



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

Education Program for Prescribers and Pharmacists

Products Covered Under this Program

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

TIRF REMS Access Education Program

Before you can enroll in the TIRF REMS Access program, you must review the Education Program, successfully complete the Knowledge Assessment, and sign the acknowledgement statements on the enrollment form.

The Education Program and Enrollment can be completed online at www.TIRFREMSaccess.com. The enrollment form may also be downloaded from the website on the Resources tab, completed and faxed into the program at **1-866-822-1487**.

Renewal of enrollment is required every 2 years. You will receive a reminder to renew your enrollment at the appropriate time.

Prescribers writing prescriptions for inpatient use only do not need to enroll in the TIRF REMS Access program.

TIRF REMS Access Program Goals:

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

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

TIRF REMS Access Education Program Overview

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

The program will address:

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

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

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

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

Appropriate Patient Selection

Indication

TIRF medicines are indicated only for the management of breakthrough pain in adult patients with cancer 18 years of age and older **who are already receiving and who are tolerant to regular opioid therapy for underlying persistent cancer pain.**

The only exception is for Actiq, and its generic equivalents, which are approved for cancer patients **16** years and older.

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

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.

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.

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.

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.

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 CYP3A4 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.

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.

Dosage and Administration				
Product	Initial dose	Max Dose Per Episode	Frequency	Titration
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.

Dosage and Administration				
Product	Initial dose	Max Dose Per Episode	Frequency	Titration
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).	<p>If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength.</p> <p>Patients should not take more than 2 doses of FENTORA per breakthrough pain episode.</p> <p>Patients must wait at least 4 hours before treating another breakthrough pain episode with FENTORA.</p>	<p>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</p>	<p>Closely follow patients and change the dosage level until adequate analgesia is achieved with a single tablet.</p> <p>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.</p>
Lazanda® (fentanyl) nasal spray	Always 100 mcg.	<p>Only use LAZANDA once per cancer breakthrough pain episode; i.e. do not redose LAZANDA within an episode.</p> <p>Patients must wait at least 2 hours before treating another episode of breakthrough pain with LAZANDA</p>	Limit LAZANDA use to 4 or fewer doses per day.	<p>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.</p> <p>Patients should confirm the dose of LAZANDA that works for them with a second episode of breakthrough pain.</p>

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Dosage and Administration

Product	Initial dose	Max Dose Per Episode	Frequency	Titration
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.	<p>Titrate using 200 mcg ONSOLIS film increments.</p> <p>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.</p> <p>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.</p>
Subsys™ (fentanyl) sublingual spray	Always 100 mcg.	<p>If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength.</p> <p>Patients should not take more than 2 doses of SUBSYS per episode of breakthrough pain</p>	Patients must wait at least 4 hours before treating another episode of breakthrough pain with SUBSYS.	Closely follow patients and change the dosage level until adequate analgesia is achieved using a single dose per episode of breakthrough cancer pain.

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

Patient Counseling

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

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

Tell the patient:

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

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

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

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 Access Program

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.

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.

DEA Number or Chain ID: _____



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.

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) _____