Initial REMS Approval: 12/2011

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

Reference ID: 3064692

I. GOALS

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

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

II. REMS ELEMENTS

A. Medication Guide

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

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

B. Elements to Assure Safe Use

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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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

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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.

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Attachment 1:

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

- ABSTRAL® (fentanyl) sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge
- FENTORA® (fentanyl citrate) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl buccal soluble film)
- Approved generic equivalents of these products are also covered under this program.

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

What is the TIRF REMS Access Program?

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

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

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

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

TIRF REMS Access Program Enrollment:

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

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

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

Prescriber Education & Enrollment (Outpatient Use)

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

Enrollment Options:

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

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

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

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

Patient Program Requirements:

Patient Education - *All Prescribers Who Prescribe to Outpatients*

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

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

Prescribing

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

Monitoring

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

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

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

TIRF REMS Access Program Education Program for Prescribers and Pharmacists

Products Covered Under this Program:

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

TIRF REMS Access Education Program:

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

TIRF REMS Access Program Goals:

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

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

2. Preventing inappropriate conversion between fentanyl products.

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

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose.

TIRF REMS Access Education Program

Overview

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

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

TIRF REMS Access Education Program

Overview (cont.)

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

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

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

Appropriate Patient Selection

Indication:

- TIRF medicines are indicated only for the management of breakthrough pain in adult patient with cancer ~~18 years of~~ 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	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of FENTORA per breakthrough pain episode. Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.	For patients being converted from ACTIQ, prescribers must use the Initial Dosing Recommendations for Patients on ACTIQ found in Table 1 of the Full Prescribing Information. The doses of FENTORA in the table are starting doses and not intended to represent equianalgesic doses to ACTIQ	Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet. During titration, patients can be instructed to use multiple tablets (one on each side of the mouth in the upper/lower buccal cavity) until a maintenance dose is achieved.
Lazanda® (fentanyl) nasal spray	Always100 mcg.	Only use LAZANDA once per breakthrough pain cancer episode; i.e. do not redose LAZANDA within an episode. Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA.	Limit LAZANDA use to 4 or fewer doses per day.	If adequate analgesia was not obtained with the first 100 mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.

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

Products Covered Under this Program (cont.):

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

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

Patient Counseling

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

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

Tell the patient:

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

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

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

Patient Counseling

Tell the patient (cont.):

- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.
- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, since it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

Effective Patient Management & Follow-up

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

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

Transmucosal Immediate Release Fentanyl (TIRF) REMS

Knowledge Assessment

For real-time processing of this Knowledge Assessment electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please answer all questions below, fill in the fields at the bottom of the form, and fax all pages to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

Question 1
The patients described are all experiencing breakthrough pain, but ONE is not an appropriate patient for a TIRF medicine. Which patient should not receive a TIRF medicine?
Select one option

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

Question 2
The patients described are experiencing breakthrough pain. A TIRF medicine is NOT appropriate for one of them. Which patient should not receive a TIRF medicine?
Select one option.

A. Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past 2 months.
B. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
C. Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
D. Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.

DEA Number or Chain ID:_____

Question 3

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

Select one option.

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

Question 4

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

Select one option.

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

Question 5

A patient is starting titration with a TIRF medicine. What dose must they start with?

Select one option.

A. An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
B. The dose that the prescriber believes is appropriate based on their clinical experience.
C. The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
D. The median available dose.

Question 6

A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes, the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do?

Select one option.

A. Take another (identical) dose of the TIRF medicine immediately.
B. Take a dose of an alternative rescue medicine.
C. Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
D. Double the dose and take immediately.

DEA Number or Chain ID:_____

Question 7
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Which of the following statements is true?
Select one option.

A. The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
B. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.
C. There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
D. The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.

Question 8
Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Which of the following counseling statements is not correct?
Select one option.

A. TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.
B. Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.
C. Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.
D. Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.

Question 9
There is a risk of fatal overdose with inappropriate use of TIRF medicines. Which one of the following answers is most accurate?
Select one option.

A. TIRF medicines can be fatal if taken by children.
B. TIRF medicines can be fatal if taken by anyone for whom it is not prescribed.
C. TIRF medicines can be fatal if taken by anyone who is not opioid-tolerant.
D. All of the above.

Question 10
Which one of the following statements is most accurate regarding the safe storage and disposal of TIRF medicines?
Select one option.

A. TIRF medicines should be kept in a safe place and out of the reach of children.
B. TIRF medicines should be protected from theft.
C. Dispose of partially used or unneeded TIRF medicine by following the TIRF medicine-specific procedure specified in the Medication Guide.
D. All of the above.

DEA Number or Chain ID:_____

Question 11
Conversion between ONLY two TIRF medicines has been established and is described in the Prescribing Information for which two products?
Select one option.

A. Lazanda to Actiq
B. Actiq to Fentora
C. Abstral to Fentora
D. Fentora to Actiq

Prescriber / Authorized Pharmacy Representative _____

DEA Number _____

Chain ID (if applicable) _____

DEA Number or Chain ID:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program Prescriber Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1, 2 and 3 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

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

1. I have reviewed the TIRF REMS Access Education Program, including the Full Prescribing Information for each TIRF medicine, and I have completed the Knowledge Assessment. I understand the responsible use conditions for TIRF medicines and the risks and benefits of chronic opioid therapy.
2. I understand that TIRF medicines can be abused and that this risk should be considered when prescribing or dispensing TIRF medicines in situations where I am concerned about an increased risk of misuse, abuse, or overdose, whether accidental or intentional.
3. I understand that TIRF medicines are indicated only for the management of breakthrough pain in patients with cancer, who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.
4. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
5. I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.
6. I understand that converting patients from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis. I understand that TIRF medicines are not interchangeable with each other, regardless of route of administration, and that conversion may result in fatal overdose, unless conversion is done in accordance with labelled product-specific conversion recommendations (refer to the 'List of TIRF Medicines Available only through the TIRF REMS Access program' in Attachment 1). Note, a branded TIRF medicine and its specific generic product(s) are interchangeable.
7. I understand that the initial starting dose for TIRF medicines for <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.
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 <u>each</u> new patient, before writing the patient's first prescription for a TIRF medicine, and renew the agreement every two (2) years.
10. I will provide a completed, signed copy of the Patient-Prescriber Agreement (PPAF) to the patient and retain a copy for my records. I will also provide a completed, signed copy to the TIRF REMS Access program (through the TIRF REMS Access website or by fax) within ten (10) working days.

Prescriber Name* (please print):_____

11. At all follow-up visits, I agree to assess the patient for appropriateness of the dose of the TIRF medicine, and for signs of misuse and abuse.
12. I understand that TIRF medicines are only available through the TIRF REMS Access program. I understand and agree to comply with the TIRF REMS Access program requirements for prescribers.
13. I understand that I must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.

Prescriber Information:

Prescriber Signature* _____ **Date*** _____

First Name* _____ **Last Name*** _____ **Credentials** _____

State License Number* _____

Site Name* _____ **State Issued*** _____

Address* _____ **DEA Number*** _____

City* _____ **National Provider Identifier (NPI)*** _____

State* _____ **ZIP*** _____

Phone Number* _____

Fax Number* _____

Email* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

If you have additional practice sites, state licenses or DEA numbers that you may use when prescribing TIRF medicines, please provide the information requested below.

Prescriber Name* (please print):_____

Additional Prescriber Information (All Fields Required)

Site Name* _____	**State License Number*** _____
Address* _____	**State Issued*** _____
City* _____	**DEA Number*** _____
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	
Site Name* _____	**State License Number*** _____
Address* _____	**State Issued***
City* _____	**DEA Number***
State* _____ **ZIP*** _____	
Phone Number* _____	
Fax Number* _____	
***Required Fields**	

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

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program Patient-Prescriber Agreement Form

For real-time processing of 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" and I agree to its terms and conditions which authorize my healthcare providers to disclose my personal and medical information to the makers of TIRF medicines (TIRF Sponsors) and their agents and contractors, for the purpose of administering the TIRF REMS Access program.

Patient (*Required Fields):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Date of Birth (MM/DD/YYYY)* _____ **Phone Number*** _____
State* _____ **ZIP*** _____

Patient Representative (if required):

Signature* _____ **Date*** _____
First Name* _____ **Last Name*** _____
Relationship to Patient* _____

Patient Privacy Notice for the TIRF REMS Access Program – I allow each of my doctors, pharmacists, and other healthcare providers to share personal information, that can be used to identify myself. This includes information about my medical problems, diseases, treatment, lab and prescription information, name, address and telephone number. This information is my "Health Information"

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

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

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

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

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

Prescriber Name* (please print):_____

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

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

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

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

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

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

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

Prescriber Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program or TIRF REMS Access Program

An Overview for Patients and Caregivers

What are TIRF medicines?

TIRF medicines are prescription medicines that contain the drug fentanyl. TIRF medicines are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid (narcotic) pain medicines around-the-clock for cancer pain. Please refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

What is the TIRF REMS Access Program?

A REMS, or Risk Evaluation and Mitigation Strategy, is a program to help manage known or potential serious risks of a medicine. Because TIRF medicines have a risk of misuse, abuse, addiction, and overdose, the Food and Drug Administration (FDA) has required that all TIRF medicines only be available through a restricted program called the TIRF REMS Access program. Healthcare professionals who prescribe your TIRF medicine, as well as pharmacies that fill your prescriptions for TIRF medicine, must be enrolled in the program.

Why is the TIRF REMS Access Program needed?

Your TIRF medicine contains fentanyl, which can cause life threatening breathing problems, which can lead to death. These life threatening breathing problems can occur if you take more TIRF medicine than your healthcare provider tells you to take, or if the TIRF medicine is taken by anyone other than you.

The TIRF REMS Access program provides training for prescribers and pharmacists to help them select patients for whom TIRF medicines are appropriate. The TIRF REMS Access program also helps your healthcare provider and pharmacist provide advice and guidance to you on the correct way to use your TIRF medicine, including how to store and dispose of it.

How do I participate in the program?

You or your caregiver will be required to read and sign the TIRF REMS Access Patient-Prescriber Agreement Form to participate in the program. Your healthcare provider will explain the Patient-Prescriber Agreement Form for the TIRF REMS Access program, which you must read and sign before receiving your prescription. Your healthcare provider will ensure that the signed form is submitted to the program. You will be part of the program when your first prescription is filled at a participating pharmacy. Your healthcare provider can identify pharmacies in your area where you can bring your prescription. When you are part of the program, you can start treatment with the TIRF medicine that your healthcare provider has prescribed for you.

Reference ID: 3064692

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**.

Reference ID: 3064692

TIRF REMS Access Program Frequently Asked Questions (FAQs)

I. ALL STAKEHOLDERS FAQs
II. PATIENT FAQs
III. OUTPATIENT PHARMACY FAQs
IV. PRESCRIBER FAQs
V. INPATIENT PHARMACY FAQs
VI. DISTRIBUTOR (WHOLESALER) FAQs

Reference ID: 3064692

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.

Reference ID: 3064692

The educational materials referenced above will be available to prescribers and pharmacies through the TIRF REMS Access program. In an outpatient setting, FDA-approved Medication Guides will be provided to patients by prescribers and pharmacists during counseling about the proper use of TIRF medicines.

Inpatient Use Only- Prescribers who prescribe TIRF medicines that will only be used in an inpatient setting (e.g., hospitals, hospices, or long-term care facilities) are not required to enroll in the TIRF REMS Access program. Similarly, patients who receive TIRF medicines in an inpatient setting are not required to enroll in the TIRF REMS Access program. Long term care and hospice patients who obtain their medications from outpatient pharmacies must be enrolled.

Why does the TIRF REMS Access program require prescriber enrollment for outpatient prescribing?

Prescriber enrollment is required to help ensure that prescribers receive education on the risks and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

To become enrolled, prescribers must review the TIRF REMS Access Education Program including the Full Prescribing Information and successfully complete the Knowledge Assessment.

Are there requirements for prescribers for inpatient use in the TIRF REMS Access program?

No. Healthcare providers who prescribe TIRF medicines for inpatient use only are not required to enroll in the TIRF REMS Access program.

Why does the TIRF REMS Access program require pharmacy enrollment?

Pharmacy enrollment is required to help ensure that pharmacists receive education on the risks and safe use of TIRF medicines. Additionally, the educational materials will help them understand the requirements of the TIRF REMS Access program.

Only enrolled pharmacies are eligible to receive shipments of TIRF medicines and/or to dispense prescriptions written by enrolled prescribers for outpatients. A designated authorized pharmacist must review the Education Program and successfully complete the Knowledge Assessment. Only then can the authorized pharmacist complete enrollment on behalf of the pharmacy. The authorized pharmacist will train other staff within the pharmacy in the appropriate dispensing of TIRF medicines according to the TIRF REMS Access program.

Prescriptions for outpatient use written by prescribers who are not enrolled in the REMS will not be authorized by the TIRF REMS Access program and TIRF medicines will not be dispensed to an outpatient who is not enrolled.

Why does the TIRF REMS Access program require a Patient-Prescriber Agreement Form?

The TIRF REMS Access program requires all prescribers to complete and sign a TIRF REMS Access Patient-Prescriber Agreement Form with each new patient, before writing the patient's first TIRF prescription. The Patient-Prescriber Agreement Form helps to ensure that each patient for whom the TIRF medicine has been prescribed is appropriately counselled on the safe

use and storage of the TIRF medicine. The prescriber must keep a copy of the signed Patient-Prescriber Agreement Form in the patient's chart, give a copy to the patient and submit a copy to the TIRF REMS Access program within 10 working days.

A Patient-Prescriber Agreement Form is not required for inpatient use of TIRF medicines

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
The TIRF REMS Access homepage contains a feature called "Pharmacy Lookup" that is available for prescribers, and distributors, to look up and find enrolled pharmacies. This information can also be obtained by calling the TIRF REMS Access call center at **1-866-822-1483**.

How can I obtain TIRF REMS Access program materials?
All TIRF REMS Access education materials and forms are available and can be downloaded from www.TIRFREMSaccess.com using Adobe Acrobat Reader. Enrollment Forms and the Patient-Prescriber Agreement Forms can be completed online at www.TIRFREMSaccess.com after reviewing the Education Program and successfully completing the Knowledge Assessment. Materials are also available by calling the TIRF REMS Access call center at **1-866-822-1483** for assistance.

How do I contact the TIRF REMS Access program?
You can contact the TIRF REMS Access program by calling the TIRF REMS Access call center at **1-866-822-1483** or by written correspondence to: TIRF REMS Access, PO Box 29036, Phoenix, AZ 85038

How can I report Adverse Events?
Promptly report suspected adverse events associated with the use of a TIRF medicines including misuse, abuse, and overdose directly to the TIRF REMS Access program at **1-866-822-1483**. You also may report adverse event information to the FDA MedWatch Reporting System by telephone at (800) FDA-1088 or by mail using Form 3500, available at www.fda.gov/medwatch.

II. PATIENT FAQs

As a patient, how do I participate with the TIRF REMS Access program?
You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an 'enrolled' pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine.

Patients in an inpatient setting are not required to participate in the TIRF REMS Access program in order to be prescribed and dispensed TIRF medicines for inpatient use only. However, if your prescriber gives you a prescription for a TIRF medicine to take at home once you leave the inpatient facility, you must sign a Patient-Prescriber Agreement Form with your prescriber to participate in the TIRF REMS Access program.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
Only pharmacies that are enrolled in the TIRF REMS Access program can dispense TIRF medicines. Your prescriber can help you find a participating pharmacy. You can also get this information by calling the TIRF REMS Access program at **1-866-822-1483**.

III. OUTPATIENT PHARMACY FAQs

How does a pharmacy enroll in the TIRF REMS Access program?

The authorized pharmacist must review the Education Program, successfully complete the Knowledge Assessment and complete the Outpatient Pharmacy Enrollment Form through the website or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

The authorized pharmacist must ensure the pharmacy enables their pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and run the standardized validation test transaction(s) to validate the system enhancements.

Before a pharmacy is able to dispense prescriptions to outpatients, an enrollment form must be received either via the website by faxing or mailing it to the TIRF REMS Access program for each pharmacy requesting enrollment in the program. (See information on pharmacy chain enrollment below.)

If I have previously enrolled in an individual TIRF REMS do I need to enroll in the shared TIRF REMS?

Outpatient Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not to agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- Once you have logged in, review your account information and make any necessary updates. You are required to agree to the shared program terms and conditions to complete enrollment for the new shared program.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Chain Pharmacy

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF

REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
    - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

If the patient's prescription is denied, will the TIRF REMS Access system explain the reason?
All TIRF prescriptions (excluding inpatient use), must go through an electronic verification system via the pharmacy management system. When a prescription is denied, an appropriately coded message will be displayed on the pharmacy management system. For assistance, please call the TIRF REMS Access call center at **1-866-822-1483** for any information related to your denial.

How does a pharmacy obtain TIRF Medicines from a distributor?
Only enrolled distributors are allowed to distribute TIRF medicines to enrolled pharmacies. The TIRF REMS Access program provides frequently updated lists of all pharmacies that are currently enrolled in the program that distributors can use to verify enrollment before distributing TIRF medicines to a pharmacy.

How does a pharmacy chain enroll in the TIRF REMS Access program?
An authorized chain pharmacy representative completes the TIRF REMS Access training, Knowledge Assessment and enrollment on behalf of all the pharmacies within the chain and then documents and manages training of all pharmacy staff by the chains' internal processes. Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.

As part of enrollment, a chain pharmacy must enable the pharmacy management system to support communication with the TIRF REMS Access system. For further information or to enroll, access the TIRF REMS Access website at www.TIRFREMSaccess.com or call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

IV. PRESCRIBER FAQs

What is the enrollment process?

The prescriber must review the Education Program, successfully complete the Knowledge Assessment and complete an enrollment form through the website, or complete and fax the signed Enrollment Form and Knowledge Assessment to the TIRF REMS Access program at **1-866-822-1487**.

A prescriber may obtain an enrollment form online from the TIRF REMS Access website (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

The program requires that a signed enrollment form and Knowledge Assessment be received by the TIRF REMS Access program for each prescriber who requests enrollment. Only healthcare providers who will prescribe TIRF medicines for outpatient use are required to be enrolled in the TIRF REMS Access program.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows prescribing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com and prescribe all TIRF medicines.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is available on the shared TIRF REMS Access website or by calling **1-866-822-1483**. We recommend that you review the TIRF REMS Access Education Program for information on all the products that are available under the TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two (2) years after your last enrollment in an individual REMS program if you wish to continue prescribing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Where do I find a list of local pharmacies that participate in the TIRF REMS Access program?
A list of participating pharmacies can be found on the TIRF REMS Access website homepage under the link “Pharmacy Lookup”. You may also call **1-866-822-1483**.

Patients can find a participating pharmacy by calling the TIRF REMS Access program at **1-866-822-1483**.

Can I write an order for TIRF Medicines for inpatient use?
Yes, prescribers can write orders for TIRF medicines for inpatient use without the prescriber or the patient being enrolled in the TIRF REMS Access program. However, the inpatient pharmacy

needs to be enrolled in the TIRF REMS Access program to receive and dispense TIRF medicines to inpatients in the healthcare facility.

If a prescriber is discharging a patient with a TIRF medicine prescription, intended to be filled by an outpatient pharmacy, then the prescriber must be enrolled in the TIRF REMS Access program and complete a Patient-Prescriber Agreement Form. The prescription for outpatient use can only be filled through an enrolled outpatient pharmacy.

Additional information on the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

V. INPATIENT PHARMACY FAQs

How do I enroll as an inpatient pharmacy?
To enroll, the inpatient pharmacy must designate an authorized pharmacist who will review the required Education Program and successfully complete the Knowledge Assessment for the TIRF REMS Access program. Upon successful completion of the Knowledge Assessment, the authorized pharmacist will complete and sign the Inpatient Pharmacy Enrollment Form through the website (www.TIRFREMSaccess.com). The Knowledge Assessment and Enrollment Form may also be completed, signed, and faxed to the TIRF REMS Access program at 1-866-822-1487.

Additional information about the TIRF REMS Access Education Program and enrollment can be obtained through the TIRF REMS Access program (www.TIRFREMSaccess.com) or by calling **1-866-822-1483**.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you are already enrolled in an individual REMS program for at least one TIRF medicine, you will be automatically transitioned to the shared TIRF REMS Access program.

- Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing this class of products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Can inpatient pharmacies obtain TIRF Medicines in a Healthcare Facility?
Yes. However, the inpatient pharmacy within or associated with the healthcare facility must be enrolled in the TIRF REMS Access program before inpatient pharmacies can purchase TIRF medicines.

Additional information can be obtained from www.TIRFREMSaccess.com or by calling the TIRF REMS Access call center at **1-866-822-1483**.

VI. DISTRIBUTOR (WHOLESALER) FAQs

Does a distributor have to enroll in the TIRF REMS Access program?
Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.

If I have previously enrolled in an individual REMS do I need to enroll in the shared TIRF REMS Access Program?
If you have previously enrolled in an individual TIRF REMS program, your enrollment information will be automatically entered into the new shared TIRF REMS program.

- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
    - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS within two years after your last enrollment in an individual REMS if you wish to continue distributing these products. You will be notified by the REMS program in advance of the need to re-enroll.

By enrolling in the shared TIRF REMS Access program a distributor/wholesaler may distribute all of the TIRF medicines. However, the decision to maintain a direct selling relationship with the wholesaler/distributor is at the sole discretion of each individual TIRF manufacturer.

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

How can enrolled distributors access a list of pharmacies that participate in the TIRF REMS Access program?
After enrollment, distributors can access the current list of enrolled pharmacies by:

- Downloading from a secure FTP site (you will be contacted regarding the TIRF REMS Access secure FTP site once your enrollment is complete).
- Utilizing the feature “Pharmacy Look Up” on a password protected section of the TIRF REMS Access website (www.TIRFREMSaccess.com)
- Calling the TIRF REMS Access call center at **1-866-822-1483**.

TIRF REMS Access Web Prototype

IMPORTANT SAFETY INFORMATION

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

TIRF REMS ACCESS

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

Log In

Selected Important Safety Information

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

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

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

TIRF medicines are indicated only for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
Patients considered opioid-tolerant are those who are taking:

- at least 60 mg of oral morphine/daily
- at least 25 mcg transdermal fentanyl/hour
- at least 30 mg of oral oxycodone daily
- at least 8 mg oral hydromorphone daily
- at least 25 mg oral oxymorphone daily
- or an equianalgesic dose of another opioid daily for a week or longer.

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

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

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

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

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

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

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

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

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

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

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

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

- Print copies from the TIRF REMS Access program website at www.TIRFREMSaccess.com.
- Contact the TIRF REMS Access program at 1-866-822-1483.

Reference ID: 3064692

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

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.

Reference ID: 3064692

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 <u>already enrolled</u> 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 <u>any</u> 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 an individual REMS program

- Select an authorized pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Outpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

- Enable the pharmacy management system to support communication with the TIRF REMS Access program, using established telecommunication standards, and run the standardized validation test transactions to validate the system enhancements.

Pharmacy Program Requirements:

Training Other Pharmacy Staff

- Ensure that all pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training as a minimum.

Enrollment Confirmation

- Confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim from your pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment you must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicine appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

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

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

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

What is the TIRF REMS Access Program?

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

To dispense TIRF medicines, your pharmacy chain will need to be enrolled in the TIRF REMS Access program.

TIRF medicines, which may have previously been available under individual product REMS programs, will be transitioned to the shared TIRF REMS Access program.

Chain Pharmacy Enrollment

To reduce the risks of inappropriate patient selection and to ensure appropriate dosing and administration of TIRF medicines, chain pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized chain pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the chain.

Chain pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program but will need to execute a TIRF REMS Access contract with their switch provider before they can order and dispense all TIRF medicines.

The authorized chain pharmacy representative who is enrolling on behalf of the chain pharmacy must acknowledge that training will occur for all pharmacy staff involved in the dispensing of TIRF medicines. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**. Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized chain pharmacy representative, on behalf of the chain pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy within the chain in the TIRF REMS Access program before shipping TIRF medicines. The chain pharmacy will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Only chain pharmacies that are enrolled in the TIRF REMS Access program will be eligible to purchase or dispense TIRF medicines. In addition, pharmacies within the chain will only be able to dispense prescriptions if the patient and the prescriber are enrolled in the TIRF REMS Access program. Patients will be automatically enrolled in the TIRF REMS Access program upon processing of their first TIRF prescription. If the patient and/or the prescriber are not

Reference ID: 3064692

enrolled in the TIRF REMS Access program, the TIRF prescription will not be authorized by the TIRF REMS Access program, the chain pharmacy will receive a rejection message and the prescription will not be dispensed to the patient.

NOTE: There are different requirements for inpatient pharmacies that only dispense for inpatient use. Please refer to "An Overview for Inpatient Pharmacies" for more information.

Overview of the TIRF REMS Access Program for Chain Pharmacies: Steps for Enrollment and Program Requirements

Chain Pharmacy Education, Enrollment & Pharmacy Management Systems

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

Enrollment Options:

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

- **Beginning mm/dd/yyyy**, your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to execute a TIRF REMS Access program contract with their switch provider before you can order and dispense all TIRF medicines.
  - Once the program is available, you will have six months to sign the new TIRF REMS Access program contract. Until you sign the new contract, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not sign the new contract within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- You will be required to re-enroll in the shared TIRF REMS Access program two years after your last enrollment in an individual TIRF REMS if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

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

- Select an authorized chain pharmacy representative to establish and oversee the TIRF REMS Access program requirements.
- Execute a TIRF REMS Access contract with your switch provider.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account and complete registration at the corporate level on behalf of your individual pharmacies.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Chain Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.
- Ensure the chain pharmacy enables the pharmacy management system to support communication with the TIRF REMS Access system, using established telecommunication standards, and ensure that the chain pharmacy runs the standardized validation test transactions to validate the system enhancements once on behalf of all their stores.

Chain Pharmacy Program Requirements:

Training Chain Pharmacy Staff

- Ensure that all chain pharmacy staff involved in the processing and dispensing of TIRF medicines have been trained to only dispense TIRF medicines in accordance with the TIRF REMS Access program requirements.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- Ensure that this training is documented and retained by the chain pharmacy. This documentation should include the pharmacist/pharmacy staff member's name, the date training was completed and the method of training, as a minimum.
- The list of pharmacy sites that have been trained should be updated by the chain Authorized Representative on the Chain Pharmacy Dashboard where all chain stores are listed at www.TIRFREMSaccess.com. This list should include the required Pharmacy Information for each pharmacy site.

Enrollment Confirmation

- Each pharmacy site must confirm that the prescriber and patient are enrolled in the TIRF REMS Access program with each prescription by submitting a pharmacy billing claim via the chain pharmacy practice management system. Submitting a claim for a patient's first TIRF prescription through the pharmacy management system will automatically enroll that patient in the TIRF REMS Access program.
- To allow the REMS system to confirm prescriber and patient enrollment the chain pharmacy practice management system must populate the following fields in the pharmacy billing claim:
    - Patient First Name,
    - Patient Last Name,
    - Patient Date of Birth,
    - Patient ZIP / Postal Zone,
    - Quantity Dispensed,
    - Days Supply,
    - Prescriber ID,
    - Prescriber Last Name
- If the prescriber or patient enrollment is not validated, or if any other rejection message is received that prevents the prescription being filled, contact the TIRF REMS Access call center at **1-866-822-1483** for further instruction.

Dispensing

- Receive approval from the TIRF REMS Access program and then prepare, label and dispense the medication.

Counseling patients and provision of Medication Guide

- Advise the patient on how to take, store and dispose of TIRF medicines appropriately.
- Provide a copy of the product specific Medication Guide to the patient with each prescription.

Monitoring

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

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

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
An Overview for Inpatient Pharmacies (e.g. hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use).

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

In order for inpatient pharmacies to dispense TIRF medicines for inpatient use only, the inpatient pharmacy must be enrolled in the TIRF REMS Access program. For inpatient administration of TIRF medicines, patient and prescriber enrollment in the TIRF REMS Access program is not required. Inpatient pharmacies must not dispense TIRF medicines for outpatient use.

Inpatient Pharmacy Enrollment
In order to reduce the risk of inappropriate patient selection, and to ensure appropriate dosing and administration of TIRF medicines, inpatient pharmacies will need to be enrolled in the TIRF REMS Access program. Enrollment requires an authorized pharmacy representative to complete the TIRF REMS Access Education Program and Knowledge Assessment on behalf of the pharmacy.

Inpatient pharmacies already enrolled in an individual REMS program for at least one TIRF medicine will automatically be transitioned to the shared TIRF REMS Access program. You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

The authorized pharmacist must ensure that inpatient pharmacists are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the TIRF REMS Access Education Program. The TIRF REMS Access Education Program is available online at the TIRF REMS Access program website www.TIRFREMSaccess.com or by contacting the TIRF REMS Access call center at **1-866-822-1483**.

Once the TIRF REMS Access Education Program and Knowledge Assessment are completed, the authorized pharmacist, on behalf of the pharmacy, will be required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements.

The supply of TIRF medicines to pharmacies is controlled by enrolled distributors, who will verify the current enrollment status of the pharmacy in the TIRF REMS Access program before shipping TIRF medicines. Pharmacies will be required to re-enroll in the TIRF REMS Access program every two years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

Reference ID: 3064692

Important Information about Outpatient Pharmacies within the Facility
Outpatient pharmacies, within or associated with the healthcare facility, that provide dispensing services to outpatients **must be separately enrolled** in the TIRF REMS Access program and comply with the TIRF REMS Access program to dispense TIRF medicines to outpatients. Please refer to "An Overview for Outpatient Pharmacies" for more information. Additionally, any prescribers who prescribe TIRF medicines to outpatients must also be enrolled in the TIRF REMS Access program.

Overview of the TIRF REMS Access Program for Inpatient Pharmacies: Steps for Enrollment and Program Requirements

Inpatient Pharmacy Education and Enrollment

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

Enrollment Options:
Option 1: If you are already enrolled in at least one individual REMS program

- **Beginning mm/dd/yyyy** your enrollment information will be automatically entered into the new shared TIRF REMS Access program. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.
  - The user ID and password you use to initially log on will become your permanent user ID and password for the shared TIRF REMS Access program.
- The TIRF REMS Access Education Program is also available on the shared TIRF REMS Access website. Alternatively, you can request this information by calling **1-866-822-1483**.
- You will be required to re-enroll in the shared TIRF REMS two (2) years after your last enrollment in an individual REMS program if you wish to continue dispensing these products. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.

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

- Select an authorized pharmacist to establish and oversee the TIRF REMS Access program requirements.
- Access the TIRF REMS Access program at www.TIRFREMSaccess.com to create an account.
- Review the TIRF REMS Access Education Program materials available at www.TIRFREMSaccess.com and successfully complete the Knowledge Assessment.
- Enroll in the TIRF REMS Access program by completing the Inpatient Pharmacy Enrollment Form and re-enroll every two (2) years. You will be notified by the TIRF REMS Access program in advance of the need to re-enroll.
- If you are unable to enroll online, please call the TIRF REMS Access program call center at **1-866-822-1483** for further assistance.

Inpatient Pharmacy Program Requirements:

Implementation

- The authorized inpatient pharmacist must establish or oversee the system, order sets, protocols, and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program.
- The authorized inpatient pharmacist must ensure that inpatient pharmacists and other relevant inpatient staff are educated on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program, as described in the Education Program.
    - Pharmacy staff can register online to access the Education Program and take the Knowledge Assessment for training purposes.
- The authorized inpatient pharmacist must ensure that the inpatient pharmacy does not sell, loan or transfer any TIRF medicines to any other pharmacy, institution, distributor, or prescriber.
- Inpatient pharmacies may not dispense TIRF medicines for outpatient use.

Monitoring

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

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

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Outpatient Pharmacy Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 - 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

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

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

Pharmacist Name* (please print):_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Please note: If you are a Chain pharmacy, please complete the Chain Pharmacy Enrollment Form which can be found on www.TIRFREMSaccess.com or call the TIRF REMS Access program at 1-866-822-1483.

Authorized Pharmacy Representative:

Authorized Pharmacist Signature* _____ **Date** _____

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

Phone Number* _____ **Email*** _____

Outpatient Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP*** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

For additional Medicaid IDs that you may use when dispensing TIRF medicines, please complete below:

Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____
Medicaid ID _____ **State Issued** _____

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

Pharmacist Name* (please print):_____

The TIRF REMS Access Program Additional Terms and Conditions

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

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

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

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

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

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

Pharmacist Name* (please print):_____

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

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

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

Pharmacist Name* (please print):_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Chain Pharmacy Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1, 2, 3 and 4 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

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

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

Chain ID*:_____

13. I understand that our pharmacy must re-enroll in the TIRF REMS Access program and successfully complete the enrollment requirements every two (2) years.
14. I understand that TIRF medicines are only available through the REMS program. I understand that the pharmacy must comply with the TIRF REMS Access program requirements for outpatient pharmacies and the terms of the agreement that follow this form.

Authorized Chain Pharmacy Representative:

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

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

Phone Number* _____ **Email*** _____

Chain Pharmacy Information:

Pharmacy Name* _____ **Chain ID*** _____

Address* _____ **Phone Number*** _____

City* _____ **Fax Number*** _____

State* _____ **ZIP*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

After submitting this form, you will receive a fax or email with instructions on how to submit test transaction(s) to the TIRF REMS Access program to ensure that your pharmacy management system has been successfully configured to allow for communication with the TIRF REMS Access program.

After successful completion of the test transaction(s) you will receive enrollment confirmation via fax or email.

Pharmacy sites that have been trained can then be updated to an enrolled status through the Chain Pharmacy Dashboard which will list all chain stores at www.TIRFREMSaccess.com

The following pharmacy information will need to be provided for each trained pharmacy site.

Pharmacy Information:

Pharmacy Name* _____ **DEA Number*** _____

Address* _____ **National Provider Identifier (NPI)*** _____

City* _____ **Medicaid ID** _____

State* _____ **ZIP** _____ **State Issued** _____

Phone Number* _____ **NCPDP Number*** _____

Fax Number* _____ **Store Number*** _____

***Required Fields**

Chain ID*:_____

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

Chain ID*:_____

The TIRF REMS Access Program Additional Terms and Conditions

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

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

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

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

This includes any future drug deemed by FDA to be included in the TIRF REMS Access Program to Providers via submission of all billing and reversal request.

Pharmacy acknowledges that billing request for the Program Drug will not pass to the payer, or cash prescription processor, if the prescriber, pharmacy or patient registration is not verified.

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

Chain ID*:_____

In addition, Pharmacy authorizes Program Sponsor and its contracting Providers, to receive from wholesaler(s) of the Program Drug(s) distribution and purchasing data, including 867 data, with respect to the Program Drug(s).

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

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

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

Chain ID*:_____

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program

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

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487.

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

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

Pharmacist Name* (please print):_____

Authorized Inpatient Pharmacist

Signature* _____ **Date** _____

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

Phone Number* _____ **Email*** _____

***Required Fields**

Inpatient Pharmacy Information

Pharmacy Name* _____

Address* _____ **DEA Number*** _____

City* _____ **Pharmacy License Number*** _____

State* _____ **ZIP*** _____ **Phone Number*** _____

Fax Number* _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **Email**

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

Pharmacist Name* (please print):_____

Important Drug Warning

Subject: Announcement of a single shared REMS (Risk Evaluation and Mitigation Strategy) program for all Transmucosal Immediate Release Fentanyl (TIRF) products due to the potential risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

The TIRF REMS Access program is a Food and Drug Administration (FDA) required risk management program

Dear Outpatient Pharmacy:

The purpose of this letter is to make you aware of a change from individual REMS programs to a shared REMS program (the TIRF REMS Access program) and to provide guidance on enrollment into the new shared REMS program **beginning mm/dd/yyyy**. The individual REMS programs are being converted to the TIRF REMS Access program to reduce the burden on the healthcare providers and the healthcare system of having multiple individual programs. The products covered under this new program include:

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

This new shared program replaces the individual product REMS that were previously available, and any prescribers, pharmacies, patients and distributors enrolled in these programs will be automatically transitioned to the new shared REMS. Outpatient pharmacies from individual product REMS will be automatically transitioned to the new shared REMS, **beginning mm/dd/yyyy**, but will need to agree to shared program terms and conditions before they can order and dispense all TIRF medicines. If you have not enrolled in one or more of these individual REMS programs and, if any of these products are dispensed for outpatient use in your pharmacy, you must enroll your pharmacy in the shared TIRF REMS Access program.

Outpatient Pharmacy Action:

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

- Your enrollment information will be automatically entered into the new shared TIRF REMS Access program, but you will need to agree to the shared program terms and conditions before you can order and dispense all TIRF medicines. Your enrollment in the shared TIRF REMS Access program allows dispensing of all TIRF medicines that are covered under the TIRF REMS Access program. The website for the shared TIRF REMS Access program can be accessed at www.TIRFREMSaccess.com.
    - Once the program is available, you will have six months to agree to the shared program terms and conditions. Until you agree to the shared program terms and conditions, you will be able to dispense those TIRF medicines with an individual REMS program, in which you were previously enrolled. However, if you do not agree to the shared program terms and conditions within six months, you will no longer be able to order or dispense any TIRF medicine.
- You can use your existing secure user ID and password from any one of your individual REMS programs to access the TIRF REMS Access website at www.TIRFREMSaccess.com.

Reference ID: 3064692

  - 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

Reference ID: 3064692

- 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.

Reference ID: 3064692

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.

Reference ID: 3064692

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

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

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

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

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

Adverse Reactions

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

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

Adverse Event Reporting

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

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the appropriate Medication Guide for the TIRF medicine you prescribe/dispense to your patient.

Reference ID: 3064692

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

Reference ID: 3064692

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 – [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.

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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”*

Reference ID: 3064692

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.

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- 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

Reference ID: 3064692

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.

Reference ID: 3064692

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.

Reference ID: 3064692

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

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

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

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

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

Adverse Reactions

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

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

Adverse Event Reporting

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

Medication Guide

It is important that you discuss the risks of TIRF medicines with your patients and encourage them to read the relevant Medication Guide. The Medication Guide provides important information on the safe and effective use of TIRF medicines and you will need to review the

Reference ID: 3064692

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

Reference ID: 3064692

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

The Transmucosal Immediate Release Fentanyl (TIRF) REMS Access Program
Wholesaler / Distributor Enrollment Form

For real-time processing of this enrollment form electronically, please go to www.TIRFREMSaccess.com and 'Log In' (if you have previously enrolled in a REMS program for one of the TIRF medicines) or 'Create an Account' to get started.

To submit this form via fax, please complete all required fields below and fax pages 1 and 2 to 1-866-822-1487. You will receive enrollment confirmation via email or fax.

TIRF medicines are available only through a FDA mandated REMS (Risk Evaluation and Mitigation Strategy), a restricted distribution program, called the TIRF REMS Access program. Under the TIRF REMS Access program, only prescribers, pharmacies, wholesalers / distributors and patients enrolled in the program are able to prescribe, dispense, distribute, purchase or receive TIRF medicines. Refer to the 'List of TIRF Medicines Available Only through the TIRF REMS Access Program' in Attachment 1.

Under the TIRF REMS Access program, wholesalers / distributors must verify the current enrollment of a pharmacy in the TIRF REMS Access program prior to distributing a TIRF medicine to that pharmacy. If the pharmacy location is not enrolled, the distributor must not fill any orders for TIRF medicines until enrollment can be confirmed.

The current list of enrolled pharmacies may be accessed via:

- receipt of a complete pharmacy registry daily in a mutually agreed format,
- a daily download from a secure FTP site,
- a password protected section of the website (www.TIRFREMSaccess.com), or
- by calling 1-866-822-1483.

Your company will receive login information (unique secure user ID and password) to access the TIRF REMS Access program website and you will be contacted regarding the secure FTP site once your enrollment is complete.

The Wholesaler / Distributor understands that TIRF medicines are only available through the TIRF REMS Access program and acknowledges that they will comply with the following program requirements:

1. The Wholesaler / Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program.
2. The Wholesaler / Distributor will ensure that TIRF medicines are only distributed to pharmacies whose enrollment has been verified in the TIRF REMS Access program.
3. The Wholesaler / Distributor will provide complete unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program, including information on shipments to enrolled pharmacies.
4. The Wholesaler / Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF Medicines are distributed in accordance with the program requirements.

Authorized Representative Name* (please print):_____

Authorized Wholesaler / Distributor Representative:

Signature* _____ **Date** _____

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

Phone Number* _____ **Email*** _____

***Required Fields**

Wholesaler / Distributor Information:

Corporate Wholesaler / Distributor Name* _____ **DEA*** _____

Address* _____

City* _____

State* _____ **ZIP*** _____ **Email*** _____

Phone Number* _____ **Fax Number*** _____

***Required Fields**

Preferred Method of Communication (please select one): ☐ **Fax** ☐ **E-mail**

^ If a DEA number is not available at corporate enter N/A for DEA number in the field above and please provide a list of Distribution Centers with their DEA numbers below.

Distribution Centers (DC) Information
Please populate the information below for each of your Distribution Centers.

DC information:

DC Name	DEA	Address	City	State	Zip Code	Title	Contact First Name	Contact Last Name	Fax Number	Email

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

Authorized Representative Name* (please print):_____

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

/s/

BOB A RAPPAPORT
12/28/2011