absorption profile of fentanyl buccal tablets~~FENTORA~~ is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets~~FENTORA~~ and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets~~FENTORA~~) (Table 4)

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving FENTORA or Actiq

Pharmacokinetic Parameter (mean)	FENTORA 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
AUC_{0-tmax} (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05
AUC_{0-inf} (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
*** Actiq (OTFC) data was dose adjusted (800 mcg to 400 mcg).

Table 4 Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or Actiq

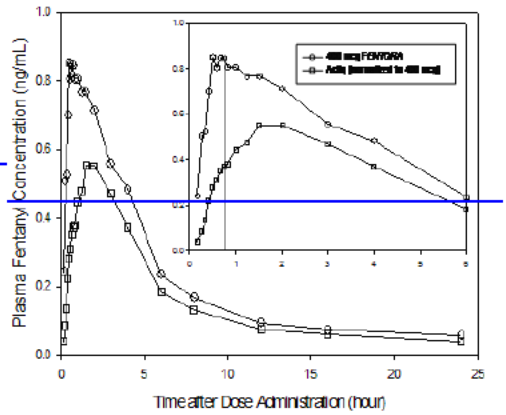
Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10 5%
Fraction Absorbed Transmucosally	48% ± 31 8%	22% ± 17 3%
T_{max} (minute)**	46 8 (20-240)	90 8 (35-240)
C_{max} (ng/mL)	1 02 ± 0 42	0 63 ± 0 21
AUC_{0-tmax} (ng•hr/mL)	0 40 ± 0 18	0 14 ± 0 05
AUC_{0-inf} (ng•hr/mL)	6 48 ± 2 98	4 79 ± 1 96

* Based on venous blood samples
** Data for T_{max} presented as median (range)
***Actiq data was dose adjusted (800 mcg to 400 mcg)

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq

Due to differences in drug delivery, measures of exposure (C_{max}, AUC_{0-tmax}, AUC_{0-inf}) associated with a given dose of fentanyl were substantially greater with fentanyl buccal tablets compared to Actiq (see Figure 1) Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]* Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours The vertical line denotes the median T_{max} for fentanyl buccal tablets

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and Actiq in Healthy Subjects



~~Actiq data was dose adjusted (800 mcg to 400 mcg)~~

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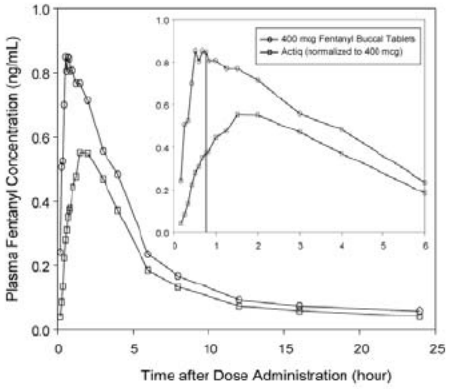


Actiq data were dose adjusted (800 mcg to 400 mcg)

Mean pharmacokinetic parameters are presented in Table 5 Mean plasma concentration versus time profiles are presented in Figure 2

Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90
T_{max} minute** (range)	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
AUC_{0-inf} (ng·hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
AUC_{0-tmax} (ng·hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
T1/2, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

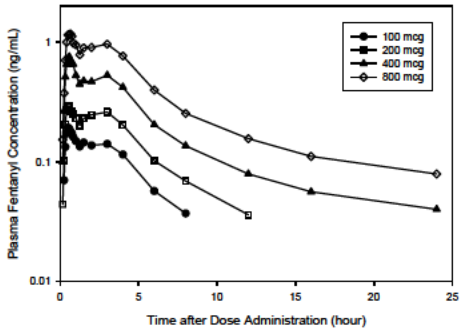
* Based on venous sampling.
** Data for T_{max} presented as median (range).

Table 5 Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0 25 ± 0 14	0 40 ± 0 18	0 97 ± 0 53	1 59 ± 0 90
T_{max}, minute** (range)	45 0 (25 0 - 181 0)	40 0 (20 0 - 180 0)	35 0 (20 0 - 180 0)	40 0 (25 0 - 180 0)
AUC_{0-inf} (ng·hr/mL)	0 98 ± 0 37	2 11 ± 1 13	4 72 ± 1 95	9 05 ± 3 72
AUC_{0-tmax} (ng·hr/mL)	0 09 ± 0 06	0 13 ± 0 09	0 34 ± 0 23	0 52 ± 0 38
T1/2, hr**	2 63 (1 47 - 13 57)	4 43 (1 85 - 20 76)	11 09 (4 63 - 20 59)	11 70 (4 63 - 28 63)

* Based on venous sampling
** Data for T_{max} presented as median (range)

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of ~~FENTORA~~ Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets~~FENTORA~~ was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched A single 200 mcg tablet was administered, followed by sampling at appropriate intervals Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	AUC_{0-tmax} (ng hr/mL)	AUC_{0-8} (ng hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement

Distribution

Fentanyl is highly lipophilic The plasma protein binding of fentanyl is 80-85% The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent The mean oral volume of distribution at steady state (Vss/F) was 25 4 L/kg

Metabolism

The metabolic pathways following buccal administration of fentanyl buccal tablets~~FENTORA~~ have not been characterized in clinical studies The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*

Elimination

Disposition of fentanyl following buccal administration of fentanyl buccal tablets~~FENTORA~~ has not been characterized in a mass balance study Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites Less than 7% of the ~~administered 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 following intravenous administration is approximately 42 L/h~~

Gender

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Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively) The observed differences between men and women were largely attributable to differences in weight

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively) The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U S subjects (57 4 kg versus 73 kg)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg AC transgenic mouse study In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2 3- and 3 4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison) In mice, at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed

Mutagenesis

Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed The systemic exposure at the dose of 300 mcg/kg was approximately 8 6-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5 7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets~~FENTORA~~ was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets~~FENTORA~~ A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets~~FENTORA~~ and 3 being placebo Patients used one tablet of study drug (either fentanyl buccal tablets~~FENTORA~~ or ~~P~~placebo) per breakthrough pain episode

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure

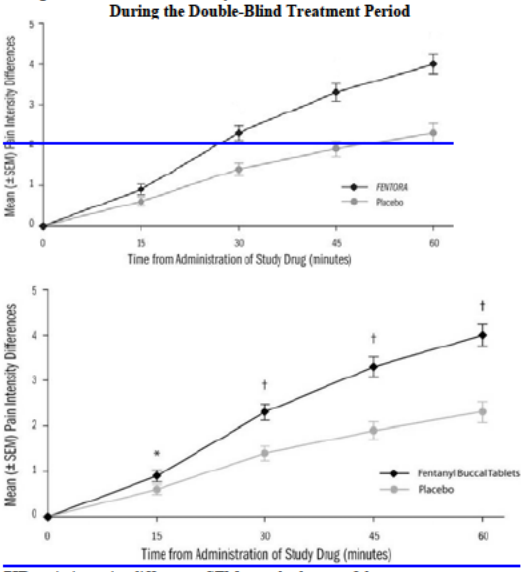
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase The distribution of successful doses is shown in Table 7 The median dose was 400 mcg

Table 7. Successful Dose of ~~FENTORA~~ Fentanyl Buccal Tablets Following Initial Titration

~~FENTORA~~ Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets ~~FENTORA~~ -treated episodes was 3 0 (0 12) while for placebo-treated episodes it was 1 8 (0 18)

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are supplied in individually sealed, child-resistant blister packages The amount of fentanyl contained in fentanyl buccal tablets~~FENTORA~~ can be fatal to a child **Patients and their caregivers must be instructed to keep ~~FENTORA~~ fentanyl buccal tablets out of the reach of children.** ***[see Boxed Warning, Overdosage (10), and Patient Counseling Information (17.1)]***

Store at 20 to 25°C (68 to 77°F) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use (See USP Controlled Room Temperature)

Protect fentanyl buccal tablets~~FENTORA~~ from freezing and moisture Do not use if the blister package has been tampered with

16.2 Disposal of ~~FENTORA~~ Fentanyl Buccal Tablets

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed ***[see Patient Counseling Information (17.2)]*** If additional assistance is required, call Teva Pharmaceuticals at 1-800-896-5855

To dispose of unused fentanyl buccal tablets~~FENTORA~~, remove fentanyl buccal ~~FENTORA~~ tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets~~FENTORA~~ blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets~~FENTORA~~, call Teva Pharmaceuticals at 1-800-896-5855

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card The blisters are child-resistant, encased in peelable foil, and provide protection from moisture Each tablet is debossed on one side with [C2], and the other side of each dosage strength is uniquely identified by the debossing

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on the tablet as described in the table below In addition, the dosage strength is indicated on the blister package and the carton See blister package and carton for product information

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC ~~63459-541-28~~80093-1150-28
200 mcg	2	Orange	NDC ~~63459-542-28~~80093-1151-28
400 mcg	4	Sage green	NDC ~~63459-544-28~~80093-1153-28
600 mcg	6	Magenta (pink)	NDC ~~63459-546-28~~80093-1154-28
800 mcg	8	Yellow	NDC ~~63459-548-28~~80093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient/Caregiver Instructions

- Before initiating treatment with fentanyl buccal tablets~~FENTORA~~, explain the statements below to patients and/or caregivers Instruct patients to read the Medication Guide each time fentanyl buccal tablets~~FENTORA is~~are dispensed because new information may be available
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets~~FENTORA~~
  - Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets~~FENTORA~~ or the TIRF REMS Access program
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the fentanyl buccal tablets~~FENTORA~~ Medication Guide with every patient before initiating treatment with fentanyl buccal tablets~~FENTORA~~
  - Advise the patient that fentanyl buccal tablets~~FENTORA is~~are 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 fentanyl buccal tablets~~FENTORA~~
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets~~FENTORA~~
  - 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, especially small children, exposed to ~~FENTORA~~ fentanyl buccal tablets are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep fentanyl buccal tablets~~FENTORA~~ tablets out of the reach of children *[see How Supplied/Storage and Handling (16.1) and Warnings and Precautions (5.3)]*
- Instruct patients not to take fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA is~~ are 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 fentanyl buccal tablets~~FENTORA~~
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e g , two 100 mcg tablets for a 200 mcg dose)
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF ~~FENTORA~~ FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of ~~FENTORA~~ fentanyl buccal tablets for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~
- Instruct patients NOT to share fentanyl buccal tablets~~FENTORA~~ and that sharing fentanyl buccal tablets~~FENTORA~~ with anyone else could result in the other individual's death due to overdose
- Make patients aware that fentanyl buccal tablets~~FENTORA~~ contain~~s~~ fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone
- Instruct patients that the active ingredient in fentanyl buccal tablets~~FENTORA~~, fentanyl, is a drug that some people abuse Fentanyl buccal tablets~~FENTORA~~ 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
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets~~FENTORA~~ and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package
- Instruct patients that fentanyl buccal~~FENTORA~~ tablets are not to be swallowed whole; this will reduce the effectiveness of the medication Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets~~FENTORA~~
- Instruct patients to use fentanyl buccal tablets~~FENTORA~~ exactly as prescribed by their doctor and not to take fentanyl buccal tablets~~FENTORA~~ more often than prescribed
- Caution patients that fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ of these dangers and counsel them accordingly
- Warn patients to not combine fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~, they should ask their doctor about the effects that fentanyl buccal tablets~~FENTORA~~ (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 Disposal of Unopened ~~FENTORA~~ Fentanyl Buccal Tablets Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed

To dispose of unused fentanyl buccal tablets~~FENTORA~~, remove fentanyl buccal~~FENTORA~~ tablets from blister packages and flush down the toilet Do not flush the fentanyl buccal tablets~~FENTORA~~ blister packages or cartons down the toilet

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets~~FENTORA~~ are provided in the fentanyl buccal tablets~~FENTORA~~ Medication Guide Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-800-896-5855) or seek assistance from their local DEA office

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~~Manufactured For Distributed By:~~
Teva Pharmaceuticals USA

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MEDICATION GUIDE

~~FENTORA® (fen-tor-a) CII~~
~~(f~~Fentanyl ~~b~~Buccal ~~t~~Tablet~~s)~~ CII
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use ~~FENTORA~~ 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~~FENTORA~~ in a safe place away from children.

Get emergency help right away if:

- **a child takes fentanyl buccal tablets~~FENTORA~~. Fentanyl buccal tablets~~FENTORA~~ can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed fentanyl buccal tablets~~FENTORA~~ uses it**
- **an adult who is not already taking opioids around-the-clock, uses fentanyl buccal tablets~~FENTORA~~.**

These are medical emergencies that can cause death. If possible, try to remove fentanyl buccal tablets~~FENTORA~~ from the mouth.

Read this Medication Guide completely before you start using fentanyl buccal tablets~~FENTORA~~, 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.

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What is the most important information I should know about fentanyl buccal tablets~~FENTORA~~?

Fentanyl buccal tablets~~FENTORA~~ can cause life-threatening breathing problems which can lead to death.

1. **Do not use fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use fentanyl buccal tablets~~FENTORA~~ exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~. **See the Medication Guide section "How should I use fentanyl buccal tablets~~FENTORA~~?" and the Instructions for Use at the end of this Medication Guide for detailed information about how to use fentanyl buccal tablets~~FENTORA~~ the right way.**

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4. **Do not switch from fentanyl buccal tabletsFENTORA to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tabletsFENTORA 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 tabletsFENTORA that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use fentanyl buccal tabletsFENTORA 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 tabletsFENTORA to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   Fentanyl buccal tabletsFENTORA ~~is~~ are a federally controlled substance (CII) because ~~it is~~they are 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 tabletsFENTORA in a safe place** to protect it from being stolen. Fentanyl buccal tabletsFENTORA 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 tabletsFENTORA ~~is~~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 tabletsFENTORA, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of fentanyl buccal tabletsFENTORA
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form.

What ~~is~~ are fentanyl buccal tabletsFENTORA?

- Fentanyl buccal tabletsFENTORA ~~is~~are a prescription medicine that contains the medicine fentanyl.
- Fentanyl buccal tabletsFENTORA ~~is~~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 tabletsFENTORA ~~is~~ 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 tabletsFENTORA if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using fentanyl buccal tabletsFENTORA.
- Fentanyl buccal tabletsFENTORA ~~is~~are only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if FENTORAfentanyl buccal tablets are~~is~~ safe and effective in children under 18 years of age.

Who should not use FENTORAfentanyl buccal tablets?

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Do not use ~~FENTORA~~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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in ~~FENTORA~~fentanyl buccal tablets. See the end of this Medication Guide for a complete list of ingredients in fentanyl buccal tablets~~FENTORA~~.

What should I tell my healthcare provider before using fentanyl buccal tablets~~FENTORA~~?

Before using fentanyl buccal tablets~~FENTORA~~, 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~~FENTORA~~ may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. Fentanyl buccal tablets~~FENTORA~~ pass~~es~~ into your breast milk. ~~It~~They can cause serious harm to your baby. You should not take fentanyl buccal tablets~~FENTORA~~ while breastfeeding.

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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 fentanyl buccal tablets~~FENTORA~~. Sometimes, the doses of certain medicines and fentanyl buccal tablets~~FENTORA~~ need to be changed if used together.

- **Do not take any medicine while using ~~FENTORA~~ 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~~FENTORA~~.**
- 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~~FENTORA~~?

Before you can begin to use fentanyl buccal tablets~~FENTORA~~:

- 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~~FENTORA~~ ~~is~~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~~FENTORA~~ prescription filled.

Using fentanyl buccal tablets~~FENTORA~~:

- **Use fentanyl buccal tablets~~FENTORA~~ exactly as prescribed. Do not use fentanyl buccal tablets~~FENTORA~~ 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 ~~FENTORA~~ the right way.**
- **Use fentanyl buccal~~FENTORA~~ tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal ~~FENTORA~~ tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using the fentanyl buccal tablet~~FENTORA~~. If there is any of the fentanyl buccal~~FENTORA~~ 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 ~~FENTORA~~ fentanyl buccal tablets for each episode of breakthrough cancer pain.
  - Use **1** dose of fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~, you can use **only 1** more dose of fentanyl buccal tablets~~FENTORA~~ as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of fentanyl buccal tablets~~FENTORA~~, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tablets~~FENTORA~~ at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tablets~~FENTORA~~.
  - If you only need to take 1 dose of fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~ for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of fentanyl buccal tablets~~FENTORA~~ for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~.
- Talk to your healthcare provider if your dose of fentanyl buccal tablets~~FENTORA~~ does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tablets~~FENTORA~~ 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

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or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.

- If you use too much fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how fentanyl buccal tablets~~FENTORA~~ affect~~s~~ you. Fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of fentanyl buccal tablets~~FENTORA~~?

Fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~?**" **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 much fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~.

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~~FENTORA~~. 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 fentanyl buccal tablets~~FENTORA~~?

- **Always keep fentanyl buccal tablets~~FENTORA~~ in a safe place away from children and from anyone for whom it has not been prescribed**. Protect fentanyl buccal tablets~~FENTORA~~ from theft.
- Store fentanyl buccal tablets~~FENTORA~~ at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze fentanyl buccal tablets~~FENTORA~~.
- Keep fentanyl buccal tablets~~FENTORA~~ in the original blister unit. Do not remove fentanyl buccal tablets~~FENTORA~~ from its blister packaging for storage in a temporary container, such as a pill box.
- Keep fentanyl buccal tablets~~FENTORA~~ dry.

How should I dispose of unused fentanyl buccal~~FENTORA~~ tablets when they are no longer needed?

- Dispose of any unused fentanyl buccal~~FENTORA~~ tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablets~~FENTORA~~ packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets~~FENTORA~~, call Teva Pharmaceuticals at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

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General information about fentanyl buccal tablets~~FENTORA~~

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use fentanyl buccal tablets~~FENTORA~~ only for the purpose for which it was prescribed. Do not give ~~FENTORA~~ fentanyl buccal tablets to other people, even if they have the same symptoms you have.** Fentanyl buccal tablets~~FENTORA~~ can harm other people and even cause death. Sharing fentanyl buccal tablets~~FENTORA~~ is against the law.

This Medication Guide summarizes the most important information about fentanyl buccal tablets~~FENTORA~~. 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~~FENTORA~~ 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 ~~FENTORA~~fentanyl buccal tablets?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Instructions for Use

Before you use ~~FENTORA~~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~~FENTORA~~ the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use fentanyl buccal tablets~~FENTORA~~.

When you get an episode of breakthrough cancer pain, use the dose of ~~FENTORA~~ fentanyl buccal tablets prescribed by your healthcare provider as follows:

- ~~FENTORA~~ Fentanyl buccal tablets come~~s~~ packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your ~~FENTORA~~ fentanyl buccal tablets will be printed in the boxed area shown as

  XXX mcg (See Figure 1).

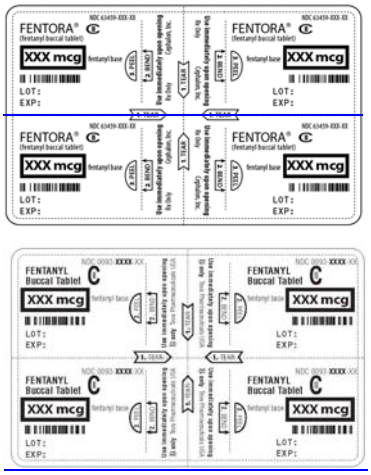

Figure 1

- Peel back foil on blister unit to expose tablet (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, ~~FENTORA~~ fentanyl buccal tablet must be used right away.
- **Use fentanyl buccal~~FENTORA~~ tablets whole**.
- **Do not crush, split, suck, or chew fentanyl buccal~~FENTORA~~ tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- You can place a ~~FENTORA~~ 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.

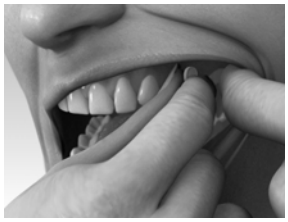

Figure 3

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).

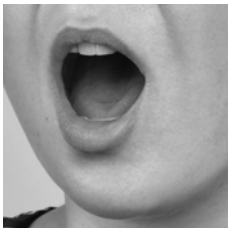

Figure 4a

Figure 4b

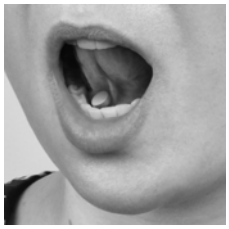

Figure 4c

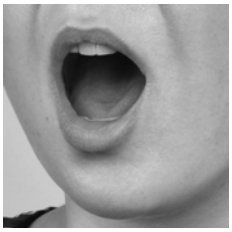

Figure 4d

- **Leave the tablet in place until it dissolves.** A fentanyl buccal~~FENTORA~~ tablet generally takes between 14 to 25 minutes to dissolve.
- After 30 minutes, if there is any fentanyl buccal tablet~~FENTORA~~ left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use ~~FENTORA~~ 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.

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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**
Fentanyl Buccal Tablets (generic equivalent of FENTORA®)	Teva Pharmaceuticals USA, 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	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 [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.

<u>Outpatient Pharmacies</u>

- 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

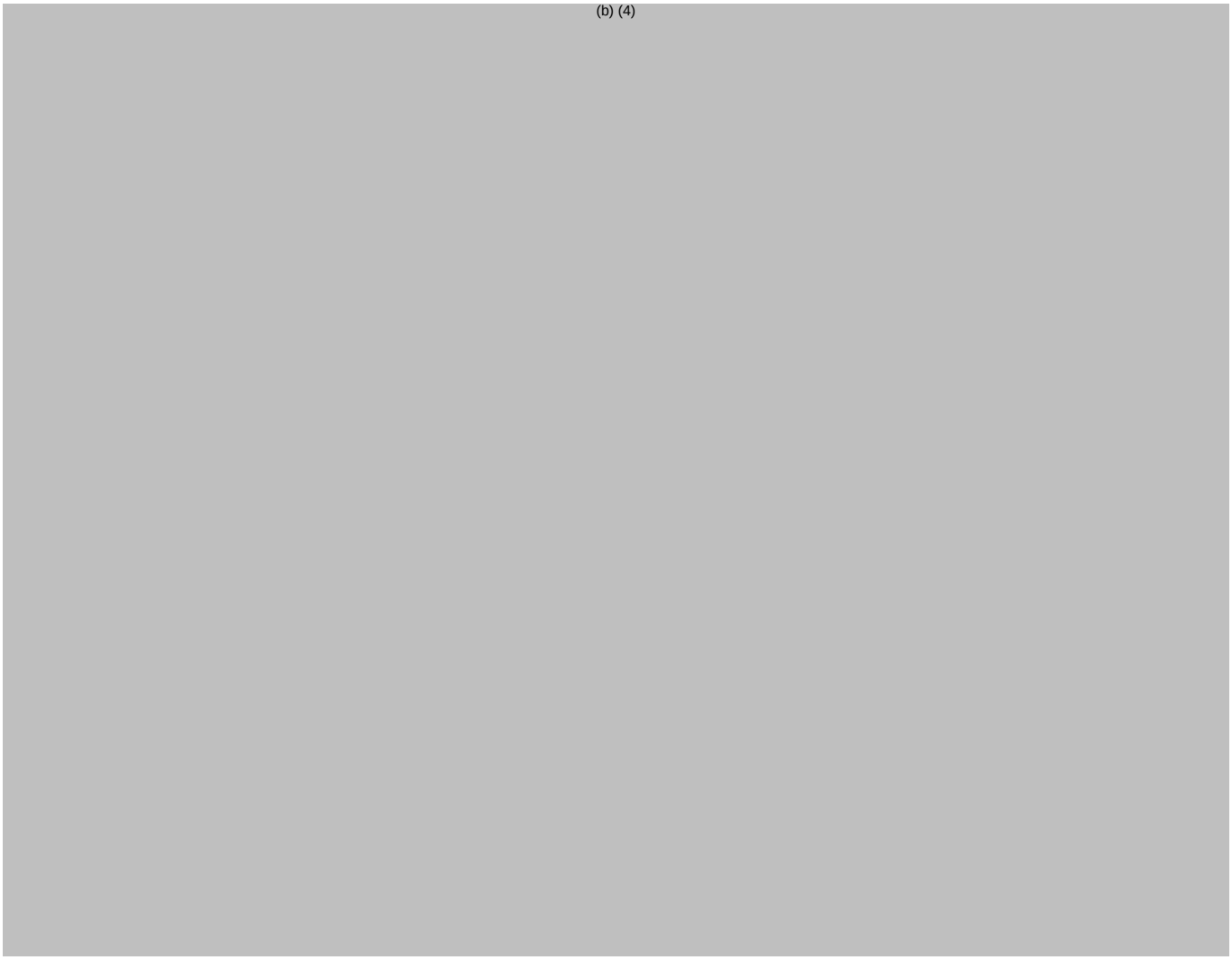
- Provide stakeholder enrollment verification in the TIRF REMS Access database
- Processing of Patient- Prescriber Agreements Forms
- Assist prescribers or patients in locating enrolled pharmacies
- Identify and transfer product complaints and potential adverse event information to TIRF Sponsors
- Provide 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:

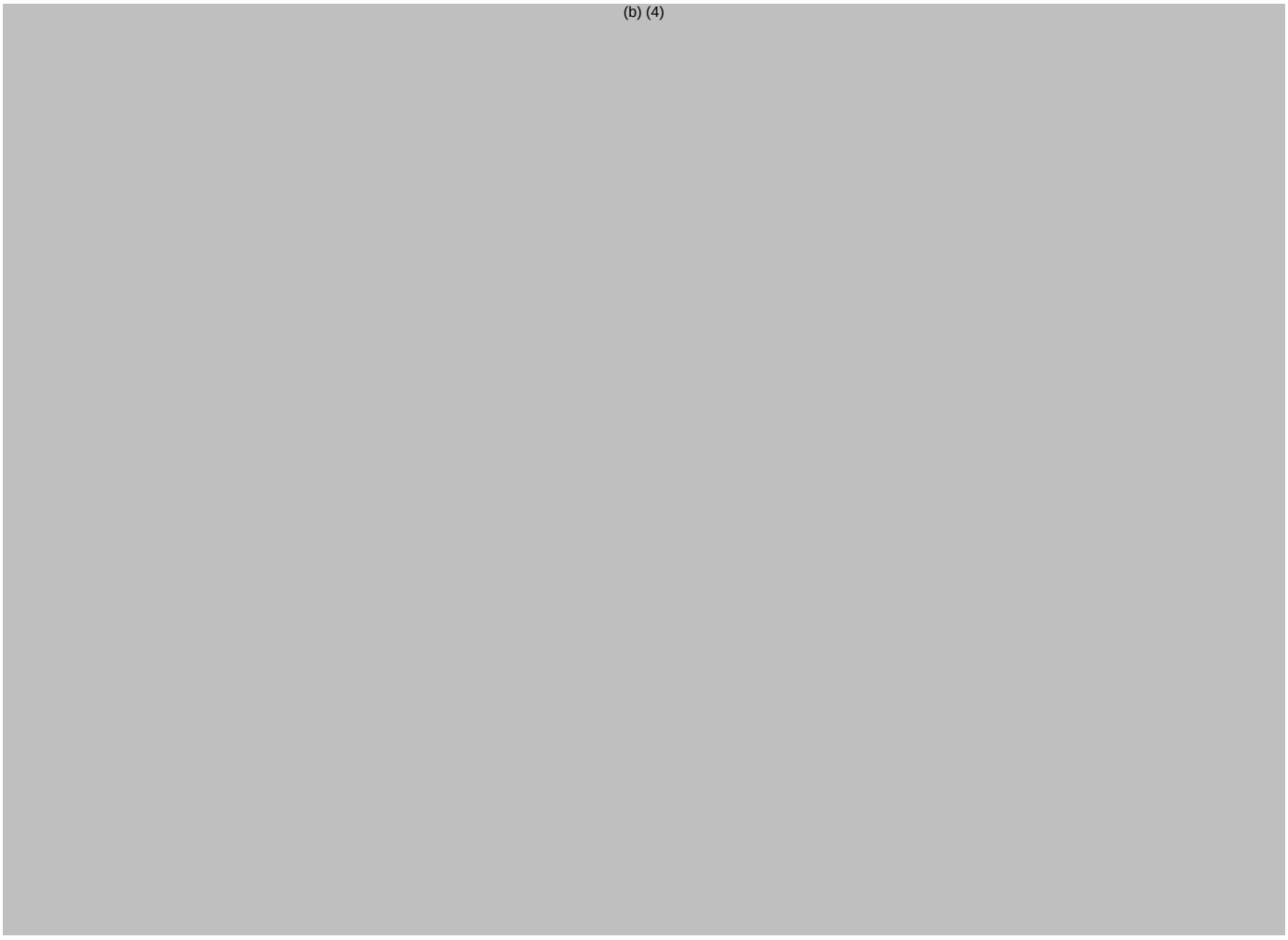
1. Number of Dear HCP letters mailed to prescribers (by date)
2. Number of returned mailings of Dear HCP letters to prescribers.
3. Number of Pharmacist letters mailed to pharmacies (by date)
4. Number of returned mailings of Pharmacist letters to pharmacies

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.)

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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* 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 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 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
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.

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.

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
- 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.

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 and generic equivalents	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 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.
Subsys™ (fentanyl) sublingual spray	Always 100 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 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 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 ~~and~~ 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* _____
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):_____

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
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

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" 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:

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

II. 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. 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 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.

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.

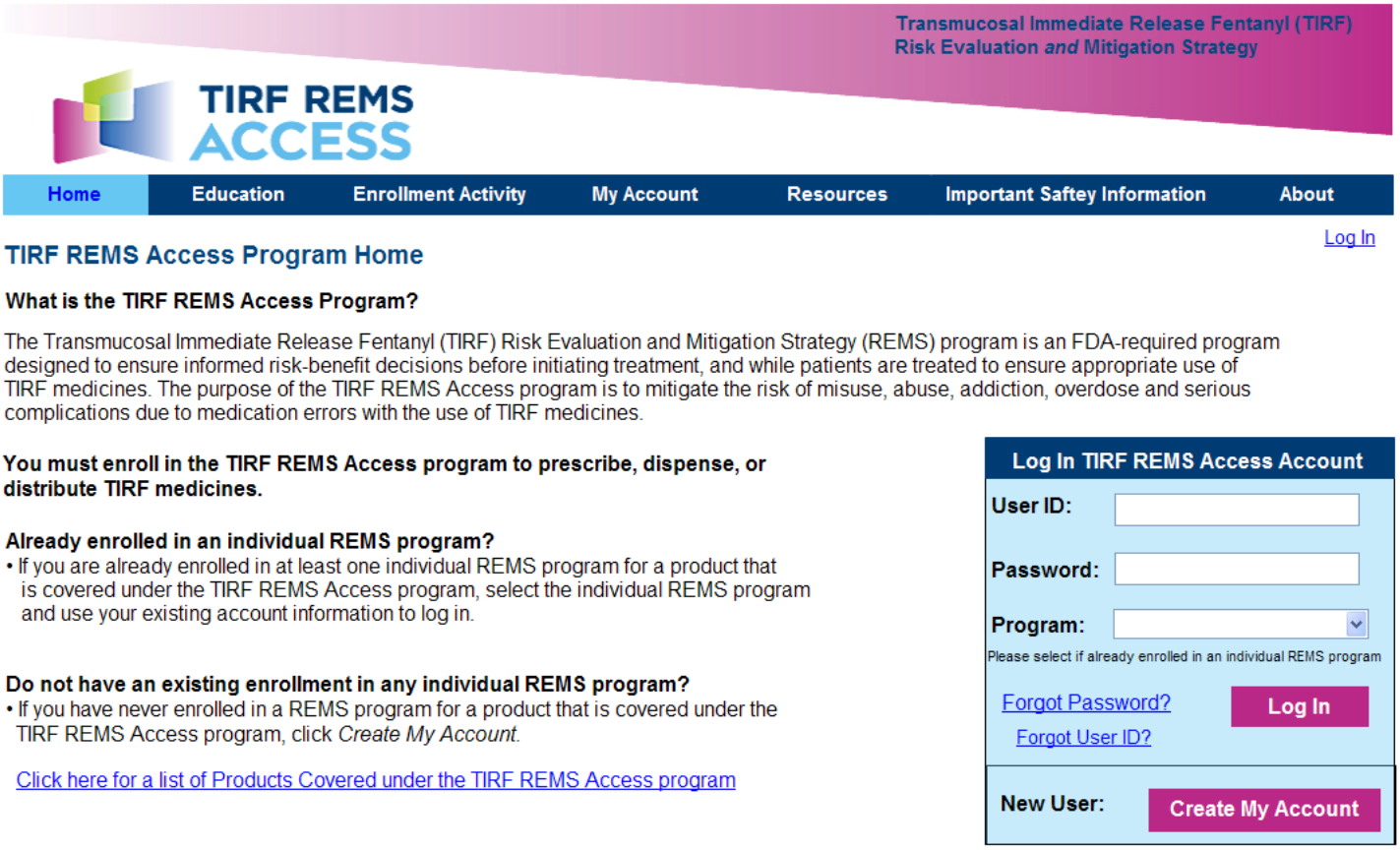
What are the TIRF REMS Access program requirements for a distributor?
To enroll in the TIRF REMS Access program, a distributor will have to complete and sign the Distributor Enrollment Form. In signing the enrollment form, the distributor is required to indicate that they understand that TIRF medicines 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:

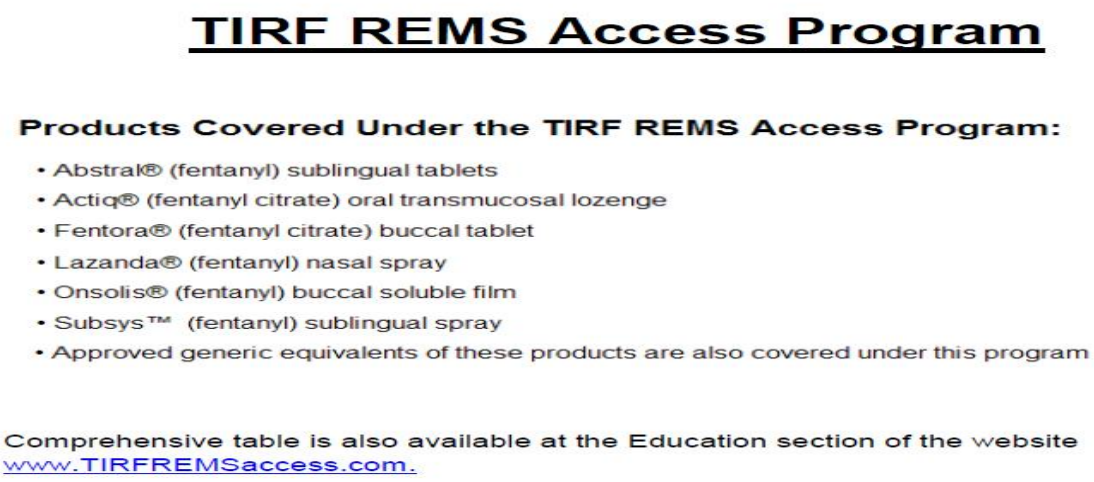
- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access 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) buccal soluble film
- Subsys™ (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 (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.

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.

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

- 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
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

- 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
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

- 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
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, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-06, 20482-001-14, 20482-001-28, 20482-002-06, 20482-002-14, 20482-002-28, 20482-004-06,
20482-004-14, 20482-004-28, 20482-006-06, 20482-006-14, 20482-006-28, 20482-008-06, 20482-008-14,
20482-008-28, 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55,
00093-1150-28, 0093-1151-28, 00093-1153-28, 00093-1154-28, 00093-1155-28

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 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[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
Fentanyl Buccal Tablets (generic equivalent of FENTORA®)	Teva Pharmaceuticals USA, Inc.	100 mcg	00093-1150-28
		200 mcg	00093-1151-28
		400 mcg	00093-1153-28
		600 mcg	00093-1154-28
		800 mcg	00093-1155-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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
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

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55253-0072-30
		800 mcg	55253-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30
SUBSYS™ (fentanyl sublingual spray)	Insys Therapeutics Inc.	100 mcg	20482-001-06 20482-001-14 20482-001-28
		200 mcg	20482-002-06 20482-002-14 20482-002-28
		400 mcg	20482-004-06 20482-004-14 20482-004-28
		600 mcg	20482-006-06 20482-006-14 20482-006-28
		800 mcg	20482-008-06 20482-008-14 20482-008-28

[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
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, 55253-0072-30, 55253-0073-30, 55253-0074-30, 55253-0075-30,
20482-001-06, 20482-001-14, 20482-001-28, 20482-002-06, 20482-002-14, 20482-002-28, 20482-004-06,
20482-004-14, 20482-004-28, 20482-006-06, 20482-006-14, 20482-006-28, 20482-008-06, 20482-008-14,
20482-008-28, 49884-459-55, 49884-460-55, 49884-461-55, 49884-462-55, 49884-463-55, 49884-464-55,
00093-1150-28, 0093-1151-28, 00093-1153-28, 00093-1154-28, 00093-1155-28

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

Chain ID*:_____

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[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
Fentanyl Buccal Tablets (generic equivalent of FENTORA®)	Teva Pharmaceuticals USA, Inc.	100 mcg	00093-1150-28
		200 mcg	00093-1151-28
		400 mcg	00093-1153-28
		600 mcg	00093-1154-28
		800 mcg	00093-1155-28
LAZANDA® (fentanyl) nasal spray	Archimedes Pharma US Inc.	100 mcg	51772-311-01
		400 mcg	51772-314-01

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
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
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

Medicine Name	Applicant/Sponsor	Dosage Strength	NDC#
Oral transmucosal fentanyl citrate lozenge (generic equivalent of ACTIQ®)	Anesta Corp	200 mcg	55253-0070-30
		400 mcg	55253-0071-30
		600 mcg	55253-0072-30
		800 mcg	55253-0073-30
		1200 mcg	55253-0074-30
		1600 mcg	55253-0075-30
SUBSYS™ (fentanyl sublingual spray)	Insys Therapeutics Inc.	100 mcg	20482-001-06 20482-001-14 20482-001-28
		200 mcg	20482-002-06 20482-002-14 20482-002-28
		400 mcg	20482-004-06 20482-004-14 20482-004-28
		600 mcg	20482-006-06 20482-006-14 20482-006-28
		800 mcg	20482-008-06 20482-008-14 20482-008-28

[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):_____

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):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

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
Closed System Pharmacy Enrollment Form

To submit this form via fax, 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. 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 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 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 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.
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.

Closed System Chain ID*:_____

Authorized Closed System Pharmacy Representative:

Authorized Pharmacy Representative Signature* _____ **Date** _____

First Name* _____ **Last Name*** _____ **Title** _____

Phone Number* _____ **Email*** _____

Closed System 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 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 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 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 – [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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- 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

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):_____

For more information about TIRF medicines, please see Full Prescribing Information, including BOXED WARNINGS

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

Attachment 1:

List of TIRF Medicines Available Only through the TIRF REMS Access Program

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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.

Branded Pharmaceutical Products R&D

June 10, 2013

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research Division of Anesthesia,
Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947, Sequence No. 0033
FENTORA® (fentanyl buccal tablet), CII

AMENDMENT TO PENDING SUPPLEMENT

Dear Dr. Rappaport:

Reference is made to the New Drug Application (NDA 021947) for the use of FENTORA (fentanyl buccal tablet) 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.

Further reference is made to submission of a Prior Approval Supplement to support the commercialization of an authorized generic of FENTORA, Fentanyl Buccal Tablets, on 21 May 2013 (Sequence No. 0031).

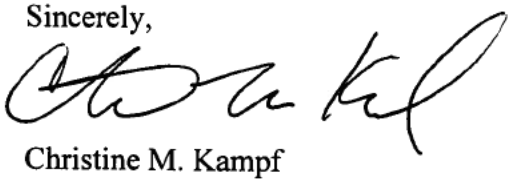
The purpose of this submission is to provide a corrected full Prescribing Information and Medication Guide ensuring complete replacement of the brand name "FENTORA" with "Fentanyl Buccal Tablets" throughout.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client and Service Pack No. 10.5.1997, antivirus engine No. 9.700.1001, virus pattern No. 9.605.00 with a release date of 6/10/13 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311.

Teva Pharmaceuticals
41 Moores Road, PO Box 4011 | Frazer, PA 19355 | Tel. 610.344.0200 | Fax 610.783.6311 | www.tevapharm-na.com

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6189 or via email at christine.kampf@tevapharm.com.

Sincerely,



Christine M. Kampf
Manager, Regulatory Affairs

Teva Branded Pharmaceutical Products R&D, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use fentanyl buccal tablets safely and effectively. See full prescribing information for fentanyl buccal tablets.

Fentanyl Buccal Tablets, CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL
See full prescribing information for complete boxed warning.
- **Due to the risk of fatal respiratory depression, fentanyl buccal tablets are 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to fentanyl buccal tablets. (2.1, 5.2)**
- **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)**
- **Fentanyl buccal tablets are 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Maintenance Dosing (2.3) 02/2013
Dosage and Administration, Administration of Fentanyl Buccal Tablets (2.4) 02/2013
Dosage and Administration, Discontinuation of Fentanyl Buccal Tablets (2.5) 02/2013

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets are an opioid agonist indicated 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. (1)
Limitations of Use:
Fentanyl buccal tablets 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 fentanyl buccal tablets. (1)
- Initial dose of fentanyl buccal tablets: 100 mcg. (2.1)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablet. Limit patient access to only one strength of fentanyl buccal tablets at any one time. (2.1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablet. (2.1)
- No more than two doses can be taken per breakthrough pain episode. (2.1)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets. (2.1)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Intolerance or hypersensitivity to fentanyl or components of fentanyl buccal tablets. (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. (5.1)
- Fentanyl buccal tablets is not bioequivalent to other fentanyl products. Do not convert from other fentanyl products on a mcg per mcg basis. (5.2)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. (5.4)
- Titrate fentanyl buccal tablets 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 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----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Administer fentanyl buccal tablets with caution to patients with hepatic or renal impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2013

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 fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Fentanyl buccal tablets must be kept out of reach of children. *[see Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of fentanyl buccal tablets with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets 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 fentanyl buccal tablets. *[see Dosage and Administration (2.1)]*

- When dispensing, do not substitute a fentanyl buccal tablets prescription for other fentanyl products.

ABUSE POTENTIAL

Fentanyl buccal tablets contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Fentanyl buccal tablets can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing fentanyl buccal tablets 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, fentanyl buccal tablets are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets are indicated 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. 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/hr of transdermal fentanyl, 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 while taking fentanyl buccal tablets.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids. For this reason, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain.

Fentanyl buccal tablets 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.

Limitations of Use:

As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]*. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets *[see Warnings and Precautions (5.11)]*.

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use.

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.

2.1 Initial Dose

Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

Patients on Actiq

The initial dose of fentanyl buccal tablets is **always** 100 mcg with the only exception being patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1). The doses of fentanyl buccal tablets in this table are starting doses and not intended to represent equianalgesic doses to Actiq. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial Fentanyl Buccal Tablets Dose*

200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*From this initial dose, titrate patient to effective dose.

b. For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablet and should proceed using multiples of this tablet strength.

All Other Patients

The initial dose of fentanyl buccal tablets is 100 mcg.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any episode of breakthrough pain.
b. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets.

2.2 Dose Titration

a. From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablets over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted.
b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg fentanyl buccal tablet for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.
c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode. During titration, one **dose** of fentanyl buccal tablets may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).
d. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets. To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal tablets available at any time.
e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.3 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use **only ONE** fentanyl buccal tablet of the appropriate strength per breakthrough pain episode.
b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode.
c. Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tablets.
d. Dosage adjustment of fentanyl buccal tablets may be required in some patients.
   Generally, the fentanyl buccal tablets 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.
e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.
f. Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue.)

2.4 Administration of Fentanyl Buccal Tablets

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer fentanyl buccal tablets.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. **Patients should not split the tablet.**

The fentanyl buccal tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.

The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.

After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.

It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets in the buccal cavity.

2.5 Discontinuation of Fentanyl Buccal Tablets

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

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*.

4 CONTRAINDICATIONS

Fentanyl buccal tablets are contraindicated in opioid non-tolerant patients.

Fentanyl buccal tablets are 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.

Fentanyl buccal tablets are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl.

5 WARNINGS AND PRECAUTIONS

See Boxed Warning

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in fentanyl buccal tablets. 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

Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and fentanyl buccal tablets are not equivalent on a microgram per microgram basis. Fentanyl buccal tablets are NOT a generic version of Actiq. **All patients should be titrated from the 100 mcg dose.**

The initial dose of fentanyl buccal tablets should be 100 mcg. Titrate each patient individually to provide adequate analgesia while minimizing side effects. *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a fentanyl buccal tablets prescription for an Actiq prescription under any circumstances. Fentanyl buccal tablets and Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl. **As a result of these differences, the substitution of the same dose of fentanyl buccal tablets for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that fentanyl buccal tablets contain a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1)]*

5.4 Additive CNS Depressant Effects

The concomitant use of fentanyl buccal tablets 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., hypoventilation, 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 fentanyl buccal tablets 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 fentanyl buccal tablets of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate fentanyl buccal tablets with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of fentanyl buccal tablets may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer fentanyl buccal tablets 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to fentanyl buccal tablets reported application site reactions. These reactions ranged from paresthesia to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients.

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Therefore, use fentanyl buccal tablets with caution in patients with bradyarrhythmias.

5.10 MAO Inhibitors

Fentanyl buccal tablets are 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.

5.11 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)]*, fentanyl buccal tablets 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 fentanyl buccal tablets, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense fentanyl buccal tablets must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute fentanyl buccal tablets 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

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.

The safety of fentanyl buccal tablets has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The most commonly observed adverse events seen with fentanyl buccal tablets are typical of opioid side effects. Opioid side effects should be expected and managed accordingly.

The clinical trials of fentanyl buccal tablets were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tablets for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tablets therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.

Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.

Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets. There was no evidence of excess toxicity in this subset of patients.

The duration of exposure to fentanyl buccal tablets varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets. Events are classified by system organ class.

Adverse Events (≥1%)

Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration

General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain

Hepatobiliary Disorders: Jaundice

Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess

Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture

Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count

Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake

Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain

Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy

Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness

Renal and Urinary Disorders: Renal Failure

Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing

Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat

Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when fentanyl buccal tablets is given concurrently with agents that affect CYP3A4 activity.

The concomitant use of fentanyl buccal tablets with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving fentanyl buccal tablets who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]*. The concomitant use of fentanyl buccal tablets with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl buccal tablets. Patients receiving fentanyl buccal tablets who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased fentanyl buccal tablets activity and the dose of fentanyl buccal tablets should be adjusted accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women. fentanyl buccal tablets 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 characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal 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 fentanyl buccal tablets.

Fentanyl (25, 50 or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100 or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses ≥100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

Published studies concur with the conducted studies regarding the lack of teratogenic potential for fentanyl. One literature report showed that administration of fentanyl (10, 100, or 500 mcg/kg) to pregnant rats from GD 7-21, via implanted microosmotic minipumps, was not teratogenic (the high dose was approximately 6-times the single human dose of 800 mcg per pain episode on a mg/m^2 basis). Another report showed that intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant rats from GD 6-18 was embryotoxic in the 30 mcg/kg group, but was not teratogenic. Conversion

to human equivalent doses indicates this is within the range of the human recommended dosing for fentanyl buccal tablets.

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100 and 400 mcg/kg). Maternal toxicity was noted at doses ≥100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at ≥100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, do not use fentanyl buccal tablets for analgesia 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 fentanyl buccal tablets 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 fentanyl buccal tablets.

8.4 Pediatric Use

The safety and efficacy of fentanyl buccal tablets have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older.

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients.

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablets 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 fentanyl buccal tablets 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 patients with cancer 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.

8.8 Race

The pharmacokinetic effects of race with the use of fentanyl buccal tablets have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl buccal tablets contain fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to other opioids including hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Fentanyl can be abused and is subject to misuse and criminal diversion.

9.2 Abuse

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated abuse of a prescription drug and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, and sometimes tolerance and/or physical dependence.

Abuse and addiction are separate and distinct from physical dependence and tolerance (see section 9 3). Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Abuse of fentanyl buccal tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of fentanyl buccal tablets with alcohol and other substances.

Fentanyl buccal tablets, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy.

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use. Withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug constitute evidence of physical dependence. 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). Clinically significant physical dependence may not occur until after several days to weeks of continued opioid usage.

Fentanyl buccal tablets should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If fentanyl buccal tablets are abruptly discontinued, or the dosage is rapidly reduced, in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea; increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of fentanyl buccal tablets 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 hypoventilation *[see Clinical Pharmacology (12.2)]*.

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the fentanyl buccal tablets tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 fentanyl buccal tablets 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

hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated.

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled.

Although muscle rigidity interfering with respiration has not been seen following the use of fentanyl buccal tablets, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent.

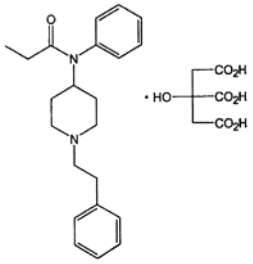
11 DESCRIPTION

Fentanyl buccal tablets are a potent opioid analgesic, intended for buccal mucosal administration.

Fentanyl buccal tablets are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

Fentanyl buccal tablets employ the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an 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 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 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 fentanyl buccal tablets should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*.

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 another oral transmucosal fentanyl citrate (Actiq). 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, Contraindications (4), Warnings and Precautions (5.2) and Overdosage (10).

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of fentanyl buccal tablets increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption

Following buccal administration of fentanyl buccal tablets, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of fentanyl buccal tablets is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is

swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets) (Table 4).

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or Actiq

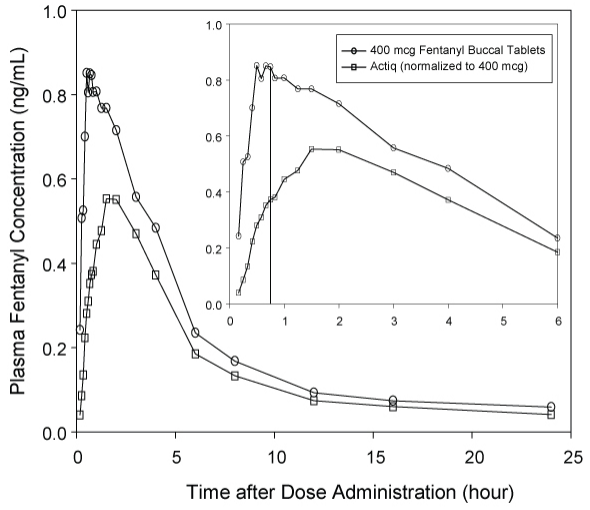
Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
***Actiq data was dose adjusted (800 mcg to 400 mcg).

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl were substantially greater with fentanyl buccal tablets compared to Actiq (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablets.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and Actiq in Healthy Subjects



Actiq data were dose adjusted (800 mcg to 400 mcg)

Mean pharmacokinetic parameters are presented in Table 5. Mean plasma concentration versus time profiles are presented in Figure 2.

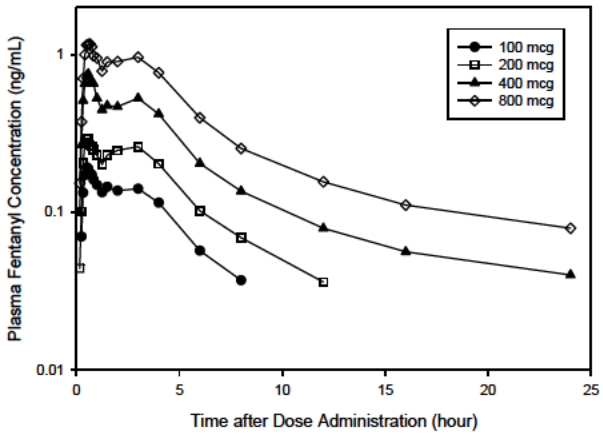
Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90

T_{max}, minute** (range)	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
T1/2, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6.

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng·hr/mL)	$AUC_{0\text{-}8}$ (ng·hr/mL)
Mucositis	1 25 ± 0 78	25 0 (15 - 45)	0 21 ± 0 16	2 33 ± 0 93
No mucositis	1 24 ± 0 77	22 5 (10 - 121)	0 25 ± 0 24	1 86 ± 0 86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement.

Distribution

Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Metabolism

The metabolic pathways following buccal administration of fentanyl buccal tablets have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Elimination

Disposition of fentanyl following buccal administration of fentanyl buccal tablets has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Gender

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2.3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In mice, at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis

Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 8.6-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets and 3 being placebo. Patients used one tablet of study drug (either fentanyl buccal tablets or placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

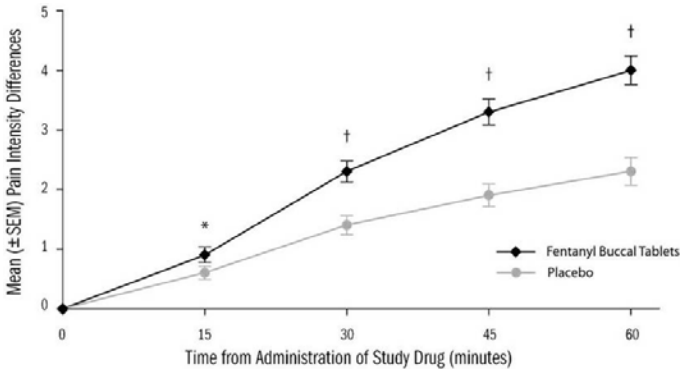
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 7. The median dose was 400 mcg.

Table 7. Successful Dose of Fentanyl Buccal Tablets Following Initial Titration

Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets -treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Fentanyl buccal tablets are supplied in individually sealed, child-resistant blister packages. The amount of fentanyl contained in fentanyl buccal tablets can be fatal to a child. **Patients and their caregivers must be instructed to keep fentanyl buccal tablets out of the reach of children.** *[see Boxed Warning, Overdosage (10), and Patient Counseling Information (17.1)]*

Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)

Protect fentanyl buccal tablets from freezing and moisture. Do not use if the blister package has been tampered with.

16.2 Disposal of Fentanyl Buccal Tablets

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed *[see Patient Counseling Information (17.2)]*. If additional assistance is required, call Teva Pharmaceuticals at 1-800-896-5855.

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855.

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with [C2], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 0093-1150-28
200 mcg	2	Orange	NDC0093-1151-28
400 mcg	4	Sage green	NDC 0093-1153-28
600 mcg	6	Magenta (pink)	NDC 0093-1154-28
800 mcg	8	Yellow	NDC 0093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient/Caregiver Instructions

- Before initiating treatment with fentanyl buccal tablets, explain the statements below to patients and/or caregivers. Instruct patients to read the Medication Guide each time fentanyl buccal tablets are dispensed because new information may be available.
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets.
  - Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets or the TIRF REMS Access program.
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the fentanyl buccal tablets Medication Guide with every patient before initiating treatment with fentanyl buccal tablets.
  - Advise the patient that fentanyl buccal tablets are 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 fentanyl buccal tablets.
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets.
  - 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, especially small children, exposed to fentanyl buccal tablets are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep fentanyl buccal tablets tablets out of the reach of children. *[see How Supplied/Storage and Handling (16.1) and Warnings and Precautions (5.3)]*
- Instruct patients not to take fentanyl buccal tablets 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 fentanyl buccal tablets are 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 fentanyl buccal tablets.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.
- Instruct patients NOT to share fentanyl buccal tablets and that sharing fentanyl buccal tablets with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablets contain fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients that the active ingredient in fentanyl buccal tablets, fentanyl, is a drug that some people abuse. Fentanyl buccal tablets 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.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.
- Instruct patients that fentanyl buccal tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets.
- Instruct patients to use fentanyl buccal tablets exactly as prescribed by their doctor and not to take fentanyl buccal tablets more often than prescribed.
- Caution patients that fentanyl buccal tablets 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 fentanyl buccal tablets of these dangers and counsel them accordingly.
- Warn patients to not combine fentanyl buccal tablets 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 fentanyl buccal tablets, they should ask their doctor about the effects that fentanyl buccal tablets (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 Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush the fentanyl buccal tablets blister packages or cartons down the toilet.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-800-896-5855) or seek assistance from their local DEA office.

FBT-002

Manufactured For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

Iss. 4/2013

MEDICATION GUIDE

Fentanyl 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 they are 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 buccal tablets pass into your breast milk. They 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 the fentanyl buccal tablet. 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 much 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 much fentanyl buccal tablets 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 1-800-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, 59°F to 86°F (15° C to 30°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.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855 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, sodium bicarbonate, sodium carbonate, citric acid, 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.**

- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as

  XXX mcg (See Figure 1).

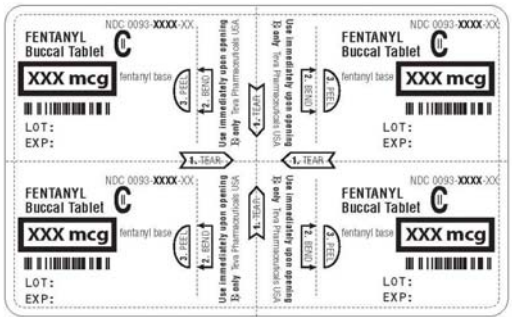


Figure 1

- Peel back foil on blister unit to expose tablet (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:
  - 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.

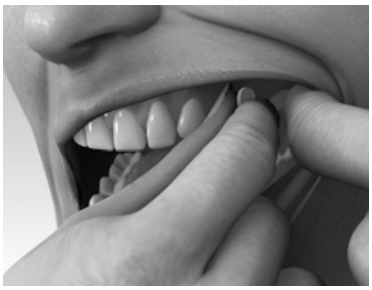


Figure 3

OR,

- 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).

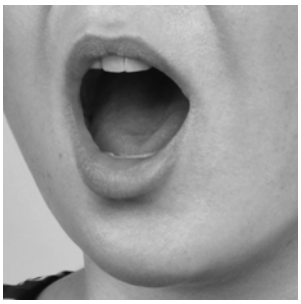


Figure 4a

Figure 4b

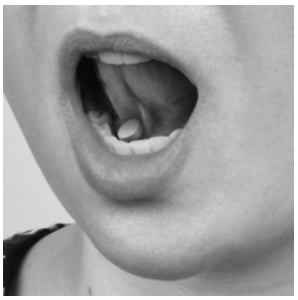


Figure 4c

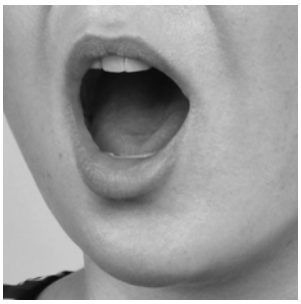


Figure 4d

- **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 For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ~~FENTORA~~ fentanyl buccal tablets safely and effectively. See full prescribing information for ~~FENTORA~~fentanyl buccal tablets.

~~FENTORA®~~ (~~F~~entanyl ~~b~~Buccal ~~t~~Tablets~~)~~, CII
Initial U.S. Approval: 1968

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

See full prescribing information for complete boxed warning.

- **Due to the risk of fatal respiratory depression, ~~FENTORA~~ fentanyl buccal tablets ~~is~~are 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 CYP3A4 inhibitors may cause fatal respiratory depression. (7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to fentanyl buccal tablets~~FENTORA~~. (2.1, 5.2)**
- **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)**
- **Fentanyl buccal tablets~~FENTORA~~ ~~is~~are 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. (5.11)**

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Maintenance Dosing (2 3) 02/2013
Dosage and Administration, Administration of ~~FENTORA~~ Fentanyl Buccal Tablets (2 4) 02/2013
Dosage and Administration, Discontinuation of ~~FENTORA~~ Fentanyl Buccal Tablets (2 5) 02/2013

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are an opioid agonist indicated 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 (1)
Limitations of Use:
Fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ (1)
- Initial dose of fentanyl buccal tablets~~FENTORA~~: 100 mcg (2 1)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablet~~FENTORA tablet~~ Limit patient access to only one strength of fentanyl buccal tablets~~FENTORA~~ at any one time (2 1)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablet~~FENTORA tablet~~ (2 1)
- No more than two doses can be taken per breakthrough pain episode (2 1)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~ (2 1)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole (2 4)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain (4)
- Intolerance or hypersensitivity to fentanyl or components of fentanyl buccal tablets~~FENTORA~~ (4)

----------WARNINGS AND PRECAUTIONS----------

- Clinically significant respiratory and CNS depression can occur Monitor patients accordingly (5 1)
- Fentanyl buccal tablets~~FENTORA~~ is not bioequivalent to other fentanyl products Do not convert from other fentanyl products on a mcg per mcg basis (5 2)
- Use with other CNS depressants and cytochrome P450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation Consider dosage adjustments if warranted (5 4)
- Titrate fentanyl buccal tablets~~FENTORA~~ 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)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding (5 8)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache (6 1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-800-896-5855 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----------

- Pregnancy: Based on animal data, may cause fetal harm (8 1)
- Administer fentanyl buccal tablets~~FENTORA~~ with caution to patients with hepatic or renal impairment (8 6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 0~~2~~4/2013

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FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: RISK OF RESPIRATORY DEPRESSION, MEDICATION ERRORS, ABUSE POTENTIAL

RESPIRATORY DEPRESSION

Fatal respiratory depression has occurred in patients treated with ~~FENTORA~~fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. The substitution of fentanyl buccal tablets~~FENTORA~~ for any other fentanyl product may result in fatal overdose.

Due to the risk of respiratory depression, fentanyl buccal tablets~~FENTORA is~~ are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients. *[see Contraindications (4)]*

Fentanyl buccal tablets~~FENTORA~~ must be kept out of reach of children. *[see Patient Counseling Information (17.1) and How Supplied/Storage and Handling (16.1)]*

The concomitant use of fentanyl buccal tablets~~FENTORA~~ with CYP3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression *[see Drug Interactions (7)]*.

MEDICATION ERRORS

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~. *[see Dosage and Administration (2.1)]*

- When dispensing, do not substitute a fentanyl buccal tablets~~FENTORA~~ prescription for other fentanyl products.

ABUSE POTENTIAL

Fentanyl buccal tablets~~FENTORA~~ contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Fentanyl buccal tablets~~FENTORA~~ can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing fentanyl buccal tablets~~FENTORA~~ 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, fentanyl buccal tablets~~FENTORA is~~are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.11)]* Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets~~FENTORA is~~are indicated 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 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/hr of transdermal fentanyl, 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 while taking fentanyl buccal tablets~~FENTORA~~.

This product **must not** be used in opioid non-tolerant patients because life-threatening hypoventilation and death could occur at any dose in patients not on a chronic regimen of opioids For this reason, fentanyl buccal tablets~~FENTORA is~~are contraindicated in the management of acute or postoperative pain

Fentanyl buccal tablets~~FENTORA is~~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

Limitations of Use:

As a part of the TIRF REMS Access program, fentanyl buccal tablets~~FENTORA~~ may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.11)]* For inpatient administration of fentanyl buccal tablets~~FENTORA~~ (e g , hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required

2 DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ *[see Warnings and Precautions (5.11)]*

As with all opioids, the safety of patients using such products is dependent on health care professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use

It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose

2.1 Initial Dose

~~FENTORA~~ Fentanyl buccal tablets ~~is~~are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) All patients should be titrated from the 100 mcg dose.

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Patients on Actiq

The initial dose of fentanyl buccal tabletsFENTORA is **always** 100 mcg with the only exception being patients already using Actiq

a For patients being converted from Actiq, prescribers must use the **Initial Dosing Recommendations for Patients on Actiq** table below (Table 1) The doses of fentanyl buccal tabletsFENTORA in this table are starting doses and not intended to represent equianalgesic doses to Actiq Patients must be instructed to stop the use of Actiq and dispose of any remaining units

Table 1. Initial Dosing Recommendations for Patients on Actiq

Current Actiq Dose (mcg)	Initial FENTORA Fentanyl Buccal Tablets Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*From this initial dose, titrate patient to effective dose

b For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tabletFENTORA tablet and should proceed using multiples of this tablet strength

All Other Patients

The initial dose of fentanyl buccal tabletsFENTORA is 100 mcg

Repeat Dosing

a In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode Thus patients should take a maximum of two doses of fentanyl buccal tabletsFENTORA for any episode of breakthrough pain

b Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tabletsFENTORA

2.2 Dose Titration

a From an initial dose, patients should be closely followed by the prescriber and the dosage strength changed until the patient reaches a dose that provides adequate analgesia with tolerable side effects Patients should record their use of fentanyl buccal tabletsFENTORA over several episodes of breakthrough pain and discuss their experience with their physician to determine if a dosage adjustment is warranted

b Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets) Titrate using multiples of the 200 mcg fentanyl buccal FENTORA tablet for doses above 400 mcg (600 mcg and 800 mcg) Note: Do not use more than 4 tablets simultaneously

c In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose of the same strength for that episode Thus patients should take a maximum of two doses of fentanyl buccal tabletsFENTORA for any breakthrough pain episode During titration, one **dose** of fentanyl buccal tabletsFENTORA may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg)

d Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tabletsFENTORA To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal FENTORA tablets available at any time

e Patients should be strongly encouraged to use all of their fentanyl buccal tabletsFENTORA tablets of one strength prior to being prescribed the next strength If this is not practical, unused fentanyl buccal tabletsFENTORA should be disposed of safely *[see How Supplied/Storage and Handling (16.2)]*. Dispose of any unopened fentanyl buccal FENTORA tablets remaining from a prescription as soon as they are no longer needed

2.3 Maintenance Dosing

a Once titrated to an effective dose, patients should generally use **only ONE** fentanyl buccal FENTORA tablet of the appropriate strength per breakthrough pain episode

b On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take **ONLY ONE** additional dose using the same strength for that episode

c Patients MUST wait **at least 4 hours** before treating another episode of breakthrough pain with fentanyl buccal tabletsFENTORA

d Dosage adjustment of fentanyl buccal tabletsFENTORA may be required in some patients
Generally, the fentanyl buccal tabletsFENTORA 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

e If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated

f Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue)

2.4 Administration of FENTORAFentanyl Buccal Tablets

Opening the Blister Package:

1 Instruct patients not to open the blister until ready to administer fentanyl buccal tabletsFENTORA

2 Separate a single blister unit from the blister card by bending and tearing apart at the perforations

3 Bend the blister unit along the line where indicated

4 Peel back the blister backing to expose the tablet **Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.**

5 Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should **immediately** place the entire fentanyl buccal FENTORA tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal FENTORA tablet under the tongue **Patients should not split the tablet.**

The fentanyl buccal FENTORA tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed

The fentanyl buccal FENTORA tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes

After 30 minutes, if remnants from the fentanyl buccal FENTORA tablet remain, they may be swallowed with a glass of water

It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tabletsFENTORA in the buccal cavity

2.5 Discontinuation of FENTORAFentanyl Buccal Tablets

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

Fentanyl buccal FENTORA tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg strengths as fentanyl base Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16.3)]*

4 CONTRAINDICATIONS

Fentanyl buccal tabletsFENTORAisare contraindicated in opioid non-tolerant patients

Fentanyl buccal tabletsFENTORA isare 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

Fentanyl buccal tabletsFENTORA ~~is~~are contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl

5 WARNINGS AND PRECAUTIONS

See Boxed Warning

5.1 Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including fentanyl, the active ingredient in fentanyl buccal tabletsFENTORA 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

~~FENTORA~~ Fentanyl buccal tablets ~~is~~are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than Actiq. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) For patients being converted from Actiq, it is necessary to follow the instructions found in Table 1 in Section 2.1, as Actiq and fentanyl buccal tabletsFENTORA are not equivalent on a microgram per microgram basis Fentanyl buccal tabletsFENTORA ~~is~~are NOT a generic version of Actiq **All patients should be titrated from the 100 mcg dose.**

The initial dose of fentanyl buccal tabletsFENTORA should be 100 mcg Titrate each patient individually to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.1)]*

When dispensing, DO NOT substitute a fentanyl buccal tabletsFENTORA prescription for an Actiq prescription under any circumstances. Fentanyl buccal tabletsFENTORA and Actiq are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tabletsFENTORA compared to other fentanyl products including Actiq that result in clinically important differences in the rate and extent of absorption of fentanyl As **a result of these differences, the substitution of the same dose of fentanyl buccal tabletsFENTORA for the same dose of Actiq or any other fentanyl product may result in a fatal overdose.**

5.3 Patient/Caregiver Instructions

Patients and their caregivers must be instructed that fentanyl buccal tabletsFENTORA contain~~s~~ a medicine in an amount which can be fatal to a child. Patients and their caregivers must be instructed to keep tablets out of the reach of children *[see How Supplied/Storage and Handling (16.1)]*

5.4 Additive CNS Depressant Effects

The concomitant use of fentanyl buccal tabletsFENTORA 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 , hypoventilation, 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 fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA of these dangers and counsel them accordingly

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, titrate fentanyl buccal tabletsFENTORA with caution in patients with chronic obstructive pulmonary disease or pre-existing medical conditions predisposing them to respiratory depression In such patients, even normal therapeutic doses of fentanyl buccal tabletsFENTORA may further decrease respiratory drive to the point of respiratory failure

5.7 Head Injuries and Increased Intracranial Pressure

Administer fentanyl buccal tabletsFENTORA 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 Application Site Reactions

In clinical trials, 10% of all patients exposed to fentanyl buccal tabletsFENTORA reported application site reactions These reactions ranged from paresthesia to ulceration and bleeding Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%) Application site reactions tended to occur early in treatment were self-limited and only resulted in treatment discontinuation for 2% of patients

5.9 Cardiac Disease

Intravenous fentanyl may produce bradycardia Therefore, use fentanyl buccal tabletsFENTORA with caution in patients with bradyarrhythmias

5.10 MAO Inhibitors

Fentanyl buccal tabletsFENTORA ~~is~~ are 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

5.11 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)]*, fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA, patient and prescriber enrollment is not required

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement
- Pharmacies that dispense fentanyl buccal tabletsFENTORA must enroll in the program and agree to comply with the REMS requirements
- Wholesalers and distributors that distribute fentanyl buccal tabletsFENTORA 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

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

The safety of fentanyl buccal tabletsFENTORA has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain The average duration of therapy was 76 days with some patients being treated for over 12 months

The most commonly observed adverse events seen with fentanyl buccal tabletsFENTORA are typical of opioid side effects Opioid side effects should be expected and managed accordingly

The clinical trials of fentanyl buccal tabletsFENTORA were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received

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fentanyl buccal tabletsFENTORA for breakthrough pain along with a concomitant opioid for persistent pain There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tabletsFENTORA therapy or cancer-related symptoms

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies

Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tabletsFENTORA There was no evidence of excess toxicity in this subset of patients

The duration of exposure to fentanyl buccal tabletsFENTORA varied greatly, and included open-label and double-blind studies The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tabletsFENTORA Events are classified by system organ class

Adverse Events (≥1%)

Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia

Cardiac Disorders: Tachycardia

Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration

General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain

Hepatobiliary Disorders: Jaundice

Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess

Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture

Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count

Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake

Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain

Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy

Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness

Renal and Urinary Disorders: Renal Failure

Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing

Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat

Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

7 DRUG INTERACTIONS

Fentanyl is metabolized mainly via the human CYP3A4 isoenzyme system; therefore potential interactions may occur when fentanyl buccal tabletsFENTORA is given concurrently with agents that affect CYP3A4 activity

The concomitant use of fentanyl buccal tabletsFENTORA with CYP3A4 inhibitors (e g , indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression Patients receiving fentanyl buccal tabletsFENTORA who begin therapy with, or increase the dose of, CYP3A4 inhibitors should be carefully monitored for signs of opioid toxicity over an extended period of time Dosage increase should be done cautiously *[see Warnings and Precautions (5.4)]* The concomitant use of fentanyl buccal tabletsFENTORA with CYP3A4 inducers (e g , barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of fentanyl buccal tabletsFENTORA Patients receiving fentanyl buccal tabletsFENTORA who stop therapy with, or decrease the dose of, CYP3A4 inducers should be monitored for signs of increased fentanyl buccal tabletsFENTORA activity and the dose of fentanyl buccal tabletsFENTORA should be adjusted accordingly

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women fentanyl buccal tabletsFENTORA 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 characteristic of neonatal abstinence syndrome in newborn infants Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl

Fentanyl is embryocidal 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 fentanyl buccal tabletsFENTORA

Fentanyl (25, 50 or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17) Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1 4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison) Fentanyl (50, 100 or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18) Maternal toxicity was noted at doses ≥100 mcg/kg No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7 5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison)

Published studies concur with the conducted studies regarding the lack of teratogenic potential for fentanyl One literature report showed that administration of fentanyl (10, 100, or 500 mcg/kg) to pregnant rats from GD 7-21, via implanted microosmotic minipumps, was not teratogenic (the high dose was approximately 6-times the single human dose of 800 mcg per pain episode on a mg/m^2 basis) Another report showed that intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant rats from GD 6-18 was embryotoxic in the 30 mcg/kg group, but was not teratogenic Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for fentanyl buccal tabletsFENTORA

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100 and 400 mcg/kg) Maternal toxicity was noted at doses ≥100 mcg/kg A reduction in pup growth and delayed attainment of developmental indices were observed at ≥100 mcg/kg No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group Pups from this group also had significantly reduced body weights throughout the lactation period The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison

8.2 Labor and Delivery

Fentanyl readily passes across the placenta to the fetus; therefore, do not use fentanyl buccal tabletsFENTORA for analgesia 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 fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA

8.4 Pediatric Use

The safety and efficacy of fentanyl buccal tabletsFENTORA have not been established in pediatric patients below the age of 18 years

8.5 Geriatric Use

Of the 304 patients with cancer in clinical studies of fentanyl buccal tabletsFENTORA, 69 (23%) were 65 years of age and older

Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients

Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain Therefore, caution should be exercised in individually titrating fentanyl buccal tabletsFENTORA 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 fentanyl buccal tabletsFENTORA 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 patients with cancer 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

8.8 Race

The pharmacokinetic effects of race with the use of fentanyl buccal tabletsFENTORA have not been systematically evaluated In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U S subjects

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Fentanyl buccal tabletsFENTORA contains fentanyl, a *mu*-opioid agonist and a Schedule II controlled substance with high potential for abuse similar to other opioids including hydromorphone, methadone, morphine, oxycodone, and oxymorphone Fentanyl can be abused and is subject to misuse and criminal diversion

9.2 Abuse

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

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated abuse of a prescription drug and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, and sometimes tolerance and/or physical dependence

Abuse and addiction are separate and distinct from physical dependence and tolerance (see section 9 3) Physicians should be aware that addiction may not be accompanied by concurrent tolerance and physical dependence in all addicts In addition, abuse of opioids can occur in the absence of true addiction

Proper assessment of patients, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs

Abuse of fentanyl buccal tabletsFENTORA poses a risk of overdose and death This risk is increased with concurrent abuse of fentanyl buccal tabletsFENTORA with alcohol and other substances

Fentanyl buccal tabletsFENTORA, like other opioids, may be diverted for non-medical use Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors) Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use Withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug constitute evidence of physical dependence 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) Clinically significant physical dependence may not occur until after several days to weeks of continued opioid usage

Fentanyl buccal tabletsFENTORA should not be abruptly discontinued *[see Dosage and Administration (2.5)]* If fentanyl buccal tabletsFENTORA isare abruptly discontinued, or the dosage is rapidly reduced, in a physically-dependent patient, an abstinence syndrome may occur Some or all of the

following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea; increased blood pressure, respiratory rate, or heart rate

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.1)]*

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of fentanyl buccal tablets~~FENTORA~~ 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 hypoventilation *[see Clinical Pharmacology (12.2)]*

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the fentanyl buccal tablets~~FENTORA~~ tablet, if still in the mouth, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, as well as 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 fentanyl buccal tablets~~FENTORA~~ 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 hypoventilation or apnea, ventilation should be assisted or controlled and oxygen administered as indicated

Patients with overdose should be carefully observed and appropriately managed until their clinical condition is well-controlled

Although muscle rigidity interfering with respiration has not been seen following the use of fentanyl buccal tablets~~FENTORA~~, this is possible with fentanyl and other opioids If it occurs, manage by the use of assisted or controlled ventilation, by an opioid antagonist, and as a final alternative, by a neuromuscular blocking agent

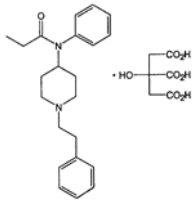
11 DESCRIPTION

~~FENTORA ((~~Fentanyl buccal tablet~~s)~~ ~~is~~are a potent opioid analgesic, intended for buccal mucosal administration

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa

Fentanyl buccal tablets~~FENTORA~~ employ~~s~~ the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa

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:



All tablet strengths are expressed as the amount of fentanyl free base, e g , the 100 microgram strength tablet contains 100 micrograms of fentanyl free base

Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an 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 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 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 fentanyl buccal tablets~~FENTORA~~ should be individually titrated to achieve the desired effect *[see Dosage and Administration (2.1)]*

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 another oral transmucosal fentanyl citrate (Actiq) 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, Contraindications (4), Warnings and Precautions (5.2) and Overdosage (10)

12.3 Pharmacokinetics

Fentanyl exhibits linear pharmacokinetics Systemic exposure to fentanyl following administration of fentanyl buccal tabletsFENTORA increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range

Absorption

Following buccal administration of fentanyl buccal tabletsFENTORA, fentanyl is readily absorbed with an absolute bioavailability of 65% The absorption profile of fentanyl buccal tabletsFENTORA is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract

In a study that compared the absolute and relative bioavailability of fentanyl buccal tabletsFENTORA and Actiq (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tabletsFENTORA) (Table 4)

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving FENTORA or Actiq

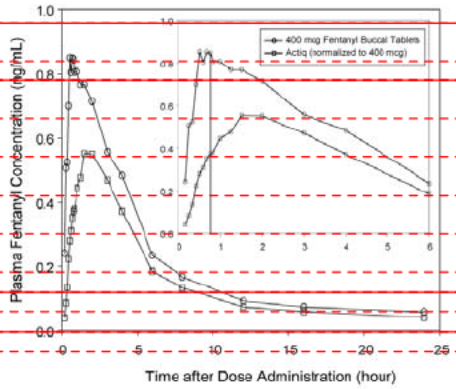
Pharmacokinetic Parameter (mean)	FENTORA 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
*** Actiq (OTFC) data was dose adjusted (800 mcg to 400 mcg).

Table 4. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or Actiq

Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	Actiq 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10 5%
Fraction Absorbed Transmucosally	48% ± 31 8%	22% ± 17 3%
T_{max} (minute)**	46 8 (20-240)	90 8 (35-240)
C_{max} (ng/mL)	1 02 ± 0 42	0 63 ± 0 21
AUC_{0-tmax} (ng•hr/mL)	0 40 ± 0 18	0 14 ± 0 05
AUC_{0-inf} (ng•hr/mL)	6 48 ± 2 98	4 79 ± 1 96

* Based on venous blood samples
** Data for T_{max} presented as median (range)
***Actiq data was dose adjusted (800 mcg to 400 mcg)

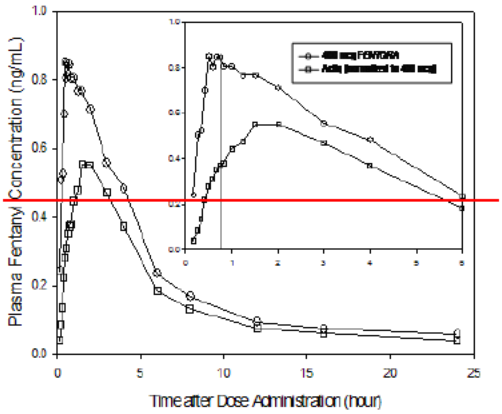


Actiq data were dose adjusted (800 mcg to 400 mcg)

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq

Due to differences in drug delivery, measures of exposure (C_{max}, AUC_{0-tmax}, AUC_{0-inf}) associated with a given dose of fentanyl were substantially greater with fentanyl buccal tablets compared to Actiq (see Figure 1) Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]* Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours The vertical line denotes the median T_{max} for fentanyl buccal tablets

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and Actiq in Healthy Subjects



~~Actiq data was dose adjusted (800 mcg to 400 mcg)~~

Mean pharmacokinetic parameters are presented in Table 5 Mean plasma concentration versus time profiles are presented in Figure 2

Table 5. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of FENTORA in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0.18	0.97 ± 0.53	1.59 ± 0.90
T_{max} minute** (range)	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
AUC_{0-inf} (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1.13	4.72 ± 1.95	9.05 ± 3.72
AUC_{0-tmax} (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
T1/2, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Table 5 Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0 25 ± 0 14	0 40 ± 0 18	0 97 ± 0 53	1 59 ± 0 90
T_{max}, minute** (range)	45 0 (25 0 - 181 0)	40 0 (20 0 - 180 0)	35 0 (20 0 - 180 0)	40 0 (25 0 - 180 0)
AUC_{0-inf} (ng•hr/mL)	0 98 ± 0 37	2 11 ± 1 13	4 72 ± 1 95	9 05 ± 3 72
AUC_{0-tmax} (ng•hr/mL)	0 09 ± 0 06	0 13 ± 0 09	0 34 ± 0 23	0 52 ± 0 38
T1/2, hr**	2 63 (1 47 - 13 57)	4 43 (1 85 - 20 76)	11 09 (4 63 - 20 59)	11 70 (4 63 - 28 63)

* Based on venous sampling
** Data for T_{max} presented as median (range)

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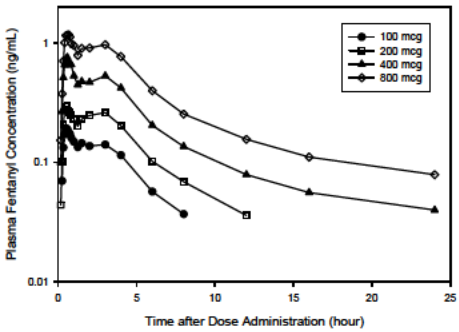
Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of ~~FENTORA~~ Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets~~FENTORA~~ was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched A single 200 mcg tablet was administered, followed by sampling at appropriate intervals Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 6

Table 6. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	AUC_{0-tmax} (ng hr/mL)	AUC_{0-8} (ng hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement

Distribution

Fentanyl is highly lipophilic The plasma protein binding of fentanyl is 80-85% The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent The mean oral volume of distribution at steady state (Vss/F) was 25 4 L/kg

Metabolism

The metabolic pathways following buccal administration of fentanyl buccal tablets~~FENTORA~~ have not been characterized in clinical studies The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*

Elimination

Disposition of fentanyl following buccal administration of fentanyl buccal tablets~~FENTORA~~ has not been characterized in a mass balance study Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h

Gender

Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively) The observed differences between men and women were largely attributable to differences in weight

Race

In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in US subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively) The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U S subjects (57 4 kg versus 73 kg)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg AC transgenic mouse study In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2 3- and 3 4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison) In mice, at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed

Mutagenesis

Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed The systemic exposure at the dose of 300 mcg/kg was approximately 8 6-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5 7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets~~FENTORA~~ was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets~~FENTORA~~ A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets~~FENTORA~~ and 3 being placebo Patients used one tablet of study drug (either fentanyl buccal tablets~~FENTORA~~ or ~~P~~placebo) per breakthrough pain episode

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered Pain intensity (0-10) was then measured at 15, 30, 45 and 60 minutes after the start of administration The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure

Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase The distribution of successful doses is shown in Table 7 The median dose was 400 mcg

Table 7. Successful Dose of ~~FENTORA~~ Fentanyl Buccal Tablets Following Initial Titration

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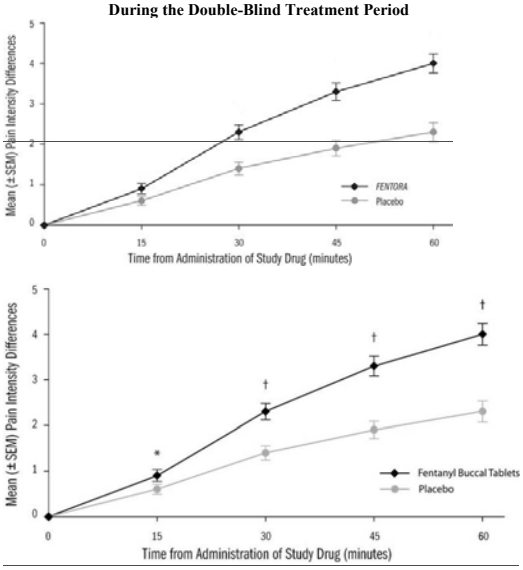
~~FENTORA~~ Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets ~~FENTORA~~-treated episodes was 3 0 (0 12) while for placebo-treated episodes it was 1 8 (0 18)

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Storage and Handling

Fentanyl buccal tablets~~FENTORA~~ ~~is~~are supplied in individually sealed, child-resistant blister packages The amount of fentanyl contained in fentanyl buccal tablets~~FENTORA~~ can be fatal to a child **Patients and their caregivers must be instructed to keep ~~FENTORA~~ fentanyl buccal tablets out of the reach of children.** *[see Boxed Warning, Overdosage (10), and Patient Counseling Information (17.1)]*

Store at 20 to 25ºC (68 to 77ºF) with excursions permitted between 15° and 30°C (59° to 86°F) until ready to use (See USP Controlled Room Temperature)

Protect fentanyl buccal tablets~~FENTORA~~ from freezing and moisture Do not use if the blister package has been tampered with

16.2 Disposal of ~~FENTORA~~Fentanyl Buccal Tablets

Patients and members of their household must be advised to dispose of any tablets remaining from a prescription as soon as they are no longer needed *[see Patient Counseling Information (17.2)]* If additional assistance is required, call Teva Pharmaceuticals at 1-800-896-5855

To dispose of unused fentanyl buccal tablets~~FENTORA~~, remove fentanyl buccal ~~FENTORA~~ tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets~~FENTORA~~ blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets~~FENTORA~~, call Teva Pharmaceuticals at 1-800-896-5855

16.3 How Supplied

Each carton contains 7 blister cards with 4 white tablets in each card The blisters are child-resistant, encased in peelable foil, and provide protection from moisture Each tablet is debossed on one side with [C], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below In addition, the dosage strength is indicated on the blister package and the carton See blister package and carton for product information

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC ~~63459-541-28~~0093-1150-28
200 mcg	2	Orange	NDC ~~63459-542-28~~0093-1151-28
400 mcg	4	Sage green	NDC ~~63459-544-28~~0093-1153-28
600 mcg	6	Magenta (pink)	NDC ~~63459-546-28~~0093-1154-28
800 mcg	8	Yellow	NDC ~~63459-548-28~~0093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient/Caregiver Instructions

- Before initiating treatment with fentanyl buccal tablets~~FENTORA~~, explain the statements below to patients and/or caregivers Instruct patients to read the Medication Guide each time fentanyl buccal tablets~~FENTORA~~ ~~is~~are dispensed because new information may be available
- TIRF REMS Access Program
  - Outpatients must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets~~FENTORA~~
  - Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets~~FENTORA~~ or the TIRF REMS Access program
  - As a component of the TIRF REMS Access program, prescribers must review the contents of the fentanyl buccal tablets~~FENTORA~~ Medication Guide with every patient before initiating treatment with fentanyl buccal tablets~~FENTORA~~
  - Advise the patient that fentanyl buccal tablets~~FENTORA~~ ~~is~~are 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 fentanyl buccal tablets~~FENTORA~~
  - Patient must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets~~FENTORA~~
  - 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, especially small children, exposed to ~~FENTORA~~ fentanyl buccal tablets are at high risk of FATAL RESPIRATORY DEPRESSION.** Patients and their caregivers must be instructed to keep fentanyl buccal tablets~~FENTORA~~ tablets out of the reach of children *[see How Supplied/Storage and Handling (16.1) and Warnings and Precautions (5.3)]*
- Instruct patients not to take fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ ~~is~~ are 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 fentanyl buccal tablets~~FENTORA~~

- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e g , two 100 mcg tablets for a 200 mcg dose)
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take **ONLY ONE ADDITIONAL DOSE OF ~~FENTORA~~ FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of ~~FENTORA~~ fentanyl buccal tablets for any breakthrough pain episode.**
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets~~FENTORA~~
- Instruct patients NOT to share fentanyl buccal tablets~~FENTORA~~ and that sharing fentanyl buccal tablets~~FENTORA~~ with anyone else could result in the other individual's death due to overdose
- Make patients aware that fentanyl buccal tablets~~FENTORA~~ contain~~s~~ fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone
- Instruct patients that the active ingredient in fentanyl buccal tablets~~FENTORA~~, fentanyl, is a drug that some people abuse Fentanyl buccal tablets~~FENTORA~~ 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
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets~~FENTORA~~ and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package
- Instruct patients that fentanyl buccal~~FENTORA~~ tablets are not to be swallowed whole; this will reduce the effectiveness of the medication Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets~~FENTORA~~
- Instruct patients to use fentanyl buccal tablets~~FENTORA~~ exactly as prescribed by their doctor and not to take fentanyl buccal tablets~~FENTORA~~ more often than prescribed
- Caution patients that fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~ of these dangers and counsel them accordingly
- Warn patients to not combine fentanyl buccal tablets~~FENTORA~~ 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 fentanyl buccal tablets~~FENTORA~~, they should ask their doctor about the effects that fentanyl buccal tablets~~FENTORA~~ (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 Disposal of Unopened ~~FENTORA~~ Fentanyl Buccal Tablets Blister Packages When No Longer Needed

Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed

To dispose of unused fentanyl buccal tablets~~FENTORA~~, remove fentanyl buccal~~FENTORA~~ tablets from blister packages and flush down the toilet Do not flush the fentanyl buccal tablets~~FENTORA~~ blister packages or cartons down the toilet

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets~~FENTORA~~ are provided in the fentanyl buccal tablets~~FENTORA~~ Medication Guide Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered

In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-800-896-5855) or seek assistance from their local DEA office

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~~Manufactured For Distributed By:~~
Teva Pharmaceuticals USA
~~North Wales~~Sellersville, PA ~~19454~~18960

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MEDICATION GUIDE

~~FENTORA® (fen-tor-a) CII~~
~~(f~~Fentanyl ~~b~~Buccal ~~t~~Tablet~~s) CII~~
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use ~~FENTORA~~ 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~~FENTORA~~ in a safe place away from children.

Get emergency help right away if:

- **a child takes fentanyl buccal tablets~~FENTORA~~. Fentanyl buccal tablets~~FENTORA~~ can cause an overdose and death in any child who takes it.**
- **an adult who has not been prescribed fentanyl buccal tablets~~FENTORA~~ uses it**
- **an adult who is not already taking opioids around-the-clock, uses fentanyl buccal tablets~~FENTORA~~.**

These are medical emergencies that can cause death. If possible, try to remove fentanyl buccal tablets~~FENTORA~~ from the mouth.

Read this Medication Guide completely before you start using fentanyl buccal tablets~~FENTORA~~, 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.

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What is the most important information I should know about fentanyl buccal tablets~~FENTORA~~?

Fentanyl buccal tablets~~FENTORA~~ can cause life-threatening breathing problems which can lead to death.

1. **Do not use fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.

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3. **Use fentanyl buccal tablets~~FENTORA~~ exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~. **See the Medication Guide section "How should I use fentanyl buccal tablets~~FENTORA~~?" and the Instructions for Use at the end of this Medication Guide for detailed information about how to use fentanyl buccal tablets~~FENTORA~~ the right way.**

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4. **Do not switch from fentanyl buccal tabletsFENTORA to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tabletsFENTORA 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 tabletsFENTORA that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use fentanyl buccal tabletsFENTORA 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 tabletsFENTORA to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   Fentanyl buccal tabletsFENTORA is are a federally controlled substance (CII) because it isthey are 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 tabletsFENTORA in a safe place** to protect it from being stolen. Fentanyl buccal tabletsFENTORA 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 tabletsFENTORA isare 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 tabletsFENTORA, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of fentanyl buccal tabletsFENTORA
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form.

What is are fentanyl buccal tabletsFENTORA?

- Fentanyl buccal tabletsFENTORA isare a prescription medicine that contains the medicine fentanyl.
- Fentanyl buccal tabletsFENTORA isare 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 tabletsFENTORA is 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 tabletsFENTORA if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using fentanyl buccal tabletsFENTORA.
- Fentanyl buccal tabletsFENTORA isare only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if FENTORAfentanyl buccal tablets areis safe and effective in children under 18 years of age.

Who should not use FENTORAfentanyl buccal tablets?

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Do not use ~~FENTORA~~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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in ~~FENTORA~~fentanyl buccal tablets. See the end of this Medication Guide for a complete list of ingredients in fentanyl buccal tablets~~FENTORA~~.

What should I tell my healthcare provider before using fentanyl buccal tablets~~FENTORA~~?

Before using fentanyl buccal tablets~~FENTORA~~, 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~~FENTORA~~ may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. Fentanyl buccal tablets~~FENTORA~~ pass~~es~~ into your breast milk. ~~It~~They can cause serious harm to your baby. You should not take fentanyl buccal tablets~~FENTORA~~ while breastfeeding.

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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 fentanyl buccal tablets~~FENTORA~~. Sometimes, the doses of certain medicines and fentanyl buccal tablets~~FENTORA~~ need to be changed if used together.

- **Do not take any medicine while using ~~FENTORA~~ 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~~FENTORA~~.**
- 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~~FENTORA~~?

Before you can begin to use fentanyl buccal tabletsFENTORA:

- 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 tabletsFENTORA isare 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 tabletsFENTORA prescription filled.

Using fentanyl buccal tabletsFENTORA:

- **Use fentanyl buccal tabletsFENTORA exactly as prescribed. Do not use fentanyl buccal tabletsFENTORA 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 FENTORA the right way.**
- **Use fentanyl buccalFENTORA tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal FENTORA tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using the fentanyl buccal tabletFENTORA. If there is any of the fentanyl buccalFENTORA 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 FENTORA fentanyl buccal tablets for each episode of breakthrough cancer pain.
  - Use **1** dose of fentanyl buccal tabletsFENTORA 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 tabletsFENTORA, you can use **only 1** more dose of fentanyl buccal tabletsFENTORA as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of fentanyl buccal tabletsFENTORA, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tabletsFENTORA at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tabletsFENTORA.
  - If you only need to take 1 dose of fentanyl buccal tabletsFENTORA for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of fentanyl buccal tabletsFENTORA for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of fentanyl buccal tabletsFENTORA for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tabletsFENTORA 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 tabletsFENTORA.
- Talk to your healthcare provider if your dose of fentanyl buccal tabletsFENTORA does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tabletsFENTORA 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.

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- 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 much fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how fentanyl buccal tablets~~FENTORA~~ affect~~s~~ you. Fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of fentanyl buccal tablets~~FENTORA~~?

Fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~?**" **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 much fentanyl buccal tablets~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~ 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~~FENTORA~~.

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~~FENTORA~~. 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 fentanyl buccal tablets~~FENTORA~~?

- **Always keep fentanyl buccal tablets~~FENTORA~~ in a safe place away from children and from anyone for whom it has not been prescribed**. Protect fentanyl buccal tablets~~FENTORA~~ from theft.
- Store fentanyl buccal tablets~~FENTORA~~ at room temperature, 59°F to 86°F (15° C to 30°C) until ready to use. Do not freeze fentanyl buccal tablets~~FENTORA~~.
- Keep fentanyl buccal tablets~~FENTORA~~ in the original blister unit. Do not remove fentanyl buccal tablets~~FENTORA~~ from its blister packaging for storage in a temporary container, such as a pill box.
- Keep fentanyl buccal tablets~~FENTORA~~ dry.

How should I dispose of unused fentanyl buccal~~FENTORA~~ tablets when they are no longer needed?

- Dispose of any unused fentanyl buccal~~FENTORA~~ tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablets~~FENTORA~~ packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets~~FENTORA~~, call Teva Pharmaceuticals at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

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General information about fentanyl buccal tablets~~FENTORA~~

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use fentanyl buccal tablets~~FENTORA~~ only for the purpose for which it was prescribed. Do not give ~~FENTORA~~ fentanyl buccal tablets to other people, even if they have the same symptoms you have.** Fentanyl buccal tablets~~FENTORA~~ can harm other people and even cause death. Sharing fentanyl buccal tablets~~FENTORA~~ is against the law.

This Medication Guide summarizes the most important information about fentanyl buccal tablets~~FENTORA~~. 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 tabletsFENTORA 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 FENTORAfentanyl buccal tablets?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Instructions for Use

Before you use FENTORAfentanyl 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 tabletsFENTORA the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use fentanyl buccal tabletsFENTORA.

When you get an episode of breakthrough cancer pain, use the dose of FENTORA fentanyl buccal tablets prescribed by your healthcare provider as follows:

- FENTORA Fentanyl buccal tablets comes packaged as a blister card containing 4 blister units. Each blister unit contains 1 FENTORA fentanyl buccal tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your FENTORA fentanyl buccal tablets will be printed in the boxed area shown as

XXX mcg (See Figure 1).

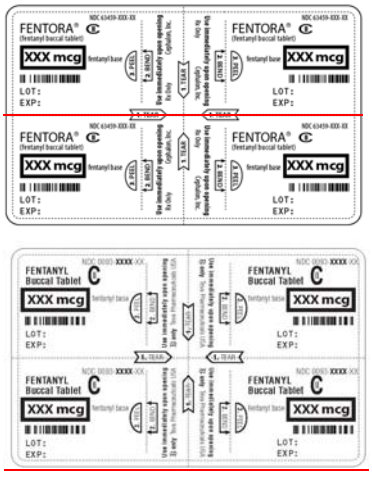

Figure 1

- Peel back foil on blister unit to expose tablet (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, ~~FENTORA~~ fentanyl buccal tablet must be used right away.
- **Use fentanyl buccal~~FENTORA~~ tablets whole**.
- **Do not crush, split, suck, or chew fentanyl buccal~~FENTORA~~ tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- You can place a ~~FENTORA~~ 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.

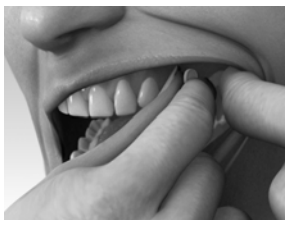

Figure 3

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).

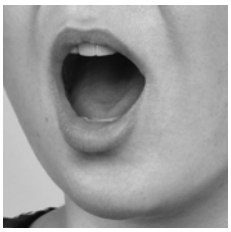

Figure 4a

Figure 4b

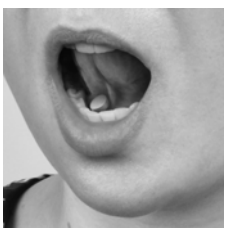

Figure 4c

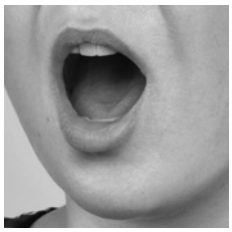

Figure 4d

- **Leave the tablet in place until it dissolves.** A fentanyl buccal~~FENTORA~~ tablet generally takes between 14 to 25 minutes to dissolve.
- After 30 minutes, if there is any fentanyl buccal tablet~~FENTORA~~ left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- If you cannot use ~~FENTORA~~ 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.

~~Distributed By:~~
~~Teva Pharmaceuticals USA, Inc.~~
~~North Wales, PA 19454~~

Manufactured For:
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MEDICATION GUIDE

Fentanyl 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 they are 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 buccal tablets pass into your breast milk. They 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 the fentanyl buccal tablet. 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 much 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 much fentanyl buccal tablets 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 1-800-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, 59°F to 86°F (15° C to 30°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.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855 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, sodium bicarbonate, sodium carbonate, citric acid, 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.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as

  XXX mcg (See Figure 1).

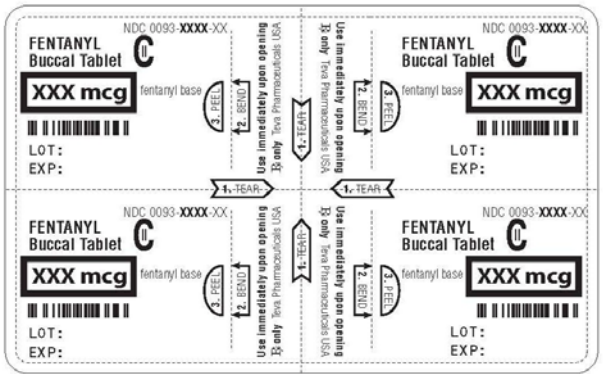

Figure 1

- Peel back foil on blister unit to expose tablet (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:
  - 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.

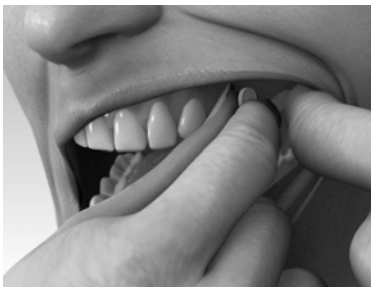

Figure 3

OR,

- 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).

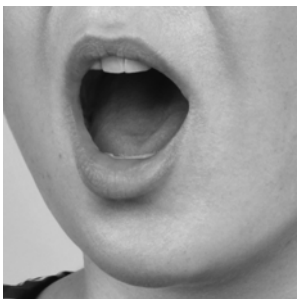

Figure 4a

Figure 4b

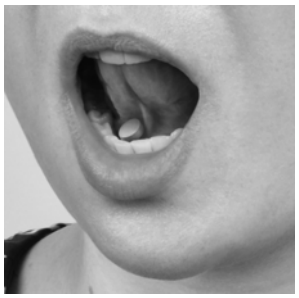

Figure 4c

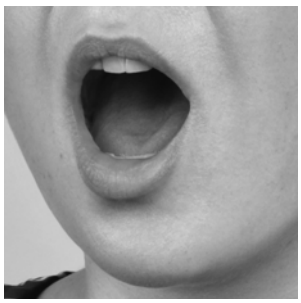

Figure 4d

- **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 For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

Revised April 2013
FBTMG-002

Iss. 4/2013

Printed in USA

MEDICATION GUIDE

~~FENTORA® (fen-tor-a)~~
Fentanyl Buccal Tablets CII
~~(fentanyl buccal tablet)~~
100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg

IMPORTANT:

Do not use ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets in a safe place away from children.

Get emergency help right away if:

- **a child takes ~~FENTORA. FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets uses it**
- **an adult who is not already taking opioids around-the-clock, uses ~~FENTORA~~fentanyl buccal tablets.**

These are medical emergencies that can cause death. If possible, try to remove ~~FENTORA~~fentanyl buccal tablets from the mouth.

Read this Medication Guide completely before you start using ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets?

~~FENTORA~~Fentanyl buccal tablets can cause life-threatening breathing problems which can lead to death.

1. **Do not use ~~FENTORA~~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 ~~FENTORA.~~fentanyl buccal tablets. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
3. **Use ~~FENTORA~~fentanyl buccal tablets exactly as prescribed by your healthcare provider.**
   - You must not use more than 2 doses of ~~FENTORA~~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 ~~FENTORA.~~fentanyl buccal tablets. **See the Medication Guide section "How should I use ~~FENTORA~~fentanyl buccal tablets?" and the Instructions for Use at the end of this Medication Guide for detailed information about how to use ~~FENTORA~~fentanyl buccal tablets the right way.**

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4. **Do not switch from ~~FENTORA~~fentanyl buccal tablets to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets that may be different than other fentanyl containing medicines you may have been taking.
5. **Do not** use ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets to anyone else**, even if they have the same symptoms you have. It may harm them or even cause death.

   ~~FENTORA is~~Fentanyl buccal tablets are a federally controlled substance (CII) because ~~it is~~they are 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 ~~FENTORA~~fentanyl buccal tablets in a safe place** to protect it from being stolen. ~~FENTORA~~ 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. ~~FENTORA is~~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 ~~FENTORA~~fentanyl buccal tablets, you must:
   - talk to your healthcare provider
   - understand the benefits and risks of ~~FENTORA~~fentanyl buccal tablets
   - agree to all of the instructions
   - sign the Patient-Prescriber Agreement form.

What ~~is FENTORA~~are fentanyl buccal tablets?

- ~~FENTORA is~~Fentanyl buccal tablets are a prescription medicine that contains the medicine fentanyl.
- ~~FENTORA is~~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.
- ~~FENTORA is~~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 ~~FENTORA~~fentanyl buccal tablets if you are not opioid tolerant.
- You must stay under your healthcare provider's care while using ~~FENTORA~~fentanyl buccal tablets.
- ~~FENTORA is~~Fentanyl buccal tablets are only:
  - available through the TIRF REMS Access program
  - given to people who are opioid tolerant

It is not known if ~~FENTORA is~~fentanyl buccal tablets are safe and effective in children under 18 years of age.

Who should not use ~~FENTORA~~fentanyl buccal tablets?

Do not use ~~FENTORA~~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:
  - pain after surgery
  - headaches or migraine
  - dental pain
- if you are allergic to any of the ingredients in ~~FENTORA.~~fentanyl buccal tablets. See the end of this Medication Guide for a complete list of ingredients in ~~FENTORA~~fentanyl buccal tablets.

What should I tell my healthcare provider before using ~~FENTORA~~fentanyl buccal tablets?

Before using ~~FENTORA~~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. ~~FENTORA~~Fentanyl buccal tablets may cause serious harm to your unborn baby.
- are breastfeeding or plan to breastfeed. ~~FENTORA passes~~Fentanyl buccal tablets pass into your breast milk. ~~It~~They can cause serious harm to your baby. You should not take ~~FENTORA~~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 ~~FENTORA.~~fentanyl buccal tablets. Sometimes, the doses of certain medicines and ~~FENTORA~~fentanyl buccal tablets need to be changed if used together.

- **Do not take any medicine while using ~~FENTORA~~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 ~~FENTORA.~~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 ~~FENTORA~~fentanyl buccal tablets?

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Before you can begin to use ~~FENTORA~~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.
- ~~FENTORA is~~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 ~~FENTORA~~fentanyl buccal tablets prescription filled.

Using ~~FENTORA~~fentanyl buccal tablets:

- **Use ~~FENTORA~~fentanyl buccal tablets exactly as prescribed. Do not use ~~FENTORA~~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 ~~FENTORA the~~fentanyl buccal tablets the right way.**
- **Use ~~FENTORA~~fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew ~~FENTORA~~fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using ~~FENTORA.~~the fentanyl buccal tablet. If there is any of the ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets for each episode of breakthrough cancer pain.
  - Use **1** dose of ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets, you can use **only 1** more dose of ~~FENTORA~~fentanyl buccal tablets as instructed by your healthcare provider.
  - If your breakthrough pain does not get better after the second dose of ~~FENTORA~~fentanyl buccal tablets, call your healthcare provider for instructions. **Do not use another dose of ~~FENTORA~~fentanyl buccal tablets at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with ~~FENTORA.~~fentanyl buccal tablets.
  - If you only need to take 1 dose of ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets for a **new** episode of breakthrough pain.
  - If you need to use 2 doses of ~~FENTORA~~fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets.
- Talk to your healthcare provider if your dose of ~~FENTORA~~fentanyl buccal tablets does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of ~~FENTORA~~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.

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- 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 much ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets?

- **Do not drive, operate heavy machinery, or do other dangerous activities** until you know how ~~FENTORA affects~~fentanyl buccal tablets affect you. ~~FENTORA~~ 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 ~~FENTORA~~fentanyl buccal tablets.** It can increase your chance of getting dangerous side effects.

What are the possible side effects of ~~FENTORA~~fentanyl buccal tablets?

~~FENTORA~~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 ~~FENTORA~~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 much ~~FENTORA~~fentanyl buccal tablets 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 ~~FENTORA~~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 ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets are:

- nausea
- vomiting
- dizziness

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- 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 ~~FENTORA~~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 ~~FENTORA~~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 ~~FENTORA.~~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 1-800-FDA-1088.

How should I store ~~FENTORA~~fentanyl buccal tablets?

- **Always keep ~~FENTORA~~fentanyl buccal tablets in a safe place away from children and from anyone for whom it has not been prescribed**. Protect ~~FENTORA~~fentanyl buccal tablets from theft.
- Store ~~FENTORA~~fentanyl buccal tablets at room temperature, 59°F to 86°F (15°C to 30°C) until ready to use. Do not freeze ~~FENTORA~~fentanyl buccal tablets.
- Keep ~~FENTORA~~fentanyl buccal tablets in the original blister unit. Do not remove ~~FENTORA~~fentanyl buccal tablets from its blister packaging for storage in a temporary container, such as a pill box.
- Keep ~~FENTORA~~fentanyl buccal tablets dry.

How should I dispose of unused ~~FENTORA~~fentanyl buccal tablets when they are no longer needed?

- Dispose of any unused ~~FENTORA~~fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the ~~FENTORA~~fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of ~~FENTORA~~fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855 or call your local Drug Enforcement Agency (DEA) office.

General information about ~~FENTORA~~fentanyl buccal tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Use ~~FENTORA~~fentanyl buccal tablets only for the purpose for which it was prescribed. Do not give ~~FENTORA~~fentanyl buccal tablets to other people, even if they have the same symptoms you have.** ~~FENTORA~~Fentanyl buccal tablets can harm other people and even cause death. Sharing ~~FENTORA~~fentanyl buccal tablets is against the law.

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This Medication Guide summarizes the most important information about ~~FENTORA.~~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 ~~FENTORA~~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.

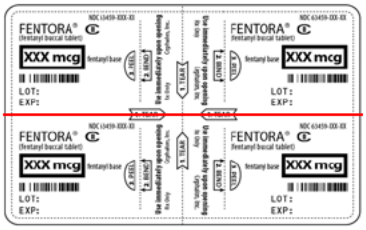
What are the ingredients in ~~FENTORA~~fentanyl buccal tablets?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Instructions for Use

Before you use ~~FENTORA~~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 ~~FENTORA~~fentanyl buccal tablets the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use ~~FENTORA~~fentanyl buccal tablets.

When you get an episode of breakthrough cancer pain, use the dose of ~~FENTORA~~fentanyl buccal tablets prescribed by your healthcare provider as follows:

- ~~FENTORA comes~~Fentanyl buccal tablets come packaged as a blister card containing 4 blister units. Each blister unit contains 1 ~~FENTORA~~ fentanyl buccal tablet. **Do not open a blister until ready to use.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your ~~FENTORA~~fentanyl buccal tablets will be printed in the boxed area shown as XXX mcg (See Figure 1).



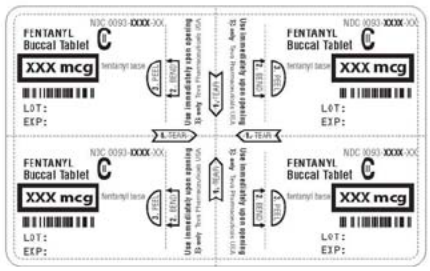


Figure 1

- Peel back foil on blister unit to expose tablet (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, ~~FENTORA~~fentanyl buccal tablet must be used right away.
- **Use ~~FENTORA~~fentanyl buccal tablets whole**.
- **Do not crush, split, suck, or chew ~~FENTORA~~fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- You can place a ~~FENTORA~~fentanyl buccal tablet:
    - 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,

- 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).

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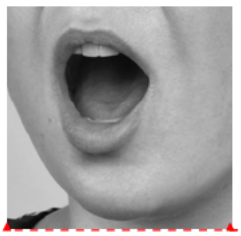

Figure 4a

Figure 4b

Figure 4c

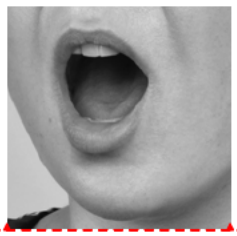

Figure 4d

- **Leave the tablet in place until it dissolves.** A ~~FENTORA~~fentanyl buccal tablet generally takes between 14 to 25 minutes to dissolve.
- After 30 minutes, if there is any ~~FENTORA~~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 ~~FENTORA~~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.

~~Distributed By~~

Manufactured For:
Teva Pharmaceuticals USA~~, Inc.~~
~~North Wales~~Sellersville, PA ~~19454~~18960

Revised ~~February~~April 2013
~~FENTMG-007~~

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Pharmaceuticals

February 28, 2014

Bob A. Rappaport, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research Division of Anesthesia,
Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947, Sequence No. 0043
FENTORA® (fentanyl buccal tablet)

PRIOR APPROVAL SUPPLEMENT – AMENDMENT

Dear Dr. Rappaport:

Reference is made to the New Drug Application (NDA 021947) for the use of FENTORA (fentanyl buccal tablet) 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. Further reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 (DMF#027320).

On 21 May 2013 (Sequence No. 0031) Teva submitted a Prior Approval Supplement (PAS) to support the commercialization of an authorized generic of FENTORA, Fentanyl Buccal Tablets. On 10 June 2013 (Sequence No. 0033) Teva submitted an Amendment to the above referenced PAS containing a revised full Prescribing Information and Medication Guide for Fentanyl Buccal Tablets. On February 6, 2014, Ms. Kimberly Compton, Senior Regulatory Project Manager, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sent a request to Teva via email to submit an Amendment to the above referenced PAS providing for the current REMS and Medication Guide for the authorized generic of FENTORA.

The purpose of this submission is to provide the current REMS documents, including the final Medication Guide, for the authorized generic of FENTORA. All REMS documents, excluding the attached product specific Medication Guide, are contained in DMF#027320.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 2.0 MB. All files were

checked and verified to be free of viruses using Trend Micro OfficeScan, client 10.5.2399, antivirus engine 9.750.1007, with a release date of Feb 28, 2014, or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact James Mann at (610) 727-6133.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6189 or via email at christine.kampf@tevapharm.com.

Sincerely,

Christine M. Kampf
Manager, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

MEDICATION GUIDE

Fentanyl 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 they are 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 buccal tablets pass into your breast milk. They 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 the fentanyl buccal tablet. 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 much 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 much fentanyl buccal tablets 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 1-800-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, 59°F to 86°F (15° C to 30°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.
  - Remove the tablets from blister packages and flush them down the toilet.
- Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.
- If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-800-896-5855 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, sodium bicarbonate, sodium carbonate, citric acid, 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.**
- Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as

  XXX mcg (See Figure 1).

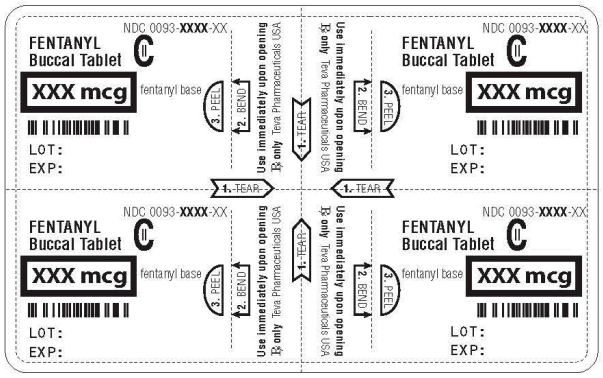

Figure 1

- Peel back foil on blister unit to expose tablet (See Figure 2).

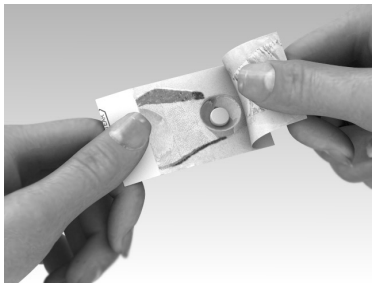

Figure 2

- 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:
  - 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.

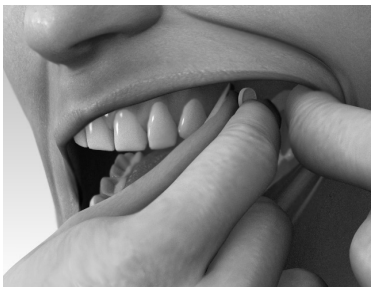

Figure 3

OR,

- 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).

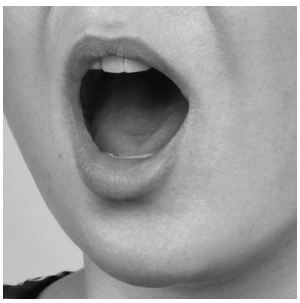

Figure 4a

Figure 4b

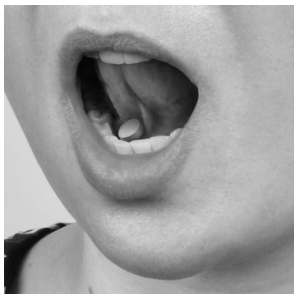

Figure 4c

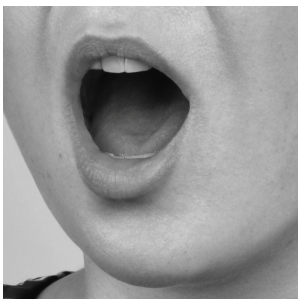

Figure 4d

- **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 For:
Teva Pharmaceuticals USA
Sellersville, PA 18960

Revised April 2013
FBTMG-002

Iss. 4/2013

Printed in USA

Compton, Kimberly

From: Baldev Rana <Baldev.Rana@tevapharm.com>
Sent: Monday, July 28, 2014 2:10 PM
To: Compton, Kimberly
Subject: RE: Change in Regulatory Contact at Teva for IND 065447, NDA 021947, IND 027428 and NDA 020747

Hello Kim,

Hope all is well. In reference to your email on July 25, 2014, we accept the Agency's recommendation to remove the content under the "Recent Major Changes" (RMC) section in Highlights. Could you please advise when we should expect the action letter?

Further, pertaining to our NDA 020747, Sequence # 0044, we had inadvertently removed Angela Randall as the Primary Labeling Contact. Could you please recommend if we should amend sequence # 0044 to include her name or would it be acceptable that the necessary correction be provided in a subsequent submission? Please note that her contact information was provided via Sequence # 0040.

Best Regards,

Baldev

Baldev B. Rana
Manager, Internal Medicine – Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.
Tel: 610-786-7876
Cell: 484-354-4186
Fax: 610-786-7051
Email: Baldev.Rana@tevapharm.com

From: Compton, Kimberly [mailto:Kimberly.Compton@fda.hhs.gov]
Sent: Friday, July 25, 2014 5:02 PM
To: Baldev Rana
Subject: RE: Change in Regulatory Contact at Teva for IND 065447, NDA 021947, IND 027428 and NDA 020747
Importance: High

HI Baldev,

Yes, that would be fine.

Thanks and have a nice weekend,
Kim

From: Baldev Rana [mailto:Baldev.Rana@tevapharm.com]
Sent: Friday, July 25, 2014 5:00 PM
To: Compton, Kimberly
Subject: Re: Change in Regulatory Contact at Teva for IND 065447, NDA 021947, IND 027428 and NDA 020747

Hello Kim,

Thank you for your comments. I will discuss with our internal team and respond on Monday. Please let me know if the proposed approach is acceptable.

Baldev B. Rana
Teva Branded Pharmaceutical Products R&D, Inc.

Sent from my iPhone.
Please disregard any typos!

On Jul 25, 2014, at 4:34 PM, "Compton, Kimberly" <Kimberly.Compton@fda.hhs.gov> wrote:

> Hello Bladev,
>
> I look forward to working with you on these projects.
>
> In fact, I have an item for Fentora on S-019, which I am trying to finally close out now. (For the authorized generic version.)
>
> It has been in house so long that the 2 items listed in the "Recent Major Changes" section in Highlights should now be removed since those changes were over 12 months ago. Since, in S-019, there are no other changes proposed for RMC section, that whole section can be removed.
>
> Dosage and Administration, Maintenance Dosing (2.3) 02/2013
> Dosage and Administration, Administration of ~~FENTORA~~ Fentanyl Buccal Tablets (2.4) 02/2013
> Dosage and Administration, Discontinuation of ~~FENTORA~~ Fentanyl Buccal Tablets (2.5) 02/2013
>
> Is this acceptable to Teva?
>
> If so, we will strike it in the version we attach to our action letter.
>
> I don't believe we have any additional changes to request to S-019 once we agree on this, so we could then move forward to an action.
>
> Thanks
> Kim
>
> ---
>
> **From:** Baldev Rana [mailto:Baldev.Rana@tevapharm.com]
> **Sent:** Thursday, July 24, 2014 4:19 PM
> **To:** Compton, Kimberly
> **Subject:** RE: Change in Regulatory Contact at Teva for IND 065447, NDA 021947, IND 027428 and NDA 020747
>
> Hello Kim,

It's my utmost pleasure meeting you and hope that we get the opportunity to work together on the aforementioned files. Please feel free to contact me if there is anything from Teva's side that is needed.

Best Regards,

Baldev

<image001.jpg>	**Baldev B. Rana** Manager, Internal Medicine – Global Regulatory Affairs Teva Branded Pharmaceutical Products R&D, Inc. Tel: 610-786-7876 Cell: 484-354-4186 Fax: 610-786-7051 Email: Baldev.Rana@tevapharm.com

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From: Christine Kampf
Sent: Thursday, July 24, 2014 3:59 PM
To: Compton, Kimberly
Cc: Baldev Rana
Subject: Change in Regulatory Contact at Teva for IND 065447, NDA 021947, IND 027428 and NDA 020747

Hi Kim,

I hope you are well! As I am sure you may have noted by now there has been some rearrangement of responsibility here at Teva with regards to the applications for FENTORA (IND 065447 & NDA 021947) and ACTIQ (IND 027428 & NDA 020747). I am no longer the primary Regulatory contact on these programs and Baldev Rana (copied) has taken over.

I wanted to take this opportunity to introduce you to Baldev and say that it has been a pleasure working with you on these programs over the past several years. I am still at Teva so if there is anything that I can help provide some background on I will continue to be available.

Please let me know if you have any questions.
Kind regards,
Christine

<image002.jpg>	**Christine M. Kampf** Senior Manager, Internal Medicine Regulatory Affairs, Branded Products Research and Development Tel: +1-610-727-6189 Cell: +1-484-631-5973 Fax: +1-610-738-6642 Christine.Kampf@tevapharm.com www.tevapharm.com

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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/

KIMBERLY A COMPTON
02/08/2016

Division of Anesthesia, Analgesia, and Addiction Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: N 021947/S-019

Name of Drug: Fentora (fentanyl buccal tablet)

Applicant: Cephalon, Inc.

Labeling Reviewed

Submission Date: 5/21/13, 6/10/13, and 2/28/14

Receipt Date: 5/21/13, 6/10/13, and 2/28/14

Background and Summary Description: The Sponsor submitted a Prior Approval Supplement seeking approval of an authorized generic version of the product.

This product is part of the Transmucosal Immediate Release Fentanyl (TIRF) product group, which has a shard Risk Evaluation and Mitigation Strategy (REMS) for the class. A REMS is required for approval of any generic whose RLD has a REMS. For this reason, a supplement was submitted for marketing approval of the authorized generic instead of simply an annual report submission, as would typically be the case when an authorized generic is introduced.

DRISK has reviewed the proposed changes to the shared REMS to support the generic version of the product. The revisions proposed to the shared TIRF REMS were determined by DRISK not to affect the safe use of the TIRFs. Therefore, in an effort to minimize the # of modifications that would induce approved ANDA members of the TIRF class to submit a supplement that would incur a fee, the proposed changes to the REMS will be implemented with the next shared TIRF REMS modification. See the DRISK review in DAARTS.

This supplement will therefore consist of reviews and the labeling (carton and container, package insert (PI) and medication guide (MG) specific to the generic version of the product.

DMEPA reviewed the carton and container labeling, PI and MG, and found them acceptable. See the reviews from Loretta Holmes in DARRTS.

The final version of the proposed PI submitted on 6/10/13, and MG submitted on 2/28/14 were compared to the last approved PI and MG for the branded product from S-008, approved 2/21/13.

Review

Additions are indicated by an <u>underlining</u> and deletions with a ~~strikethrough~~.

Throughout the label, references to the product name have been changed from ~~FENTORA~~ to fentanyl buccal tablets. Other minor changes throughout the labeling include number agreement needed when phrases changed from singular use with FENTORA, to the plural use when used with the fentanyl buccal tablets nomenclature, which is plural in nature.

I. HIGHLIGHTS

Recent Major Changes
The 3 items listed in this section are from 2/2013 and should be removed as it will be past the 1 year date when these labels are printed.

Dosage and Administration, Maintenance Dosing (2.3)	02/2013
Dosage and Administration, Administration of ~~FENTORA~~ Fentanyl Buccal Tablets (2.4)	02/2013
Dosage and Administration, Discontinuation of ~~FENTORA~~ Fentanyl Buccal Tablets (2.5)	02/2013

The firm was asked to remove this section and agreed.

II. FULL PRESCRIBING INFORMATION: CONTENTS*

No changes aside from those noted above about the replacement of the brand name of the product with the generic version are noted.

III. FULL PRESCRIBING INFORMATION

No changes aside from those noted above about the replacement of the brand name of the product with the generic version are noted in sections not specifically listed below.

16 HOW SUPPLIED/STORAGE AND HANDLING

The NDC numbers corresponding to the brand product, listed in the table of available products, have been replaced with the new NDC numbers that are specific to the generic products.

17 PATIENT COUNSELING INFORMATION

The information at the end of the PI has been updated to reflect the manufacturing info relevant to the generic version of the product.

MEDICATION GUIDE

The depiction of the branded version of the blister packaging for the product in Figure 1 has been replaced with a version that shows the blister packaging of the generic version of the product.

The information relating to the manufacturing of the product at the end of the MG has been updated to reflect that relevant to the generic version.

Recommendations

As the Agency's find the firm's proposed labeling acceptable, this supplement should be approved.

Kim Compton, Senior Regulatory Project Manager, 2-6-14, and updated 4/29/14, and 7-22-14

Matt Sullivan, M.S., Acting Chief, Project Management Staff, 7/25/2014

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

/s/

KIMBERLY A COMPTON
08/22/2014

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

ADDENDUM TO FINAL RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	February 26, 2016
Reviewer(s):	Somya Dunn, M.D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Director:	Claudia Manzo, Pharm. D. Office of Medication Error Prevention & Risk Management (OMEPRM)
Drug Name(s):	fentanyl buccal tablet (authorized generic of Fentora)
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:	sNDA (S-019) / 021947
Submission Number:	0031, 033, 0043
Applicant/sponsor:	Cephalon
OSE RCM #:	2013-2624
TSI #:	290

*** This document contains proprietary and confidential information that should not be released to the public. ***

This addendum serves to update the previous Final Risk Evaluation and Mitigation Strategy (REMS) Review for the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) for an authorized generic of Fentora® (fentanyl buccal tablet) NDA 21-947 dated April 15, 2014.

The REMS was originally submitted by Cephalon Incorporated (Cephalon), on May 21, 2013, and amended in submissions dated June 10, 2013 and February 28, 2014. The DRISK review was completed on April 15, 2014 as noted. However, the approval letter has not been sent to the Sponsor to date. During this time, there was a TIRF modification approval on December 24, 2014. Therefore, the DRISK review does not contain the most updated REMS as an attachment. This addendum serves to attach the most current approved TIRF 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*** _____ ***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):_____

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):_____

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,

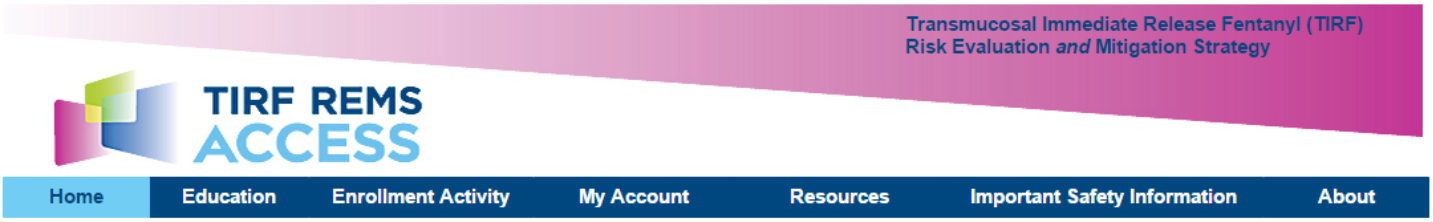
TIRF REMS Access Industry Group

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 <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
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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

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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:

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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.
- 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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- 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
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- Approved generic equivalents of these products are also covered under this program.

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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

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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:

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- 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

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
02/26/2016

CLAUDIA B MANZO
02/26/2016
concur

Pharmaceuticals

February 14, 2017

Sharon Hertz, M.D., Division Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia, and Addiction Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947, Sequence No. xxxx
FENTORA® (fentanyl) Buccal Tablet, CII
PRIOR APPROVAL SUPPLEMENT - AMENDMEMT

Dear Dr. Hertz:

Reference is made to New Drug Application (NDA) No. 021947 for the use of FENTORA (fentanyl buccal tablet) 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. Further reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011; the shared REMS documents for this program are housed in DMF #027320. Reference is also made to Prior Approval Supplement (PAS) S-019, submitted May 21, 2013 to support the commercialization of an authorized generic of FENTORA, subsequent Amendments to S-019 submitted June 10, 2013 and February 28, 2014, and FDA approval letter for S-024 and S-025 received on December 16, 2016.

The purpose of this submission is to provide current labeling for a pending approval authorized generic of FENTORA. Updates to the FENTORA USPI and Medication Guide were recently approved in S-024 and S-025. Therefore, these updates are being incorporated into draft labeling for the authorized generic supplement. Although changes have been made to the Medication Guide, no other REMS related documents have been modified as a result of these proposed revisions.

Due to the extensive nature of revisions to the FENTORA USPI and Medication Guide, tracked versions are not being provided. The following documents are included for review:

- "Clean" WORD and PDF versions of the proposed PI
- "Clean" WORD and PDF versions of the Medication Guide

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 6 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150 Service Pack 1, antivirus engine 9.900.1008, pattern 13.219.00 with a release date of February 14, 2016 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at (610) 786-7311 or via email at Kevin.Tompkins@tevapharm.com.

If there are other questions regarding this submission please do not hesitate to contact me at (610) 727-6148 or via email at karen.riddick@tevapharm.com.

Sincerely,

Karen Riddick, MS

Associate Labeling Director, Branded Products

Regulatory Affairs, Global Labeling and Brand Management

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use fentanyl buccal tablets safely and effectively. See full prescribing information for fentanyl buccal tablets.

Fentanyl Buccal Tablets, CII
Initial U.S. Approval: 1968

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, fentanyl buccal tablets are contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (5.1)**
- **Accidental ingestion of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5 2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to fentanyl buccal tablets. (5.5)**
- **When dispensing, do not substitute with any other fentanyl products. (5.5)**
- **Fentanyl buccal tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.6)**
- **Fentanyl buccal tablets are 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. (5.7)**
- **Prolonged use of fentanyl buccal tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets are an opioid agonist indicated 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. (1)

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablets.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, or dental pain.
- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to patients enrolled in the TIRF REMS Access program. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

----------DOSAGE AND ADMINISTRATION----------

- Patients must require and use around-the-clock opioids when taking fentanyl buccal tablets. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initial dose of fentanyl buccal tablets: 100 mcg. (2.2)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablets. Limit patient access to only one strength of fentanyl buccal tablets at any one time. (2.3)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablets. (2.4)
- 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 fentanyl buccal tablets. (2.2)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole. (2.5)
- When opioid therapy is no longer required, consider discontinuing fentanyl buccal tablets along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

Buccal Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of fentanyl buccal tablets. (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of fentanyl buccal tablets in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of fentanyl buccal tablets in patients with impaired consciousness or coma. (5.13)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.18)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with fentanyl buccal tablets because they may reduce analgesic effect of fentanyl buccal tablets or precipitate withdrawal symptoms. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)

- Lactation: Not recommended. (8 2)
- Renal and Hepatic Impairment: Administer fentanyl buccal tablets with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious life-threatening and/or fatal respiratory depression has occurred in patients treated with fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of fentanyl buccal tablets or following a dose increase. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.1)]*.

Due to the risk of respiratory depression, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients *[see Contraindications (4)]*.

Accidental Ingestion

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.2)]*.

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. Fentanyl buccal tablets must be kept out of reach of children *[see Warnings and Precautions (5.2)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl buccal tablets with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl buccal tablets and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of fentanyl buccal tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to fentanyl buccal tablets *[see Dosage and Administration (2.1)]*.**
- **When dispensing, do not substitute a fentanyl buccal tablets prescription for other fentanyl products.**

Addiction, Abuse, and Misuse

Fentanyl buccal tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing fentanyl buccal tablets, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.6)]*.

Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose, fentanyl buccal tablets are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.7)]*. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets 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 *[see Warnings and Precautions (5.8)]*.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets are indicated 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.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablets.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, and dental pain *[see Contraindications (4)]*.

- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.7)]*. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets *[see Warnings and Precautions (5.7)]*.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.6)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with fentanyl buccal tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.1)]*.
- Instruct patients and caregivers to take steps to store fentanyl buccal tablets securely and to properly dispose of unused fentanyl buccal tablets as soon as no longer needed *[see Warnings and Precautions (5.2, 5.6), Patient Counseling Information (17)]*.
- Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Warnings and Precautions (5.5)]*.
- Fentanyl buccal tablets are NOT a generic version of any other transmucosal fentanyl product *[see Warnings and Precautions (5.5)]*.

2.2 Initial Dosage

The initial dose of fentanyl buccal tablets is always 100 mcg with the only exception being patients already using ACTIQ.

Patients on ACTIQ

a. For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ table below (Table 1). The doses of fentanyl buccal tablets in this table are starting doses and not intended to represent equianalgesic doses to ACTIQ. Patients must be instructed to stop the use of ACTIQ and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

Current ACTIQ Dose (mcg)	Initial Fentanyl Buccal Tablets Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*****From this initial dose, titrate patient to effective dose.

b. For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablets and should proceed using multiples of this tablet strength.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any episode of breakthrough pain.

b. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.

2.3 Dose Titration

a. From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablets over several episodes of breakthrough pain and discuss their experience with their healthcare provider to determine if a dosage adjustment is warranted.

b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg fentanyl buccal tablets for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.

c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode. During titration, one **dose** of fentanyl buccal tablets may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).

d. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets. To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal tablets available at any time.

e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely *[see How Supplied/Storage and Handling (16)]*. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.4 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use only ONE fentanyl buccal tablet of the appropriate strength per breakthrough pain episode.

b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode.

c. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.

d. Dosage adjustment of fentanyl buccal tablets may be required in some patients.
Generally, the fentanyl buccal tablets 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.

e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.

f. Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue).

2.5 Administration of Fentanyl Buccal Tablets

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer fentanyl buccal tablets.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should immediately place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. Patients should not split the tablet.
The fentanyl buccal tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.
The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.
After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.
It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets in the buccal cavity.

2.6 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing fentanyl buccal tablets along with a gradual downward titration of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, fentanyl buccal tablets therapy can usually be discontinued immediately. *[see Drug Abuse and Dependence (9.3*

2.7 Disposal of Fentanyl Buccal Tablets

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279.

3 DOSAGE FORMS AND STRENGTHS

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Fentanyl Buccal Tablets are contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients *[see Indications and Usage (1); Warnings and Precautions (5.1)]*.
- Significant respiratory depression *[see Warnings and Precautions (5.1)]*.
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department *[see Indications and Usage (1)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*.
- Known hypersensitivity (e.g. anaphylaxis) to fentanyl or components of fentanyl buccal tablets (e.g., anaphylaxis) *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of fentanyl buccal tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of fentanyl buccal tablets.

To reduce the risk of respiratory depression, proper dosing and titration of fentanyl buccal tablets are essential *[see Dosage and Administration (2.3)]*. Overestimating the fentanyl buccal tablets dosage can result in a fatal overdose with the first dose. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.5)]*.

Fentanyl buccal tablets could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

Patients and their caregivers must be informed that fentanyl buccal tablets contain a medicine in an amount which can be fatal to a child. Healthcare providers 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.

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 *[see Patient Counseling Information (17)]*.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of fentanyl buccal tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.1)]*, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl buccal tablets-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl buccal tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl buccal tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of fentanyl buccal tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl buccal tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (including Alcohol)

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl buccal tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when fentanyl buccal tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.5 Risk of Medication Errors

When prescribing, do not convert a patient to fentanyl buccal tablets from any other fentanyl product on a mcg per mcg basis as fentanyl buccal tablets and other fentanyl products are not equivalent on a microgram per microgram basis.

Fentanyl buccal tablets are not a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, do not substitute a fentanyl buccal tablets prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and fentanyl buccal tablets are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of fentanyl buccal tablets or any other fentanyl product may result in a fatal overdose.

There are no safe conversion directions available for patients on any other fentanyl products except ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Dosage and Administration (2.1)]*.Therefore, for opioid tolerant patients, the initial dose of fentanyl buccal tablets should always be 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.3)]*.

5.6 Addiction, Abuse, and Misuse

Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance. As an opioid, fentanyl buccal tablets expose users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed fentanyl buccal tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl buccal tablets, and monitor all patients receiving fentanyl buccal tablets for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as fentanyl buccal tablets, but use in such patients necessitates intensive counseling about the risks and proper use of fentanyl buccal tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing fentanyl buccal tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.7 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)]*, fentanyl buccal tablets are 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 fentanyl buccal tablets, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense fentanyl buccal tablets must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute fentanyl buccal tablets 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.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of fentanyl buccal tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: fentanyl buccal tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of fentanyl buccal tablets *[see Warnings and Precautions (5.1)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.1)]*.

Monitor such patients closely, particularly when initiating and titrating fentanyl buccal tablets and when fentanyl buccal tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.1)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl buccal tablets with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

Fentanyl buccal tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of fentanyl buccal tablets. In patients with circulatory shock, fentanyl buccal tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of fentanyl buccal tablets in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), fentanyl buccal tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl buccal tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of fentanyl buccal tablets in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions
Fentanyl buccal tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in fentanyl buccal tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders
The fentanyl in fentanyl buccal tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during fentanyl buccal tablets therapy.

5.16 Risks of Driving and Operating Machinery
Fentanyl buccal tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of fentanyl buccal tablets and know how they will react to the medication.

5.17 Cardiac Disease
Intravenous fentanyl may produce bradycardia. Therefore, use fentanyl buccal tablets with caution in patients with bradyarrhythmias.

5.18 Application Site Reactions
Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding *[see Adverse Reactions (6)]*.

5.19 MAO Inhibitors
Fentanyl buccal tablets are 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 *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.1)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.8)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*

6.1 Clinical Studies Experience
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.

The safety of fentanyl buccal tablets has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The clinical trials of fentanyl buccal tablets were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tablets for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tablets therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MedDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets. There was no evidence of excess toxicity in this subset of patients.

Application Site Reactions: In clinical trials, 10% of all patients exposed to fentanyl buccal tablets reported application site reactions. These reactions ranged from paresthesias to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment, were self-limited and only resulted in treatment discontinuation for 2% of patients.

The duration of exposure to fentanyl buccal tablets varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets. Events are classified by system organ class.

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy
Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of fentanyl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders:

- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Endocrine Disorders:
- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.
Immune System Disorders:
- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in fentanyl buccal tablets.
General Disorders and Administration Site Conditions: Drug withdrawal syndrome

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with fentanyl buccal tablets.

Table 4: Clinically Significant Drug Interactions with Fentanyl Buccal Tablets

Inhibitors of CYP3A4	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention	If concomitant use is necessary, consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention	If concomitant use is necessary, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl buccal tablets dosage reduction and monitor for signs of respiratory depression.
Examples	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to 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.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.10)]*.
Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.10)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.1)]*.
Intervention	The use of fentanyl buccal tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact	May reduce the analgesic effect of fentanyl buccal tablets and/or precipitate withdrawal symptoms.
Intervention	Avoid concomitant use.
Examples	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of fentanyl buccal tablets and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Monitor patients for signs of urinary retention or reduced gastric motility when fentanyl buccal tablets are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.8)]*. Available data with fentanyl buccal tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.8)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl buccal tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including fentanyl buccal tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

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.

Animal Data

Fentanyl (25, 50, or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses $\geq$100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of fentanyl buccal tablets on a mg/m^2 basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of fentanyl buccal tablets based on a mg/m^2 basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 6 times the human dose of 800 mcg fentanyl buccal tablets per pain episode on a mg/m^2 basis and produced mean steady-state plasma levels that are approximately 5 times higher than the mean C_{max} observed following administration of 800 mcg dose of fentanyl buccal tablets in humans.

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100, and 400 mcg/kg). Maternal toxicity was noted at doses $\geq$100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at $\geq$100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with fentanyl buccal tablets.

Clinical Considerations

Monitor infants exposed to fentanyl buccal tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2) Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and efficacy of fentanyl buccal tablets have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use
Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablets in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of fentanyl buccal tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment
Insufficient information exists to make recommendations regarding the use of fentanyl buccal tablets 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 Sex
Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant sex differences were noted either in dosage requirement or in observed adverse reactions.

8.8 Race
The pharmacokinetic effects of race with the use of fentanyl buccal tablets have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance.

9.2 Abuse
Fentanyl buccal tablets contain fentanyl, a substance with high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Fentanyl buccal tablets can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.6)]*.
All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. 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, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance *[see Drug Abuse and Dependence (9.3)]*. Health care providers 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 true addiction.

Fentanyl buccal tablets, 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.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of Fentanyl Buccal Tablets
Fentanyl buccal tablets are for oral transmucosal use only. Abuse of fentanyl buccal tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of fentanyl buccal tablets with alcohol and other central nervous system depressants.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with fentanyl buccal tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in fentanyl buccal tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

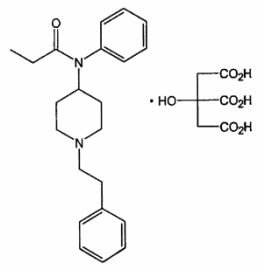
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Fentanyl buccal tablets are an opioid agonist, intended for buccal mucosal administration.
Fentanyl buccal tablets are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

Fentanyl buccal tablets employ the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.
Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the 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 a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and to electrical stimulation.
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). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 in the small intestine is delayed 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 biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension.

Effects on the Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
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 *[see Dosage and Administration (2.1)]*.

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)]*.

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. 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. 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 *[see Warnings and Precautions (5.1)]*.

12.3 Pharmacokinetics
Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of fentanyl buccal tablets increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption
Following buccal administration of fentanyl buccal tablets, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of fentanyl buccal tablets is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets and ACTIQ (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets) (Table 5).

Table 5. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or ACTIQ

Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	ACTIQ 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05

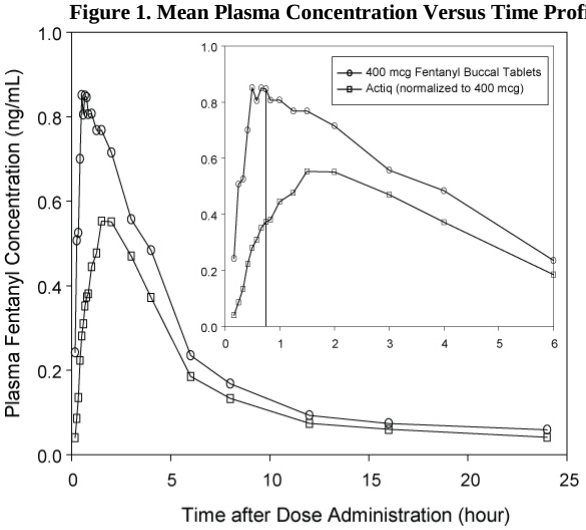
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
***ACTIQ data was dose adjusted (800 mcg to 400 mcg).

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl buccal tablets compared to ACTIQ (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.2) and Warnings and Precautions (5.5)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablets.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and ACTIQ in Healthy Subjects



Actiq data were dose adjusted (800 mcg to 400 mcg)

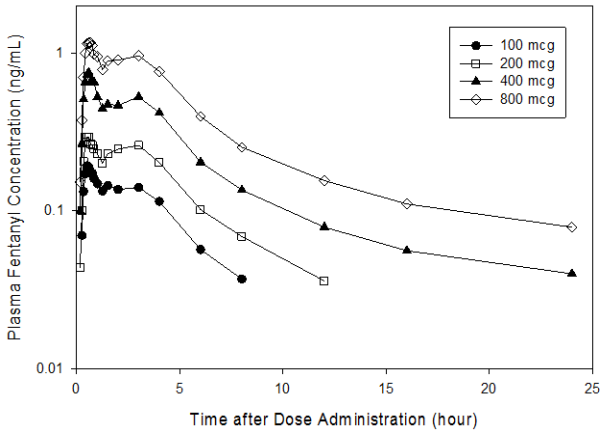
Mean pharmacokinetic parameters are presented in Table 6. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 6. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0 18	0.97 ± 0.53	1.59 ± 0.90
T_{max}, minute (range)**	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1 13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
$T_{1/2}$, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 7.

Table 7. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng•hr/mL)	$AUC_{0\text{-}8}$ (ng•hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement.

Distribution
Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Elimination

Metabolism
The metabolic pathways following buccal administration of fentanyl buccal tablets have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Excretion
Disposition of fentanyl following buccal administration of fentanyl buccal tablets has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Sex
Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race
In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2 3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis
Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 8.6 times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

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 fentanyl buccal tablets.

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets and 3 being placebo. Patients used one tablet of study drug (either fentanyl buccal tablets or placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45, and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

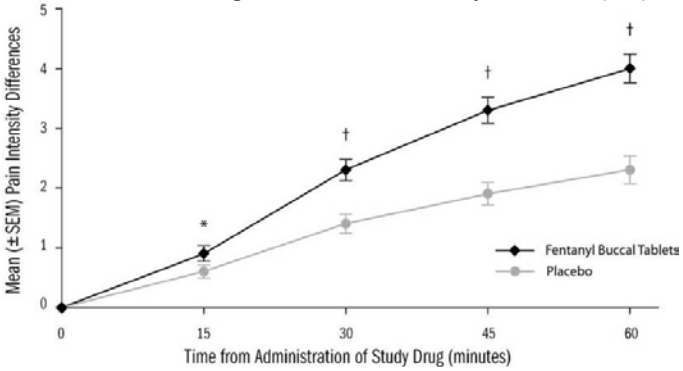
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 8. The median dose was 400 mcg.

Table 8. Successful Dose of Fentanyl Buccal Tablets Following Initial Titration

Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl buccal tablets are supplied in individually sealed, child-resistant blister packages. Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with [redacted], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 0093-1150-28
200 mcg	2	Orange	NDC 0093-1151-28
400 mcg	4	Sage green	NDC 0093-1153-28
600 mcg	6	Magenta (pink)	NDC 0093-1154-28
800 mcg	8	Yellow	NDC 0093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Storage and Handling
Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)
Protect fentanyl buccal tablets from freezing and moisture. Do not use if the blister package has been tampered with.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting fentanyl buccal tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.1)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Ingestion

- Healthcare providers 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 *[see Warnings and Precautions (5.2)]*.
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.
- Instruct patients to take steps to store fentanyl buccal tablets securely and to dispose of unused fentanyl buccal tablets *[see Dosage and Administration (2.7), Patient Counseling Information; Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed (17)]*.
- Instruct patients and caregivers to keep both used and unused fentanyl buccal tablets out of the reach of children *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)
Inform patients that potentially fatal additive effects may occur if fentanyl buccal tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Addiction, Abuse, and Misuse
Inform patients that the use of fentanyl buccal tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.6)]*. Instruct patients not to share fentanyl buccal tablets with others and to take steps to protect fentanyl buccal tablets from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS
Advise patients of the following information pertaining to the TIRF REMS

- Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets.
- Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets or the TIRF REMS Access program.
- As required by the TIRF REMS Access program, review the contents of the fentanyl buccal tablets Medication Guide with every patient before initiating treatment with fentanyl buccal tablets.
- Advise the patient that fentanyl buccal tablets 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 fentanyl buccal tablets.
- Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.10), Drug Interactions (7)]*.

MAOI Interaction
Inform patients to avoid taking fentanyl buccal tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking fentanyl buccal tablets *[see Warnings and Precautions (5.10, 5.19); Drug Interactions (7)]*.

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Important Administration Instructions *[see Dosage and Administration (2)]*

- Instruct patients not to take fentanyl buccal tablets 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 fentanyl buccal tablets are 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 fentanyl buccal tablets.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode.
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.
- Instruct patients NOT to share fentanyl buccal tablets and that sharing fentanyl buccal tablets with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablets contain fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.

- Instruct patients that fentanyl buccal tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets.
- Instruct patients to use fentanyl buccal tablets exactly as prescribed by their doctor and not to take fentanyl buccal tablets more often than prescribed.
- Provide patients and their caregivers with a Medication Guide each time fentanyl buccal tablets are dispensed because new information may be available.

Hypotension
Inform patients that fentanyl buccal tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)]*.

Anaphylaxis
Inform patients that anaphylaxis have been reported with ingredients contained in fentanyl buccal tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of fentanyl buccal tablets can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that fentanyl buccal tablets can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)Nonclinical Toxicology (13.1)]*.

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery
Inform patients that fentanyl buccal tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed
- Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.
- To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush the fentanyl buccal tablets blister packages or cartons down the toilet.
- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-888-483-8279) or seek assistance from their local DEA office.

FBT-003

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:
Do not use fentanyl buccal tablets 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 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.

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is 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.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- 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.
- 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
- 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.
- 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.

Do not take 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 at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- 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.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.

- 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.**
- **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.
- Do not stop taking fentanyl buccal tablets 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.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **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.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- 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.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets 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.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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, 59°F to 86°F (15°C to 30°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.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 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, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient 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.**
- **Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as**

XXX mcg **(See Figure 1).**

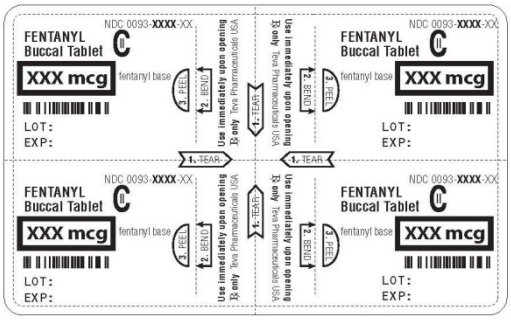


Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

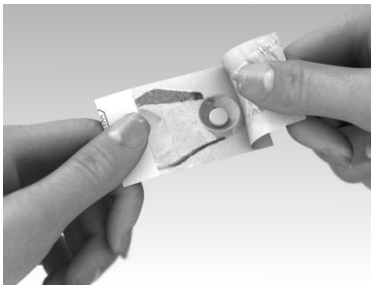


Figure 2

- **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 tablets 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:**
  - **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.**

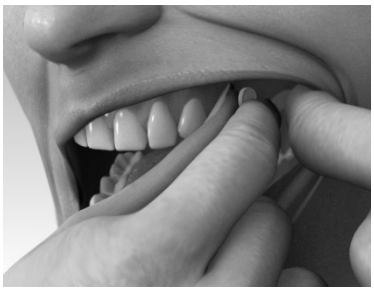


Figure 3

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).**

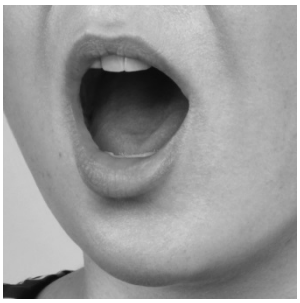


Figure 4a

Figure 4b

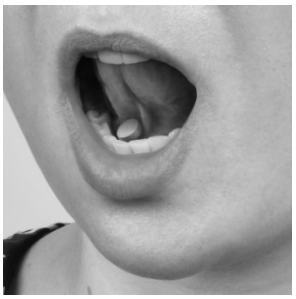


Figure 4c

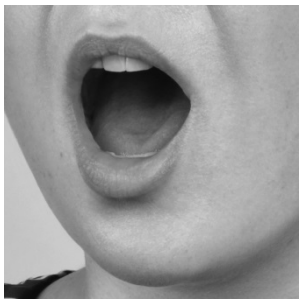


Figure 4d

- **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.**

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454 call 1-888-483-8279

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised 12 2016
FBTMG-003

Printed in USA

Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:

Do not use fentanyl buccal tablets 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 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.

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is 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.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- 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.
- 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
- 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.
- 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.

Do not take 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 at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- 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.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problem

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.
- 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.**
- **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.
- Do not stop taking fentanyl buccal tablets 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.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **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.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- 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.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets 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.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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, 59°F to 86°F (15°C to 30°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.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 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, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient 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.**
- **Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as**

XXX mcg **(See Figure 1).**

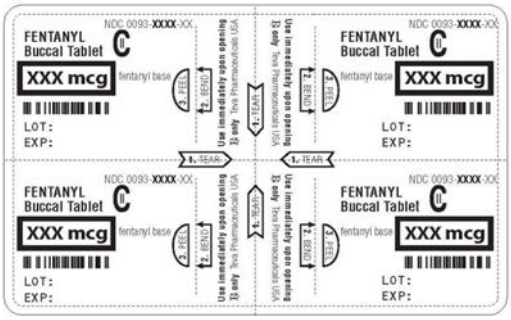


Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

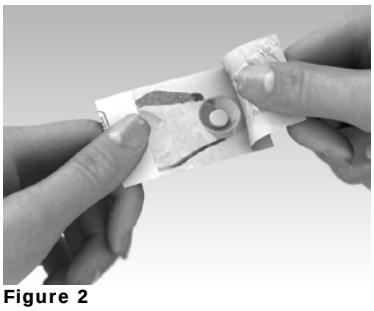


Figure 2

- **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 tablets 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:**
  - **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.**

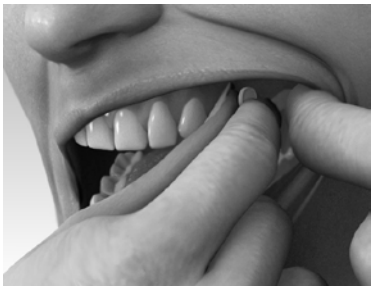


Figure 3

OR,

- **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).**

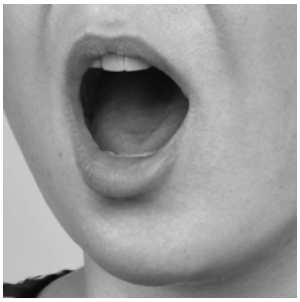


Figure 4a

Figure 4b

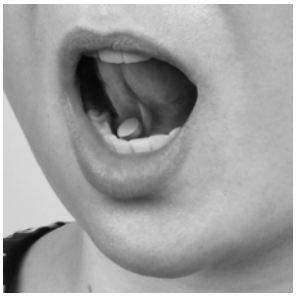


Figure 4c

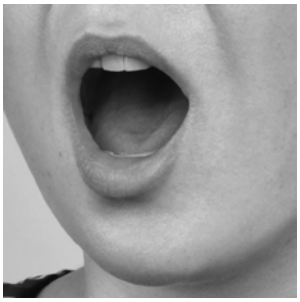


Figure 4d

- **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.**

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454 call 1-888-483-8279

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised 12 2016
FBTMG-003

Printed in USA

Division of Anesthesia, Analgesia, and Addiction Products

Addendum to REGULATORY PROJECT MANAGER LABELING REVIEW Dated August 20, 2014

Application: N 021947/S-019
Name of Drug: Fentora (fentanyl buccal tablet)
Applicant: Cephalon, Inc.

Labeling Reviewed

Submission and Receipt Dates: 5/21/13, 6/10/13, 2/28/14, and 2/14/17

This addendum focuses on the material submitted 2/14/17 in order to provide the most up-to-date version of the labeling approved for the product. The earlier versions of the labeling for the authorized generic (AG) version of the product were fully reviewed in the PM Labeling Review dated 8/22/14 in DARRTS.

Background and Summary Description: The Sponsor submitted a Prior Approval Supplement seeking approval of an authorized generic version of the product.

This product is part of the Transmucosal Immediate Release Fentanyl (TIRF) product group, which has a shard Risk Evaluation and Mitigation Strategy (REMS) for the class. A REMS is required for approval of any generic whose RLD has a REMS. For this reason, a supplement was submitted for marketing approval of the authorized generic instead of simply an annual report submission, as would typically be the case when an authorized generic is introduced.

DRISK has reviewed the proposed changes to the shared REMS to support the generic version of the product and found them acceptable. See the separate DRISK reviews in DAARTS dated 4/18/14 and 2/26/16, by Cathy Miller and Somya Dunn, respectively.

DMEPA reviewed the carton and container labeling, PI and MG, and found them acceptable. See the reviews from Loretta Holmes in DARRTS dated 1/7/14.

Prior to this sNDA being approved, a class-wide Safety Labeling Change (SLC) was required for all immediate-release opioids which required a major revision to the approved package insert (PI) and Medication Guide (MG) for each product in the TIRF class. That SLC was approved on 12/16/16 and for this NDA, was S-024. For a detailed review and summary of the changes approved to the labeling as a result of the SLC (S-024), see the reviews by Priyanka Kumar and Mark Liberatore/Judy Racoosin in DARRTS dated 12/15/16 and 12/16/16, respectively.

After approval of S-024, the firm submitted revised proposed labeling for the AG version of the product to reflect the newly approved labeling which incorporated the SLC. The final version of the proposed PI and MG for the AG version of the product, submitted on 2/14/17, was compared to the last approved PI and MG for the branded product from S-024, approved 12/16/16.

Review

As major changes to the PI were approved with the Dec 2016 S-024 approval, a Recent Major Changes section was reintroduced to the Highlights section of the PI as required by current labeling rules. The language in the updated proposed AG version of the PI in this section is identical to that approved in the branded version in S-024, so is acceptable.

As was true in the earlier proposed version of the labeling for the AG, throughout the labeling, references to the product name have been changed from ~~FENTORA~~ to fentanyl buccal tablets. Other minor changes throughout the labeling include number agreement needed when phrases changed from singular use with FENTORA, to the plural use when used with the fentanyl buccal tablets nomenclature, which is plural in nature and the removal of references to the www.FENTORA.com website.

The updated version of the labeling for the AG version of the product incorporate all of the SLCs approved in S-024.

Recommendations

As the Agency finds the firm's proposed amended labeling acceptable, this supplement should be approved.

Kim Compton, Senior Regulatory Project Manager, 3/31/17, updated 4/4/17

Matt Sullivan, M.S., Acting Chief, Project Management Staff, 4/5/17

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

/s/

KIMBERLY A COMPTON
04/05/2017

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947/S-019
Communication Type:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	KC 2-8-16
Clearance History by:	Sullivan4-5 Fields 4/7/17 Lehrfeld 3/29/2017 Liberatore 2/9/16, 3/29/17 SRT4/4/17 Racoosin 3/3/16 Hertz 4-7
Finalized:	
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 "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. **Note:** Remember to check for acceptability of facility **prior to issuing approval letter**.

Version: 1/04/2017

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

NDA 021947/S-019

SUPPLEMENT APPROVAL

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Tien M. Huynh, Associate III
Regulatory Affairs, Branded Products R&D

Dear Mr. Huynh:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl buccal tablets).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated December 28, 2016.

This Prior Approval supplemental new drug application proposes changes to the prescribing information, carton/container labels, and modification to the approved REMS, to include addition of an authorized generic of FENTORA.

APPROVAL & LABELING

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.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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, *SPL Standard for Content of Labeling Technical Qs and As*, available at, http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 021947/S-019**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for FENTORA (fentanyl buccal tablets) was originally approved on July 20, 2011, and a REMS modification was approved on December 28, 2011, as part of the approval of the transmucosal immediate-release fentanyl (TIRF) REMS shared system. The TIRF REMS was last modified on December 24, 2014. 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.

The proposed modifications to the FENTORA REMS (which is part of the TIRF REMS) consist of adding the authorized generic and a Medication Guide that is identical to that of the branded product, except that only the authorized generic (fentanyl buccal tablets) is listed as the product name

Your proposed modified REMS submitted on May 21, 2014, amended on December 10, 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:
https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60

Other products may be added in the future if additional TIRF NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on June 5, 2012.

There are no changes to the REMS assessment plan described in our August 21, 2014, REMS Assessment Acknowledgement/REMS Assessment Plan Revision letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, 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 FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication
b) A determination of the implications of a change in the benefit-risk profile for the current REMS
c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications,* provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021947 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute another authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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:

NDA 021947 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021947/S-0xx
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021947/S-0xx
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021947/S-0xx
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 021947/S-0xx
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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 NDA 021947

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.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

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 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.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Kimberly Compton, RPh, Senior Regulatory Project Manager at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling
REMS

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use fentanyl buccal tablets safely and effectively. See full prescribing information for fentanyl buccal tablets.

Fentanyl Buccal Tablets, CII
Initial U.S. Approval: 1968

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, fentanyl buccal tablets are contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (5.1)**
- **Accidental ingestion of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5 2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to fentanyl buccal tablets. (5.5)**
- **When dispensing, do not substitute with any other fentanyl products. (5.5)**
- **Fentanyl buccal tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.6)**
- **Fentanyl buccal tablets are 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. (5.7)**
- **Prolonged use of fentanyl buccal tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

----------INDICATIONS AND USAGE----------

Fentanyl buccal tablets are an opioid agonist indicated 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. (1)

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablets.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, or dental pain.
- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to patients enrolled in the TIRF REMS Access program. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

----------DOSAGE AND ADMINISTRATION----------

- Patients must require and use around-the-clock opioids when taking fentanyl buccal tablets. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initial dose of fentanyl buccal tablets: 100 mcg. (2.2)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablets. Limit patient access to only one strength of fentanyl buccal tablets at any one time. (2.3)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablets. (2.4)
- 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 fentanyl buccal tablets. (2.2)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole. (2.5)
- When opioid therapy is no longer required, consider discontinuing fentanyl buccal tablets along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.6)

----------DOSAGE FORMS AND STRENGTHS----------

Buccal Tablets: 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. (3)

----------CONTRAINDICATIONS----------

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of fentanyl buccal tablets. (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of fentanyl buccal tablets in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of fentanyl buccal tablets in patients with impaired consciousness or coma. (5.13)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.18)

----------ADVERSE REACTIONS----------

Most common (frequency ≥10%): nausea, dizziness, vomiting, fatigue, anemia, constipation, edema peripheral, asthenia, dehydration and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with fentanyl buccal tablets because they may reduce analgesic effect of fentanyl buccal tablets or precipitate withdrawal symptoms. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)

- Lactation: Not recommended. (8 2)
- Renal and Hepatic Impairment: Administer fentanyl buccal tablets with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious life-threatening and/or fatal respiratory depression has occurred in patients treated with fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of fentanyl buccal tablets or following a dose increase. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.1)]*.

Due to the risk of respiratory depression, fentanyl buccal tablets are contraindicated in the management of acute or postoperative pain including headache/migraine and in opioid non-tolerant patients *[see Contraindications (4)]*.

Accidental Ingestion

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.2)]*.

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. Fentanyl buccal tablets must be kept out of reach of children *[see Warnings and Precautions (5.2)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl buccal tablets with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl buccal tablets and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of fentanyl buccal tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to fentanyl buccal tablets *[see Dosage and Administration (2.1)]*.**
- **When dispensing, do not substitute a fentanyl buccal tablets prescription for other fentanyl products.**

Addiction, Abuse, and Misuse

Fentanyl buccal tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing fentanyl buccal tablets, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.6)]*.

Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose, fentanyl buccal tablets are available only through a restricted program required by the Food and Drug Administration, called a 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 Warnings and Precautions (5.7)]*. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets 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 *[see Warnings and Precautions (5.8)]*.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets are indicated 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.

Patients considered opioid tolerant are those who are taking around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg of oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking fentanyl buccal tablets.

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, and dental pain *[see Contraindications (4)]*.

- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.7)]*. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets *[see Warnings and Precautions (5.7)]*.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.6)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with fentanyl buccal tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.1)]*.
- Instruct patients and caregivers to take steps to store fentanyl buccal tablets securely and to properly dispose of unused fentanyl buccal tablets as soon as no longer needed *[see Warnings and Precautions (5.2, 5.6), Patient Counseling Information (17)]*.
- Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Warnings and Precautions (5.5)]*.
- Fentanyl buccal tablets are NOT a generic version of any other transmucosal fentanyl product *[see Warnings and Precautions (5.5)]*.

2.2 Initial Dosage

The initial dose of fentanyl buccal tablets is always 100 mcg with the only exception being patients already using ACTIQ.

Patients on ACTIQ

a. For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ table below (Table 1). The doses of fentanyl buccal tablets in this table are starting doses and not intended to represent equianalgesic doses to ACTIQ. Patients must be instructed to stop the use of ACTIQ and dispose of any remaining units.

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

Current ACTIQ Dose (mcg)	Initial Fentanyl Buccal Tablets Dose*
200	100 mcg tablet
400	100 mcg tablet
600	200 mcg tablet
800	200 mcg tablet
1200	2 x 200 mcg tablets
1600	2 x 200 mcg tablets

*From this initial dose, titrate patient to effective dose.

b. For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg fentanyl buccal tablets and should proceed using multiples of this tablet strength.

Repeat Dosing

a. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any episode of breakthrough pain.

b. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.

2.3 Dose Titration

a. From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablets over several episodes of breakthrough pain and discuss their experience with their healthcare provider to determine if a dosage adjustment is warranted.

b. Patients whose initial dose is 100 mcg and who need to titrate to a higher dose, can be instructed to use two 100 mcg tablets (one on each side of the mouth in the buccal cavity) with their next breakthrough pain episode. If this dosage is not successful, the patient may be instructed to place two 100 mcg tablets on each side of the mouth in the buccal cavity (total of four 100 mcg tablets). Titrate using multiples of the 200 mcg fentanyl buccal tablets for doses above 400 mcg (600 mcg and 800 mcg). Note: Do not use more than 4 tablets simultaneously.

c. In cases where the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose of the same strength for that episode. Thus patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode. During titration, one **dose** of fentanyl buccal tablets may include administration of 1 to 4 tablets of the same dosage strength (100 mcg or 200 mcg).

d. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets. To reduce the risk of overdose during titration, patients should have only one strength of fentanyl buccal tablets available at any time.

e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely *[see How Supplied/Storage and Handling (16)]*. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.4 Maintenance Dosing

a. Once titrated to an effective dose, patients should generally use only ONE fentanyl buccal tablet of the appropriate strength per breakthrough pain episode.

b. On occasion when the breakthrough pain episode is not relieved after 30 minutes, patients may take ONLY ONE additional dose using the same strength for that episode.

c. Patients MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.

d. Dosage adjustment of fentanyl buccal tablets may be required in some patients.
Generally, the fentanyl buccal tablets 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.

e. If the patient experiences greater than four breakthrough pain episodes per day, the dose of the around-the-clock opioid used for persistent pain should be re-evaluated.

f. Once an effective dose is determined using the titration scheme outlined above, an alternate route of administration is sublingual (placing the tablet under the tongue).

2.5 Administration of Fentanyl Buccal Tablets

Opening the Blister Package:

1. Instruct patients not to open the blister until ready to administer fentanyl buccal tablets.
2. Separate a single blister unit from the blister card by bending and tearing apart at the perforations.
3. Bend the blister unit along the line where indicated.
4. Peel back the blister backing to expose the tablet. Patients should NOT attempt to push the tablet through the blister as this may cause damage to the tablet.
5. Do not store the tablet once it has been removed from the blister package as the tablet integrity may be compromised and, more importantly, because this increases the risk of accidental exposure to the tablet.

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should immediately place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. Patients should not split the tablet.
The fentanyl buccal tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.
The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.
After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.
It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets in the buccal cavity.

2.6 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing fentanyl buccal tablets along with a gradual downward titration of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, fentanyl buccal tablets therapy can usually be discontinued immediately. *[see Drug Abuse and Dependence (9.3*

2.7 Disposal of Fentanyl Buccal Tablets

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279.

3 DOSAGE FORMS AND STRENGTHS

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Fentanyl Buccal Tablets are contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients *[see Indications and Usage (1); Warnings and Precautions (5.1)]*.
- Significant respiratory depression *[see Warnings and Precautions (5.1)]*.
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department *[see Indications and Usage (1)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*.
- Known hypersensitivity (e.g. anaphylaxis) to fentanyl or components of fentanyl buccal tablets (e.g., anaphylaxis) *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of fentanyl buccal tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of fentanyl buccal tablets.

To reduce the risk of respiratory depression, proper dosing and titration of fentanyl buccal tablets are essential *[see Dosage and Administration (2.3)]*. Overestimating the fentanyl buccal tablets dosage can result in a fatal overdose with the first dose. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.5)]*.

Fentanyl buccal tablets could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

Patients and their caregivers must be informed that fentanyl buccal tablets contain a medicine in an amount which can be fatal to a child. Healthcare providers 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.

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 *[see Patient Counseling Information (17)]*.

Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets *Medication Guide*. Encourage patients to read this information in its entirety and give them an opportunity to have their questions answered.

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of fentanyl buccal tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.1)]*, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl buccal tablets-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl buccal tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl buccal tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of fentanyl buccal tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl buccal tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (including Alcohol)

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl buccal tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when fentanyl buccal tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.5 Risk of Medication Errors

When prescribing, do not convert a patient to fentanyl buccal tablets from any other fentanyl product on a mcg per mcg basis as fentanyl buccal tablets and other fentanyl products are not equivalent on a microgram per microgram basis.

Fentanyl buccal tablets are not a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, do not substitute a fentanyl buccal tablets prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and fentanyl buccal tablets are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of fentanyl buccal tablets or any other fentanyl product may result in a fatal overdose.

There are no safe conversion directions available for patients on any other fentanyl products except ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Dosage and Administration (2.1)]*.Therefore, for opioid tolerant patients, the initial dose of fentanyl buccal tablets should always be 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.3)]*.

5.6 Addiction, Abuse, and Misuse

Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance. As an opioid, fentanyl buccal tablets expose users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed fentanyl buccal tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl buccal tablets, and monitor all patients receiving fentanyl buccal tablets for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as fentanyl buccal tablets, but use in such patients necessitates intensive counseling about the risks and proper use of fentanyl buccal tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing fentanyl buccal tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.7 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)]*, fentanyl buccal tablets are 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 fentanyl buccal tablets, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tablets 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 fentanyl buccal tablets, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense fentanyl buccal tablets must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute fentanyl buccal tablets 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.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of fentanyl buccal tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: fentanyl buccal tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of fentanyl buccal tablets *[see Warnings and Precautions (5.1)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.1)]*.

Monitor such patients closely, particularly when initiating and titrating fentanyl buccal tablets and when fentanyl buccal tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.1)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl buccal tablets with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

Fentanyl buccal tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of fentanyl buccal tablets. In patients with circulatory shock, fentanyl buccal tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of fentanyl buccal tablets in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), fentanyl buccal tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl buccal tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of fentanyl buccal tablets in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions
Fentanyl buccal tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in fentanyl buccal tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders
The fentanyl in fentanyl buccal tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during fentanyl buccal tablets therapy.

5.16 Risks of Driving and Operating Machinery
Fentanyl buccal tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of fentanyl buccal tablets and know how they will react to the medication.

5.17 Cardiac Disease
Intravenous fentanyl may produce bradycardia. Therefore, use fentanyl buccal tablets with caution in patients with bradyarrhythmias.

5.18 Application Site Reactions
Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding *[see Adverse Reactions (6)]*.

5.19 MAO Inhibitors
Fentanyl buccal tablets are 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 *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.1)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.8)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*

6.1 Clinical Studies Experience
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.

The safety of fentanyl buccal tablets has been evaluated in 304 opioid-tolerant cancer patients with breakthrough pain. The average duration of therapy was 76 days with some patients being treated for over 12 months.

The clinical trials of fentanyl buccal tablets were designed to evaluate safety and efficacy in treating patients with cancer and breakthrough pain; all patients were taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone or transdermal fentanyl, for their persistent pain.

The adverse event data presented here reflect the actual percentage of patients experiencing each adverse effect among patients who received fentanyl buccal tablets for breakthrough pain along with a concomitant opioid for persistent pain. There has been no attempt to correct for concomitant use of other opioids, duration of fentanyl buccal tablets therapy or cancer-related symptoms.

Table 2 lists, by maximum dose received, adverse events with an overall frequency of 5% or greater within the total population that occurred during titration. The ability to assign a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 2.
Adverse Events Which Occurred During Titration at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=45)	200 mcg (N=34)	400 mcg (N=53)	600 mcg (N=56)	800 mcg (N=113)	Total (N=304)*
Gastrointestinal disorders						
Nausea	4 (9)	5 (15)	10 (19)	13 (23)	18 (16)	50 (17)
Vomiting	0	2 (6)	2 (4)	7 (13)	3 (3)	14 (5)
General disorders and administration site conditions						
Fatigue	3 (7)	1 (3)	9 (17)	1 (2)	5 (4)	19 (6)
Nervous system disorders						
Dizziness	5 (11)	2 (6)	12 (23)	18 (32)	21 (19)	58 (19)
Somnolence	2 (4)	2 (6)	6 (12)	7 (13)	3 (3)	20 (7)
Headache	1 (2)	3 (9)	4 (8)	8 (14)	10 (9)	26 (9)

* Three hundred and two (302) patients were included in the safety analysis.

Table 3 lists, by successful dose, adverse events with an overall frequency of ≥5% within the total population that occurred after a successful dose had been determined.

Table 3.
Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class MeDRA preferred term, n (%)	100 mcg (N=19)	200 mcg (N=31)	400 mcg (N=44)	600 mcg (N=48)	800 mcg (N=58)	Total (N=200)
Blood and lymphatic system disorders						
Anemia	6 (32)	4 (13)	4 (9)	5 (10)	7 (13)	26 (13)
Neutropenia	0	2 (6)	1 (2)	4 (8)	4 (7)	11 (6)
Gastrointestinal disorders						
Nausea	8 (42)	5 (16)	14 (32)	13 (27)	17 (31)	57 (29)
Vomiting	7 (37)	5 (16)	9 (20)	8 (17)	11 (20)	40 (20)
Constipation	5 (26)	4 (13)	5 (11)	4 (8)	6 (11)	24 (12)
Diarrhea	3 (16)	0	4 (9)	3 (6)	5 (9)	15 (8)
Abdominal pain	2 (11)	1 (3)	4 (9)	7 (15)	4 (7)	18 (9)
General disorders and administration site conditions						
Edema peripheral	6 (32)	5 (16)	4 (9)	5 (10)	3 (5)	23 (12)
Asthenia	3 (16)	5 (16)	2 (5)	3 (6)	8 (15)	21 (11)
Fatigue	3 (16)	3 (10)	9 (20)	9 (19)	8 (15)	32 (16)
Infections and infestations						
Pneumonia	1 (5)	5 (16)	1 (2)	1 (2)	4 (7)	12 (6)
Investigations						
Weight decreased	1 (5)	1 (3)	3 (7)	2 (4)	6 (11)	13 (7)
Metabolism and nutrition disorders						
Dehydration	4 (21)	0	4 (9)	6 (13)	7 (13)	21 (11)
Anorexia	1 (5)	2 (6)	4 (9)	3 (6)	6 (11)	16 (8)
Hypokalemia	0	2 (6)	0	1 (2)	8 (15)	11 (6)
Musculoskeletal and connective tissue disorders						
Back pain	2 (11)	0	2 (5)	3 (6)	2 (4)	9 (5)
Arthralgia	0	1 (3)	3 (7)	4 (8)	3 (5)	11 (6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Cancer pain	3 (16)	1 (3)	3 (7)	2 (4)	1 (2)	10 (5)
Nervous system disorders						
Dizziness	5 (26)	3 (10)	5 (11)	6 (13)	6 (11)	25 (13)
Headache	2 (11)	1 (3)	4 (9)	5 (10)	8 (15)	20 (10)
Somnolence	0	1 (3)	4 (9)	4 (8)	8 (15)	17 (9)
Psychiatric disorders						
Confusional state	3 (16)	1 (3)	2 (5)	3 (6)	5 (9)	14 (7)
Depression	2 (11)	1 (3)	4 (9)	3 (6)	5 (9)	15 (8)
Insomnia	2 (11)	1 (3)	3 (7)	2 (4)	4 (7)	12 (6)
Respiratory, thoracic, and mediastinal disorders						
Cough	1 (5)	1 (3)	2 (5)	4 (8)	5 (9)	13 (7)
Dyspnea	1 (5)	6 (19)	0	7 (15)	4 (7)	18 (9)

In addition, a small number of patients (n=11) with Grade 1 mucositis were included in clinical trials designed to support the safety of fentanyl buccal tablets. There was no evidence of excess toxicity in this subset of patients.

Application Site Reactions: In clinical trials, 10% of all patients exposed to fentanyl buccal tablets reported application site reactions. These reactions ranged from paresthesias to ulceration and bleeding. Application site reactions occurring in ≥1% of patients were pain (4%), ulcer (3%), and irritation (3%). Application site reactions tended to occur early in treatment, were self-limited and only resulted in treatment discontinuation for 2% of patients.

The duration of exposure to fentanyl buccal tablets varied greatly, and included open-label and double-blind studies. The frequencies listed below represent the ≥1% of patients (and not listed in Tables 2 and 3 above) from three clinical trials (titration and post-titration periods combined) who experienced that event while receiving fentanyl buccal tablets. Events are classified by system organ class.

Adverse Events (≥1%)
Blood and Lymphatic System Disorders: Thrombocytopenia, Leukopenia
Cardiac Disorders: Tachycardia
Gastrointestinal Disorders: Stomatitis, Dry Mouth, Dyspepsia, Upper Abdominal Pain, Abdominal Distension, Dysphagia, Gingival Pain, Stomach Discomfort, Gastroesophageal Reflux Disease, Glossodynia, Mouth Ulceration
General Disorders and Administration Site Conditions: Pyrexia, Application Site Pain, Application Site Ulcer, Chest Pain, Chills, Application Site Irritation, Edema, Mucosal Inflammation, Pain
Hepatobiliary Disorders: Jaundice
Infections and Infestations: Oral Candidiasis, Urinary Tract Infection, Cellulitis, Nasopharyngitis, Sinusitis, Upper Respiratory Tract Infection, Influenza, Tooth Abscess
Injury, Poisoning and Procedural Complications: Fall, Spinal Compression Fracture
Investigations: Decreased Hemoglobin, Increased Blood Glucose, Decreased Hematocrit, Decreased Platelet Count
Metabolism and Nutrition Disorders: Decreased Appetite, Hypoalbuminemia, Hypercalcemia, Hypomagnesemia, Hyponatremia, Reduced Oral Intake
Musculoskeletal and Connective Tissue Disorders: Pain in Extremity, Myalgia, Chest Wall Pain, Muscle Spasms, Neck Pain, Shoulder Pain
Nervous System Disorders: Hypoesthesia, Dysgeusia, Lethargy, Peripheral Neuropathy, Paresthesia, Balance Disorder, Migraine, Neuropathy
Psychiatric Disorders: Anxiety, Disorientation, Euphoric Mood, Hallucination, Nervousness
Renal and Urinary Disorders: Renal Failure
Respiratory, Thoracic and Mediastinal Disorders: Pharyngolaryngeal Pain, Exertional Dyspnea, Pleural Effusion, Decreased Breathing Sounds, Wheezing
Skin and Subcutaneous Tissue Disorders: Pruritus, Rash, Hyperhidrosis, Cold Sweat
Vascular Disorders: Hypertension, Hypotension, Pallor, Deep Vein Thrombosis

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of fentanyl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders:

- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Endocrine Disorders:
- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.
Immune System Disorders:
- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in fentanyl buccal tablets.
General Disorders and Administration Site Conditions: Drug withdrawal syndrome

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with fentanyl buccal tablets.

Table 4: Clinically Significant Drug Interactions with Fentanyl Buccal Tablets

Inhibitors of CYP3A4	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention	If concomitant use is necessary, consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention	If concomitant use is necessary, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl buccal tablets dosage reduction and monitor for signs of respiratory depression.
Examples	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to 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.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.10)]*.
Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.10)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.1)]*.
Intervention	The use of fentanyl buccal tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact	May reduce the analgesic effect of fentanyl buccal tablets and/or precipitate withdrawal symptoms.
Intervention	Avoid concomitant use.
Examples	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of fentanyl buccal tablets and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Monitor patients for signs of urinary retention or reduced gastric motility when fentanyl buccal tablets are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.8)]*. Available data with fentanyl buccal tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.8)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl buccal tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including fentanyl buccal tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

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.

Animal Data

Fentanyl (25, 50, or 100 mcg/kg) was administered subcutaneously to pregnant rats during the period of organogenesis (Gestation Day, GD 6-17). Maternal toxicity and a decrease in fetal weights were observed at 100 mcg/kg but no teratogenicity was seen in the study (100 mcg/kg dose is equivalent to 1.4-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison). Fentanyl (50, 100, or 250 mcg/kg) was also administered subcutaneously to pregnant rabbits during the period of organogenesis (GD 6-18). Maternal toxicity was noted at doses $\geq$100 mcg/kg. No teratogenicity was seen in the study (250 mcg/kg dose is equivalent to 7.5-times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison).

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of fentanyl buccal tablets on a mg/m^2 basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of fentanyl buccal tablets based on a mg/m^2 basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 6 times the human dose of 800 mcg fentanyl buccal tablets per pain episode on a mg/m^2 basis and produced mean steady-state plasma levels that are approximately 5 times higher than the mean C_{max} observed following administration of 800 mcg dose of fentanyl buccal tablets in humans.

In a postnatal development study, pregnant rats were treated from GD 6 through lactation day (LD) 20 with subcutaneous doses of fentanyl (25, 50, 100, and 400 mcg/kg). Maternal toxicity was noted at doses $\geq$100 mcg/kg. A reduction in pup growth and delayed attainment of developmental indices were observed at $\geq$100 mcg/kg. No difference in the number of live pups/litter was seen at birth, however, pup survival at LD 4 was reduced to 48% at 400 mcg/kg and by LD 21 pup survival was reduced to 30% and 26% at 100 and 400 mcg/kg, respectively. During lactation, fentanyl-related clinical signs (decreased activity, skin cold to touch, and moribund appearance) were noted in the F1 pups, most prominently in the 400 mcg/kg group. Pups from this group also had significantly reduced body weights throughout the lactation period. The dose of fentanyl administered to rats at which no developmental toxicity in the F1 generation was seen was 50 mcg/kg which is approximately equal the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with fentanyl buccal tablets.

Clinical Considerations

Monitor infants exposed to fentanyl buccal tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2) Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use
The safety and efficacy of fentanyl buccal tablets have not been established in pediatric patients below the age of 18 years.

8.5 Geriatric Use
Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablets in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of fentanyl buccal tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment
Insufficient information exists to make recommendations regarding the use of fentanyl buccal tablets 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 Sex
Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant sex differences were noted either in dosage requirement or in observed adverse reactions.

8.8 Race
The pharmacokinetic effects of race with the use of fentanyl buccal tablets have not been systematically evaluated. In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance.

9.2 Abuse
Fentanyl buccal tablets contain fentanyl, a substance with high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Fentanyl buccal tablets can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.6)]*.
All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. 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, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance *[see Drug Abuse and Dependence (9.3)]*. Health care providers 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 true addiction.

Fentanyl buccal tablets, 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.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of Fentanyl Buccal Tablets
Fentanyl buccal tablets are for oral transmucosal use only. Abuse of fentanyl buccal tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of fentanyl buccal tablets with alcohol and other central nervous system depressants.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdose with fentanyl buccal tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in fentanyl buccal tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

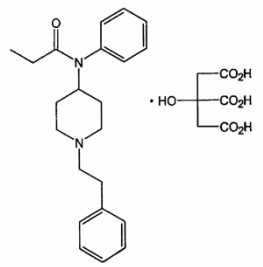
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Fentanyl buccal tablets are an opioid agonist, intended for buccal mucosal administration.
Fentanyl buccal tablets are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

Fentanyl buccal tablets employ the OraVescent® drug delivery technology, which generates a reaction that releases carbon dioxide when the tablet comes in contact with saliva. It is believed that transient pH changes accompanying the reaction may optimize dissolution (at a lower pH) and membrane permeation (at a higher pH) of fentanyl through the buccal mucosa.

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:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.
Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the 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 a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and to electrical stimulation.
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). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

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 in the small intestine is delayed 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 biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension.

Effects on the Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
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 *[see Dosage and Administration (2.1)]*.

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)]*.

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. 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. 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 *[see Warnings and Precautions (5.1)]*.

12.3 Pharmacokinetics
Fentanyl exhibits linear pharmacokinetics. Systemic exposure to fentanyl following administration of fentanyl buccal tablets increases linearly in an approximate dose-proportional manner over the 100- to 800-mcg dose range.

Absorption
Following buccal administration of fentanyl buccal tablets, fentanyl is readily absorbed with an absolute bioavailability of 65%. The absorption profile of fentanyl buccal tablets is largely the result of an initial absorption from the buccal mucosa, with peak plasma concentrations following venous sampling generally attained within an hour after buccal administration. Approximately 50% of the total dose administered is absorbed transmucosally and becomes systemically available. The remaining half of the total dose is swallowed and undergoes more prolonged absorption from the gastrointestinal tract.

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets and ACTIQ (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets) (Table 5).

Table 5. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or ACTIQ

Pharmacokinetic Parameter (mean)	Fentanyl Buccal Tablets 400 mcg	ACTIQ 400 mcg (adjusted dose)***
Absolute Bioavailability	65% ± 20%	47% ± 10.5%
Fraction Absorbed Transmucosally	48% ± 31.8%	22% ± 17.3%
T_{max} (minute)**	46.8 (20-240)	90.8 (35-240)
C_{max} (ng/mL)	1.02 ± 0.42	0.63 ± 0.21
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.40 ± 0.18	0.14 ± 0.05

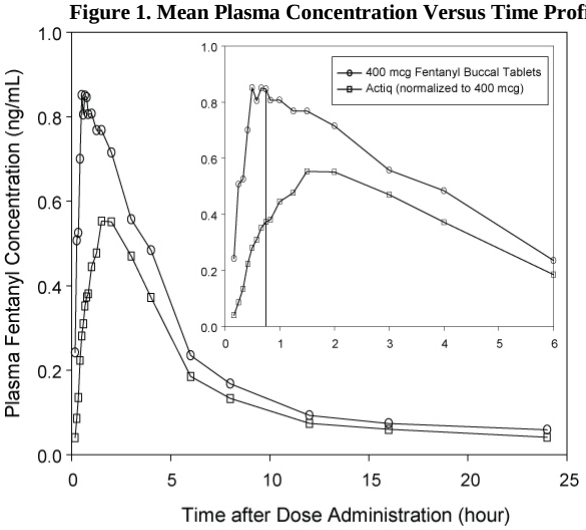
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

* Based on venous blood samples.
** Data for T_{max} presented as median (range).
***ACTIQ data was dose adjusted (800 mcg to 400 mcg).

Similarly, in another bioavailability study exposure following administration of fentanyl buccal tablets was also greater (approximately 50%) compared to Actiq.

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl buccal tablets compared to ACTIQ (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.2) and Warnings and Precautions (5.5)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablets.

Figure 1. Mean Plasma Concentration Versus Time Profiles Following Single Doses of Fentanyl Buccal Tablets and ACTIQ in Healthy Subjects



Actiq data were dose adjusted (800 mcg to 400 mcg)

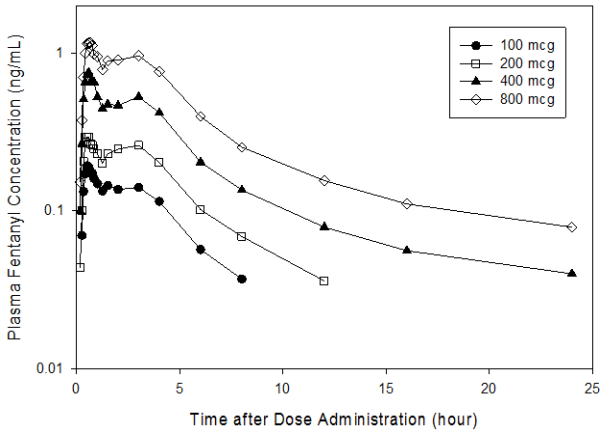
Mean pharmacokinetic parameters are presented in Table 6. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 6. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0 18	0.97 ± 0.53	1.59 ± 0.90
T_{max}, minute (range)**	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1 13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
$T_{1/2}$, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

* Based on venous sampling.
** Data for T_{max} presented as median (range).

Figure 2. Mean Plasma Concentration Versus Time Profiles Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects



Dwell time (defined as the length of time that the tablet takes to fully disintegrate following buccal administration), does not appear to affect early systemic exposure to fentanyl.

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 7.

Table 7. Pharmacokinetic Parameters in Patients with Mucositis

Patient status	C_{max} (ng/mL)	t_{max} (min)	$AUC_{0\text{-}tmax}$ (ng•hr/mL)	$AUC_{0\text{-}8}$ (ng•hr/mL)
Mucositis	1.25 ± 0.78	25.0 (15 - 45)	0.21 ± 0.16	2.33 ± 0.93
No mucositis	1.24 ± 0.77	22.5 (10 - 121)	0.25 ± 0.24	1.86 ± 0.86

Following sublingual tablet placement, systemic exposure (as measured by AUC and C_{max}) of fentanyl is equivalent to systemic exposure following buccal tablet placement.

Distribution
Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80-85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean oral volume of distribution at steady state (Vss/F) was 25.4 L/kg.

Elimination

Metabolism
The metabolic pathways following buccal administration of fentanyl buccal tablets have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active *[see Drug Interactions (7)]*.

Excretion
Disposition of fentanyl following buccal administration of fentanyl buccal tablets has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered 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 following intravenous administration is approximately 42 L/h.

Sex
Systemic exposure was higher for women than men (mean C_{max} and AUC values were approximately 28% and 22% higher, respectively). The observed differences between men and women were largely attributable to differences in weight.

Race
In studies conducted in healthy Japanese subjects, systemic exposure was generally higher than that observed in U.S. subjects (mean C_{max} and AUC values were approximately 50% and 20% higher, respectively). The observed differences were largely attributed to the lower mean weight of the Japanese subjects compared to U.S. subjects (57.4 kg versus 73 kg).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2 3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

Mutagenesis
Fentanyl citrate was not mutagenic in the Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay. Fentanyl citrate was not clastogenic in the *in vivo* mouse micronucleus assay.

Impairment of Fertility

In a fertility study, female rats were administered fentanyl subcutaneously for 14 days prior to mating with untreated males at doses up to 300 mcg/kg and no effects on female fertility were observed. The systemic exposure at the dose of 300 mcg/kg was approximately 8.6 times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison. Males were administered fentanyl subcutaneously for 28 days prior to mating with untreated females at doses up to 300 mcg/kg. At 300 mcg/kg, adverse effects on sperm parameters, which affected fertility, were observed. These effects included decreased percent mobile sperm, decreased sperm concentrations as well as an increase in the percent abnormal sperm. The dose in males at which no effects on fertility were observed was 100 mcg/kg, which is approximately 5.7- times the exposure of a single human dose of 800 mcg per pain episode, based on an AUC comparison.

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 fentanyl buccal tablets.

14 CLINICAL STUDIES

The efficacy of fentanyl buccal tablets was demonstrated in a double-blind, placebo-controlled, cross-over study in opioid tolerant patients with cancer and breakthrough pain. Patients considered opioid tolerant were those who were taking at least 60 mg of oral morphine daily, at least 25 mcg/hour of transdermal fentanyl, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid daily for a week or longer.

In this trial, patients were titrated in an open-label manner to a successful dose of fentanyl buccal tablets. A successful dose was defined as the dose in which a patient obtained adequate analgesia with tolerable side effects. Patients who identified a successful dose were randomized to a sequence of 10 treatments with 7 being the successful dose of fentanyl buccal tablets and 3 being placebo. Patients used one tablet of study drug (either fentanyl buccal tablets or placebo) per breakthrough pain episode.

Patients assessed pain intensity on a scale that rated the pain as 0=none to 10=worst possible pain. With each episode of breakthrough pain, pain intensity was assessed first and then treatment was administered. Pain intensity (0-10) was then measured at 15, 30, 45, and 60 minutes after the start of administration. The sum of differences in pain intensity scores at 15 and 30 minutes from baseline ($SPID_{30}$) was the primary efficacy measure.

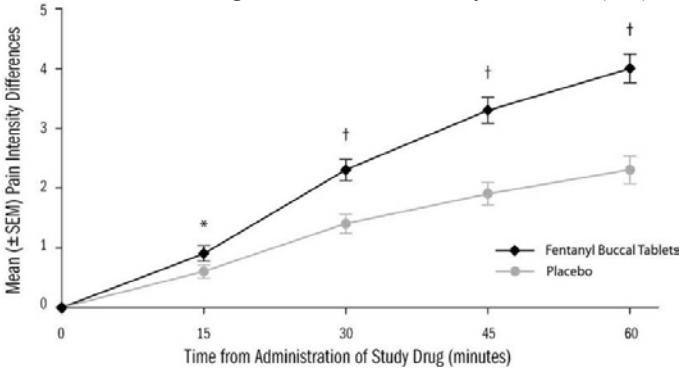
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 8. The median dose was 400 mcg.

Table 8. Successful Dose of Fentanyl Buccal Tablets Following Initial Titration

Fentanyl Buccal Tablets Dose	n (%) (N=80)
100 mcg	13 (16)
200 mcg	11 (14)
400 mcg	21 (26)
600 mcg	10 (13)
800 mcg	25 (31)

The LS mean (SE) $SPID_{30}$ for fentanyl buccal tablets-treated episodes was 3.0 (0.12) while for placebo-treated episodes it was 1.8 (0.18).

Figure 3. Mean Pain Intensity Differences (PID) at Each Time Point During the Double-Blind Treatment Period



PID=pain intensity difference; SEM=standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

Fentanyl buccal tablets are supplied in individually sealed, child-resistant blister packages. Each carton contains 7 blister cards with 4 white tablets in each card. The blisters are child-resistant, encased in peelable foil, and provide protection from moisture. Each tablet is debossed on one side with [redacted], and the other side of each dosage strength is uniquely identified by the debossing on the tablet as described in the table below. In addition, the dosage strength is indicated on the blister package and the carton. See blister package and carton for product information.

Dosage Strength	Debossing	Carton/Blister Package Color	NDC Number
100 mcg	1	Blue	NDC 0093-1150-28
200 mcg	2	Orange	NDC 0093-1151-28
400 mcg	4	Sage green	NDC 0093-1153-28
600 mcg	6	Magenta (pink)	NDC 0093-1154-28
800 mcg	8	Yellow	NDC 0093-1155-28

Note: Carton/blister package colors are a secondary aid in product identification. Please be sure to confirm the printed dosage before dispensing.

Storage and Handling
Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)
Protect fentanyl buccal tablets from freezing and moisture. Do not use if the blister package has been tampered with.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting fentanyl buccal tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.1)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Ingestion

- Healthcare providers 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 *[see Warnings and Precautions (5.2)]*.
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.
- Instruct patients to take steps to store fentanyl buccal tablets securely and to dispose of unused fentanyl buccal tablets *[see Dosage and Administration (2.7), Patient Counseling Information; Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed (17)]*.
- Instruct patients and caregivers to keep both used and unused fentanyl buccal tablets out of the reach of children *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)
Inform patients that potentially fatal additive effects may occur if fentanyl buccal tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Addiction, Abuse, and Misuse
Inform patients that the use of fentanyl buccal tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.6)]*. Instruct patients not to share fentanyl buccal tablets with others and to take steps to protect fentanyl buccal tablets from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS
Advise patients of the following information pertaining to the TIRF REMS

- Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets.
- Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets or the TIRF REMS Access program.
- As required by the TIRF REMS Access program, review the contents of the fentanyl buccal tablets Medication Guide with every patient before initiating treatment with fentanyl buccal tablets.
- Advise the patient that fentanyl buccal tablets 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 fentanyl buccal tablets.
- Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.10), Drug Interactions (7)]*.

MAOI Interaction
Inform patients to avoid taking fentanyl buccal tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking fentanyl buccal tablets *[see Warnings and Precautions (5.10, 5.19); Drug Interactions (7)]*.

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Important Administration Instructions *[see Dosage and Administration (2)]*

- Instruct patients not to take fentanyl buccal tablets 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 fentanyl buccal tablets are 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 fentanyl buccal tablets.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode.
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.
- Instruct patients NOT to share fentanyl buccal tablets and that sharing fentanyl buccal tablets with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablets contain fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.

- Instruct patients that fentanyl buccal tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets.
- Instruct patients to use fentanyl buccal tablets exactly as prescribed by their doctor and not to take fentanyl buccal tablets more often than prescribed.
- Provide patients and their caregivers with a Medication Guide each time fentanyl buccal tablets are dispensed because new information may be available.

Hypotension
Inform patients that fentanyl buccal tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)]*.

Anaphylaxis
Inform patients that anaphylaxis have been reported with ingredients contained in fentanyl buccal tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of fentanyl buccal tablets can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that fentanyl buccal tablets can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)Nonclinical Toxicology (13.1)]*.

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery
Inform patients that fentanyl buccal tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed
- Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.
- To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush the fentanyl buccal tablets blister packages or cartons down the toilet.
- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-888-483-8279) or seek assistance from their local DEA office.

FBT-003

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:
Do not use fentanyl buccal tablets 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 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.

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is 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.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- 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.
- 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
- 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.
- 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.

Do not take 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 at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- 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.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.

- 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.**
- **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.
- Do not stop taking fentanyl buccal tablets 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.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **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.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- 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.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets 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.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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, 59°F to 86°F (15°C to 30°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.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 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, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient 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.**
- **Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as**

XXX mcg **(See Figure 1).**

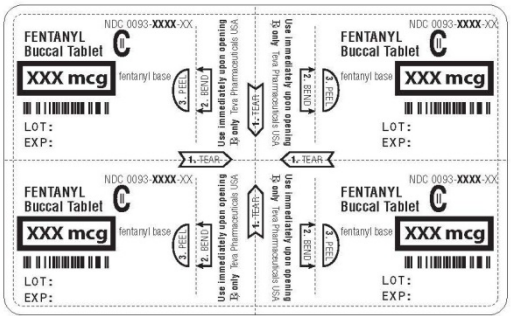


Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

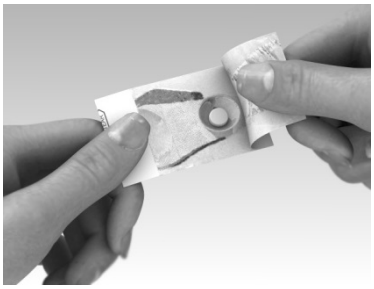


Figure 2

- **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 tablets 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:**
  - **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.**

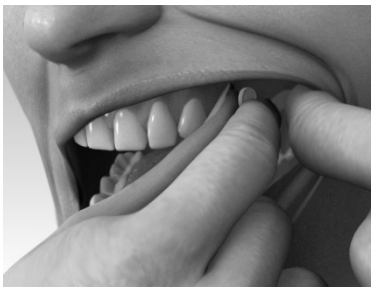


Figure 3

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).**

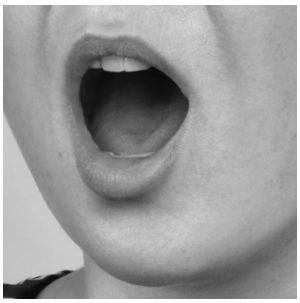


Figure 4a

Figure 4b

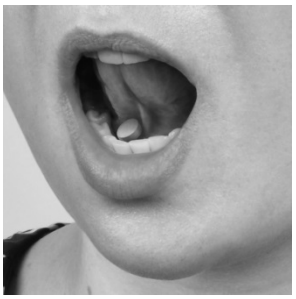


Figure 4c

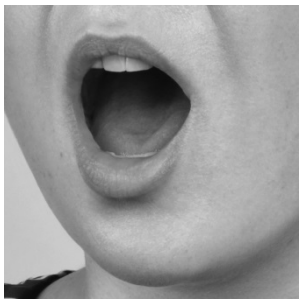


Figure 4d

- **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.**

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454 call 1-888-483-8279

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Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:

Do not use fentanyl buccal tablets 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 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.

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is 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.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- 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.
- 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
- 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.
- 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.

Do not take 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 at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- 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.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problem

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.
- 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.**
- **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.
- Do not stop taking fentanyl buccal tablets 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.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **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.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- 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.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets 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.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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, 59°F to 86°F (15°C to 30°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.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 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, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient 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.**
- **Separate one of the blister units from the blister card by tearing apart at the perforations. Bend the blister unit along the line where indicated. The product strength of your fentanyl buccal tablets will be printed in the boxed area shown as**

XXX mcg **(See Figure 1).**

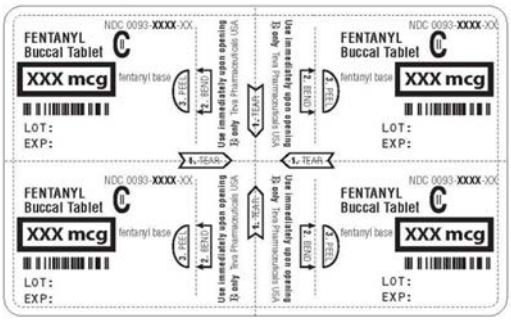

Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

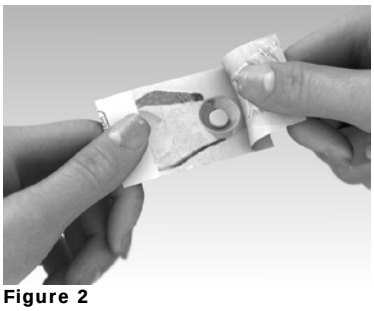

Figure 2

- **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 tablets 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:**
  - **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.**

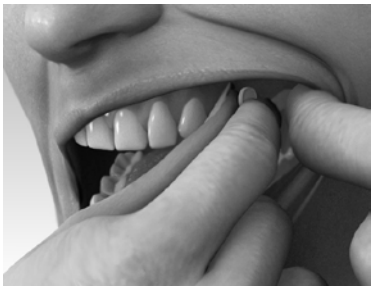

Figure 3

OR,

- **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).**

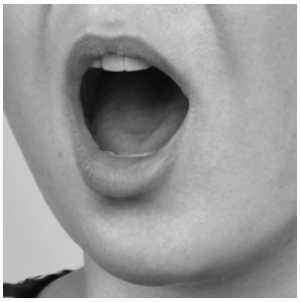
Figure 4a


Figure 4b

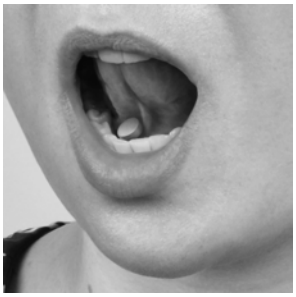
Figure 4c

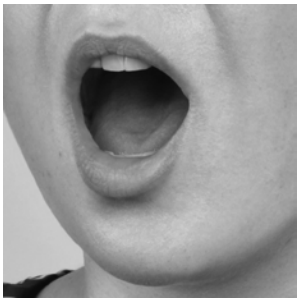
Figure 4d

- **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.**

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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*** _____ ***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):_____

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):_____

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,

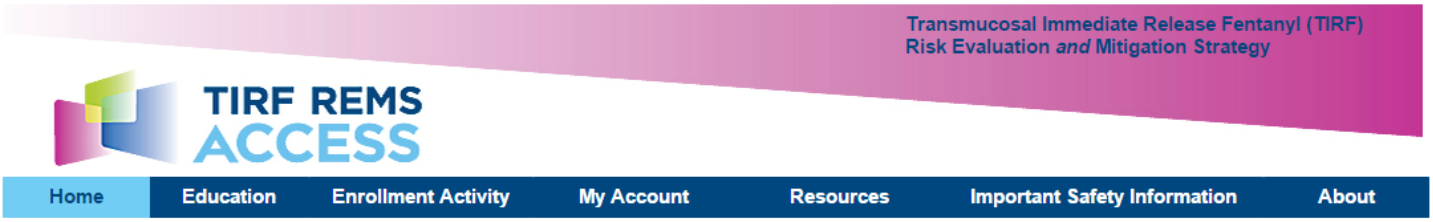
TIRF REMS Access Industry Group

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
- 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
- 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

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

/s/

SHARON H HERTZ
04/11/2017

Branded Pharmaceutical Products R&D

May 21, 2014

Dr. Robert Rappaport, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthetic, Analgesia and Addiction Products
HFD-170, 5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947; SN0048
FENTORA® (fentanyl buccal tablet), CII

PRIOR APPROVAL SUPPLEMENT
TIRF REMS MODIFICATION 3

Dear Dr. Rappaport:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceuticals' NDA 021947 for FENTORA® (fentanyl buccal tablet) and NDA 020747 for ACTIQ® (fentanyl citrate) oral transmucosal lozenge 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 these applications 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*," Teva Pharmaceuticals 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 submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at 610-786-7311.

If there are any questions concerning this submission, please do not hesitate to contact me at (610) 727-6246, or via email at douglas.harnish@tevapharm.com. In my absence, please contact Jennifer Pansch at (763) 488-4930 or via email at Jennifer.pansch@tevapharm.com.

41 Moores Road
PO Box 4011
Frazer, PA 19355

Sincerely,

Douglas C. Harnish, PhD
Director, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

November 26, 2014

Dr. Sharon Hertz, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947; Sequence No. 0056
FENTORA® (fentanyl buccal tablet), CII

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT – TIRF REMS MODIFICATION 3

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceuticals' NDA 021947 for FENTRORA® (fentanyl buccal tablet) and NDA 020747 for ACTIQ® (fentanyl citrate) oral transmucosal lozenge 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*," Teva Pharmaceuticals 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.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 3 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 10.5.1083, antivirus engine 9.750.1007, virus pattern 11.301.00 with a release date of November 26. 2014 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact James Mann at 610-727-6133 or james.mann@tevpahrm.com.

If there are any questions concerning this submission, please do not hesitate to contact me at 610-786-7876, or via email at baldev.rana@tevapharm.com, or in my absence, Douglas Harnish at 610-727-6246 or via email at douglas.harnish@tevapharm.com.

Sincerely,

Baldev B. Rana
Manager, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

December 11, 2014

Dr. Sharon Hertz, M.D., Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia and Analgesia Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947; Sequence No. 0057
FENTORA® (fentanyl buccal tablet), CII

AMENDMENT TO PRIOR APPROVAL SUPPLEMENT – TIRF REMS MODIFICATION 3

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceuticals' NDA 021947 for FENTRORA® (fentanyl buccal tablet) and NDA 020747 for ACTIQ® (fentanyl citrate) oral transmucosal lozenge which is contained in DMF #027320. Furthermore, 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 as well as reference is made to Teva's approved Medication Guide submitted in Section 1.14.2.2 via Sequence # 0055 on November 21, 2014.

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 hereby notifies FDA of its submission of an amendment to Modification #3 to the TIRF REMS DMF #027320 in Sequence # 0013 on 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 on 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 DMF 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 screen prints in the clean versions. No new changes requiring additional FDA review are proposed at this time.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 2 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.1454, antivirus engine 9.800.1009, virus pattern 11.337.00 with a release date of December 11, 2014 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact James Mann at 610-727-6133 or james.mann@tevpahrm.com.

If there are any questions concerning this submission, please do not hesitate to contact me at 610-786-7876, or via email at baldev.rana@tevapharm.com, or in my absence, Douglas Harnish at 610-727-6246 or via email at douglas.harnish@tevapharm.com.

Sincerely,

Baldev B. Rana
Manager, Regulatory Affairs
Teva Branded Pharmaceutical Products R&D, Inc.

DOCUMENT INFORMATION PAGE

DARRTS COMMUNICATION

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947/S-022
CommunicationType:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	KC/10-31-14, 12/20/14 (from returned, cleared template)
Clearance History by:	Sullivan 11-6 Liberatore, 11/5/14 Lehrfeld 11/5/14 Miller/11/4/14; 12/3/14 SRT 12/18/14 Racoosin 11/2/14; 11/6/14
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

NDA 021947/S-022

SUPPLEMENT APPROVAL

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Baldev B. Rana
Manager, Regulatory Affairs

Dear Ms. Rana:

Please refer to your Supplemental New Drug Application (sNDA) dated May 21, 2014, received May 21, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl buccal tablets).

We acknowledge receipt of your amendments dated November 26, and December 11, 2014. We also refer to the May 20, November 25, 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 new drug application provides for modifications to the approved REMS for FENTORA (fentanyl buccal tablets), 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 FENTORA (fentanyl buccal tablets) 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

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
   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
   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 Pharmacis
   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
   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, amended on December 10, 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 to the TIRF REMS Access Program in the future if additional TIRF NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on June 5, 2012. There are no changes to the revised REMS assessment plan attached to our August 21, 2014, REMS Assessment Acknowledgment/REMS Assessment Plan Revisions letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. Also, 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.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 021947 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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:

NDA 021947
REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021947
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021947
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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 NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, Senior Regulatory Project Manager, at 301-796-1191.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director for Safety
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
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*** _____ ***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):_____

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):_____

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,

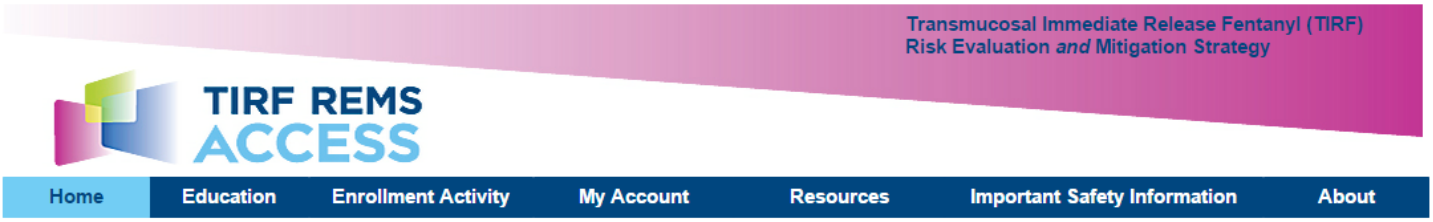
TIRF REMS Access Industry Group

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 <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 – [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
- 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

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

/s/

JUDITH A RACOOSIN
12/24/2014

Sullivan, Matthew

From: Sullivan, Matthew
Sent: Friday, January 23, 2015 4:18 PM
To: Sullivan, Matthew (Matthew.Sullivan@fda.hhs.gov)
Cc: Compton, Kimberly
Subject: Error in Dec 24, 2014, FDA letter regarding TIRF REMS documents

Good afternoon -

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.

Please let me know if you have any questions,

Thanks,
Matt

Matthew W. Sullivan, M.S.
Supervisory Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Food and Drug Administration
Phone 301-796-1245
Fax 301-796-9723
matthew.sullivan@fda.hhs.gov

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

/s/

MATTHEW W SULLIVAN
01/23/2015

NEW SUPPLEMENT FOR NDA 021947/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION DUE TO SAFETY LABEL CHANGES
SUBMITED IN SUPPLEMENT S-025

June 12, 2017

Sharon Hertz, MD
Director, Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947; Sequence No. 0093
FENTORA® (fentanyl buccal tablet), CII
TIRF REMS CORRESPONDENCE

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceutical's FENTORA® (fentanyl buccal tablet); NDA 021947 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*," Teva Pharmaceuticals 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 letter, to the DMF #027320 in eCTD sequence 0029 on June 09, 2017. As requested by the Agency, the proposed modification 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 stand alone submission to clarify it as a one-time (single-use) communication rather than a new document being appended into REMS itself.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office. This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 2.0 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150 Service Pack 1, antivirus engine 9.900.1008, virus pattern 13.463.00 with a release date of June 12, 2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at 610-786-7311or via email at kevin.tompkins@tevapharm.com.

If there are any questions concerning this submission, please do not hesitate to contact me at 610-786-7206 or via email at xuan-tien.huynh@tevapharm.com, or in my absence, Douglas Harnish at 610-727-6246 or via email at douglas.harnish@tevapharm.com.

Sincerely,

Xuan-Tien Huynh. M.S.
Associate III, Pain & Migraine
Regulatory Affairs, Teva Branded Pharmaceuticals

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947
Communication Type:	Form
Communication Group:	Memorandum to File; OpenGoal Date for REMS Modifications Due to Approved or Ordered Safety Labeling Changes
Communication Name:	Administrative Forms
Communication ID:	(FRM-ADMIN-65)(FRM-BLAADMIN-65)
Drafted by:	M. Liberatore 6/21/17
Clearance History:	
Finalized:	M. Liberatore 6/21/17
Filename:	
Use Statement:	Use to open the 60 or 180 day goal date for a REMS modification supplement that is submitted due to safety-related labeling changes
Notes:	**DO NOT USE TO DOCUMENT TELECONS!** When documenting a teleconference, use the appropriate **CORRESPONDENCE function code** and **sent via VERBAL.** For additional instructions, please see http://inside.fda.gov:9003/downloads/CDER/OfficeofBusinessProcessSupport/UCM210177.pdf.

Version: 04/29/2015

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

OPEN GOAL DATE

REMS Modifications Due to Approved or Ordered Safety Labeling Changes

DATE: June 12, 2017

FROM: Mark Liberatore, PharmD; Safety RPM, DAAAP

DRUG: Fentora (fentanyl)

NDA # 021947

- **REMS Modification Supplement #:** S-027
- **Labeling Supplement #** S-024, S-025
- **Date of Labeling Supplement Approval:** December 16, 2016

This memo opens the 60 or 180 day goal date for the above referenced REMS modification supplement according the information provided below:

> **60 Day Goal Date**: If FDA considers the REMS modifications to be **conforming**, enter the date of receipt of the conforming REMS modification supplement or amendment that conforms to the approved or ordered labeling changes in DARRTS. DARRTS will calculate the action goal date.

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

/s/

MARK A LIBERATORE
06/21/2017

TIRF REMS CORRESPONDENCE

August 21, 2017

Sharon Hertz, MD
Director, Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: **NDA 021947, Sequence No. 0098**
FENTORA® (fentanyl buccal tablet), CII
DMF Annual Report (Reporting Period: August 21, 2016 – August 20, 2017)

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceutical's FENTORA® (fentanyl buccal tablet), NDA 021947 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*," Teva Pharmaceuticals 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.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office.

This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 1.5 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150 Service pack 1, antivirus engine 9.950.1006, virus pattern 13.607.00 with a release date of August 21, 2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins (610) 786-7311 or via email at Kevin.tompkins@tevapharm.com.

If there are any questions concerning this submission, please do not hesitate to contact me at 610-786-7206 or via email at xuan-tien.huynh@tevapharm.com, or in my absence, Douglas Harnish at 610-727-6246 or via email at douglas.harnish@tevapharm.com.

Sincerely,

Xuan-Tien Huynh
Associate III, Pain & Migraine
Regulatory Affairs, Teva Branded Pharmaceuticals

TIRF REMS CORRESPONDENCE
REMS Final for approved NDA 021947, Supplement S-000
PRIOR APPROVAL SUPPLEMENT

August 30, 2017

Sharon Hertz, MD
Director, Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 021947; Sequence No. 0100
FENTORA® (fentanyl buccal tablet), CII
TIRF REMS CORRESPONDENCE

Dear Dr. Hertz:

Reference is made to the Single Shared REMS for Transmucosal Immediate Release Fentanyl (TIRF) products approved on December 28, 2011 for Teva Pharmaceutical's FENTORA® (fentanyl buccal tablet); NDA 021947 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. 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 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.

Teva Branded Pharmaceutical Products R&D, Inc., requests that all information in this file be treated as confidential within the meaning of 21 CFR §314.430, and that no information from the file be made public without our written consent to an authorized member of your office. This submission has been prepared in eCTD format and is being submitted through the Electronic Submissions Gateway. This submission size is approximately 1.0 MB. All files were checked and verified to be free of viruses using Trend Micro OfficeScan, client 11.0.4150 Service Pack 1,

antivirus engine 9.950.1006, virus pattern 13.625.00 with a release date of August 30, 2017 or later. If there are any technical questions regarding the format, validation, or electronic delivery of this submission, please contact Kevin Tompkins at 610-786-7311or via email at kevin.tompkins@tevapharm.com.

If there are any questions concerning this submission, please do not hesitate to contact me at 610-786-7206 or via email at xuan-tien.huynh@tevapharm.com, or in my absence, Douglas Harnish at 610-727-6246 or via email at douglas.harnish@tevapharm.com.

Sincerely,

Xuan-Tien Huynh. M.S.
Associate III, Pain & Migraine
Regulatory Affairs, Teva Branded Pharmaceuticals

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 021947/S-027
Communication Type:	Correspondence
Communication Group:	sNDA Action
Communication Name:	Approval
Communication ID:	COR-SNDAACTION-05
Drafted by:	M. Liberatore 7/11/17
Clearance History by:	J. Racoosin DRISK 7/11/17 P. Jani/7-12-17 M. Sullivan8-9
Finalized:	M. Liberatore 8/9/17
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 "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. **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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021947/S-027

SUPPLEMENT APPROVAL

Cephalon, Inc.
41 Moores Road
P.O. Box 4011
Frazer, PA 19355

Attention: Xuan-Tien Huynh, M.S.
Associate III, Pain & Migraine

Dear Ms. Huynh:

Please refer to your Supplemental New Drug Application (sNDA) dated June 12, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FENTORA (fentanyl citrate).

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 new drug application proposes modifications to the approved TIRF REMS to align the REMS document and materials with the labeling approved in supplement S-024 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 FENTORA 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 FENTORA 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 August 29, 2017, and appended to this letter, is approved.

This REMS uses a shared system for the elements to assure safe use and the REMS assessments. This shared system, known as the TIRF REMS Program, currently includes the products listed on the FDA REMS website, available at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17.

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments for the TIRF REMS Program remains the same as that approved on June 5, 2012.

There are no changes to the REMS assessment plan described in our August 21, 2014, REMS Assessment Acknowledgment/REMS Assessment Plan Revision letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, 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 also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the

proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021947 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

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:

NDA 021947 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021947/S-000/
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021947/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021947/S-000/
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021947/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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 NDA 021947

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 have any questions, call Mark Liberatore, PharmD; Safety Regulatory Project Manager, at (301) 796-2221.

Sincerely,

{See appended electronic signature page}

Judith A. Racoosin, MD, MPH
Deputy Director of Safety
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
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):

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 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):_____

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 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**.

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,

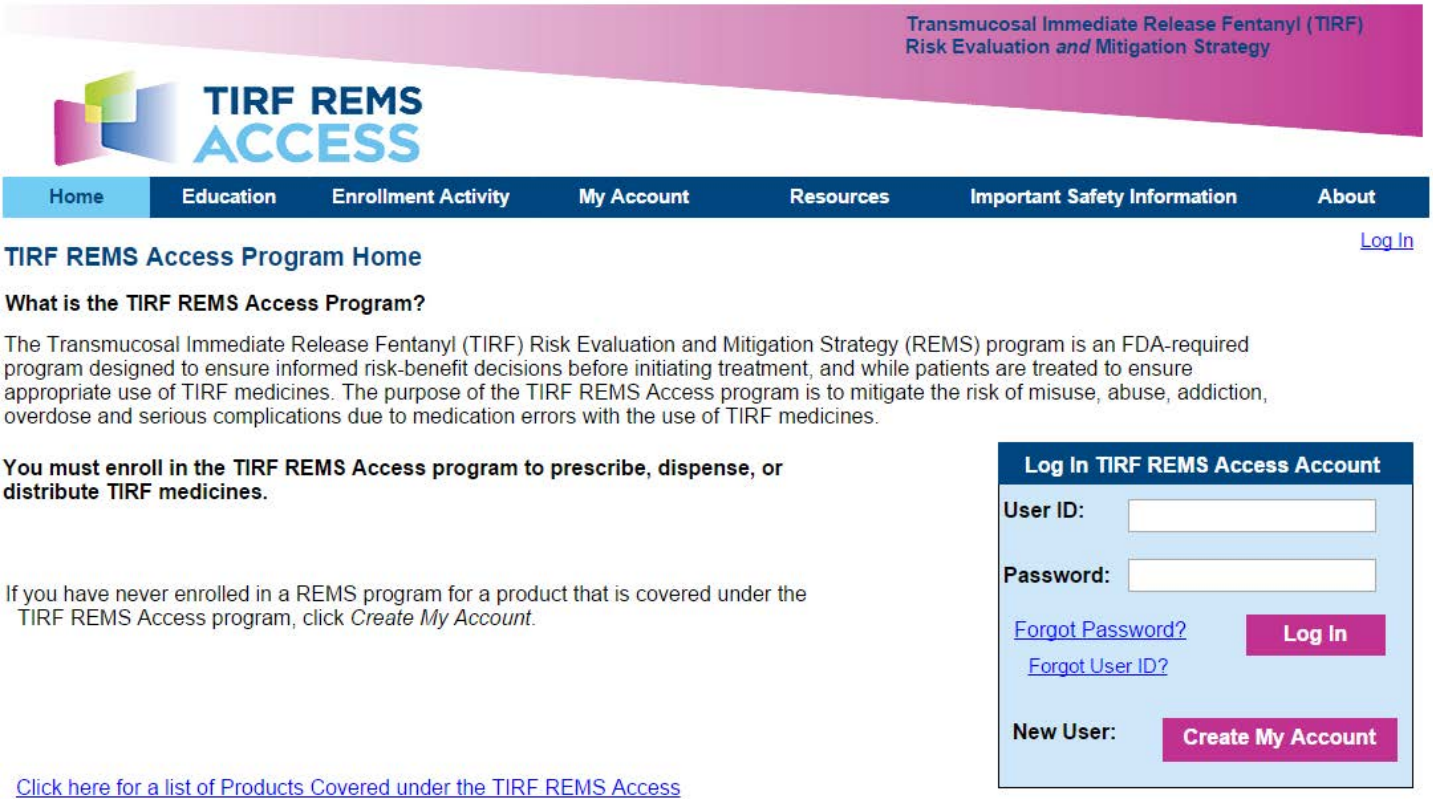
TIRF REMS Access Industry Group

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):_____

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"*

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.

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 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)
- 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/

SHARON H HERTZ on behalf of JUDITH A RACOOSIN
09/07/2017