

### 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<sup>®</sup> (fentanyl) sublingual tablets
- Actiq<sup>®</sup> (fentanyl citrate) oral transmucosal lozenge
- Fentora<sup>®</sup> (fentanyl citrate) buccal tablet
- Lazanda<sup>®</sup> (fentanyl) nasal spray
- Onsolis<sup>®</sup> (fentanyl buccal soluble film)
- Subsys<sup>™</sup> (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](http://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](http://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](http://www.TIRFREMSaccess.com) to create an account.
- Review the TIRF REMS Access Education Program materials available at [www.TIRFREMSaccess.com](http://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<sup>®</sup> 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](http://www.TIRFREMSaccess.com) or can be ordered by calling 1-866-822-1483:**

- Overview for Outpatient Pharmacies

**Current as of 6/1/2013. This document may not be part of the latest approved REMS.**

The TIRF REMS Access Program: Dear Outpatient Pharmacy Letter

- 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](http://www.TIRFREMSaccess.com).

**To access the above information and to enroll in the TIRF REMS Access program, visit [www.TIRFREMSaccess.com](http://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<sup>®</sup> 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](http://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](http://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”**

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Dear Inpatient Pharmacy:

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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](http://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](http://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.