

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

# 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](http://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](http://www.TIRFREMSaccess.com).
- This Education Program is NOT a substitute for reading the Full Prescribing Information for each TIRF medicine.
- Please also review the Full Prescribing Information and familiarize yourself with the contents of the Medication Guide for each product prescribed.

# Appropriate Patient Selection

## Indication:

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

# Appropriate Patient Selection (cont.)

## Definition of Opioid Tolerance:

- Patients considered opioid-tolerant are those who are taking, **for one week or longer**, at least:
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - 60 mg oral hydrocodone/day
  - OR an equianalgesic dose of another oral opioid daily
- Patients must remain on around-the-clock opioids when taking a TIRF medicine.

## Appropriate Patient Selection (cont.)

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

### Contraindications:

- TIRF medicines **must not** be used in opioid non-tolerant patients or in
  - the management of acute or postoperative pain including headache/migraine, dental pain, or acute pain in the emergency department,
  - acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment,
  - known or suspected gastrointestinal obstruction, including paralytic ileus,
  - known hypersensitivity to fentanyl, or components of the TIRF medicine.

## **Appropriate Patient Selection (cont.)**

Please see each TIRF medicine's Full Prescribing Information for a full list of specific situations in which TIRF medicines are not indicated or are contraindicated.

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

# Determine Patient-Specific Risk Factors

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

- **TIRF medicines contain fentanyl, an opioid agonist** and Schedule II controlled substance. TIRF medicines contain fentanyl, which has a high potential for abuse similar to other opioids. TIRF medicines can be abused and are subject to misuse, addiction, and criminal diversion.
- These risks should be considered when prescribing or dispensing TIRF medicines in situations where the prescriber or pharmacist is concerned about an increased risk of misuse, abuse, addiction, or overdose.
- Risk factors for opioid abuse include:
  - A history of past or current alcohol or drug abuse
  - A history of psychiatric illness
  - A family history of illicit drug use or alcohol abuse
- Drug seeking tactics include:
  - emergency calls or visits near the end of office hours
  - refusal to undergo appropriate examination, testing, or referral
  - repeated loss of prescriptions
  - tampering with prescriptions

# Determine Patient-Specific Risk Factors

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

- reluctance to provide prior medical records or contact information for other treating healthcare providers
- “doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction
- Concerns about abuse and addiction should not prevent the proper management of pain.
- All patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even under appropriate medical use

# Determine Patient-Specific Risk Factors

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

- Measures to help limit abuse of opioid products:
  - Proper assessment of patients
  - Safe prescribing practices
  - Periodic re-evaluation of therapy
  - Proper dispensing and storage
  - Keeping detailed records of prescribing information
  - Keeping a signed TIRF REMS Access Patient-Prescriber Agreement Form
  - Informing patients/caregivers to protect against theft and misuse of TIRF medicines
- TIRF medicines, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.

# Determine Patient-Specific Risk Factors

## 2. Accidental Ingestion or Exposure

- **TIRF medicines contain fentanyl in an amount which can be fatal in:**
  - children,
  - individuals for whom it is not prescribed, and
  - those who are not opioid-tolerant
- Inform patients that these products have a rapid onset of action.
- Instruct patients to take steps to store TIRF medicines in a safe place out of reach of children.
- Prescribers and pharmacists must specifically question patients or their caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

# Determine Patient-Specific Risk Factors

## 2. Accidental Ingestion or Exposure (cont.)

- Any accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Talk with your patients about safe and appropriate storage and disposal of TIRF medicines.

# Determine Patient-Specific Risk Factors

## 3. Drug Interactions

- Fentanyl is metabolized mainly via the human cytochrome P450 (CYP3A4) isoenzyme system; therefore, potential drug interactions may occur when TIRF medicines are given concurrently with agents that affect CYP3A4 activity.
- Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may increase plasma concentrations of fentanyl and prolong opioid adverse reactions which may cause potentially fatal respiratory depression.
- Patients receiving TIRF medicines who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Dosage increases should be done conservatively.
- Due to the additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.

# Determine Patient-Specific Risk Factors

## 3. Drug Interactions (cont.)

- The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
- Monoamine Oxidase Inhibitors (MAOIs) interactions with opioids may manifest as serotonin syndrome.
- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics may reduce the analgesic effect of TIRF medicines and/or precipitate withdrawal symptoms.
- Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
- The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

# Determine Patient-Specific Risk Factors

## 4. Pregnancy

- Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts.
- If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

# Dosage and Administration General

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

## Appropriate Conversion

- TIRF medicines are **not interchangeable** with each other, regardless of route of administration. Differences exist in the pharmacokinetics of TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed.
- TIRF medicines are **not equivalent** to any other fentanyl product, including another TIRF medicine, on a microgram-per-microgram basis. The only exception is for substitution of a generic equivalent for a branded TIRF medicine.
- Substantial differences exist in the pharmacokinetic profiles of different fentanyl products that result in clinically important differences in the extent of absorption of fentanyl that could result in a fatal overdose.

# Dosage and Administration General

## Appropriate Conversion (cont.)

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

# Maintenance/Dose Adjustments for all TIRF Medicines

- Once a dose that provides adequate analgesia and minimizes adverse reactions is found, that dose should be prescribed for each subsequent episode of breakthrough cancer pain.
- Patients must wait at least 2 or 4 hours before treating another episode of breakthrough pain with their TIRF medicines. Please refer to the TIRF medicine's Full Prescribing Information to determine the time between doses.
- Limit the use of TIRF medicines to 4 or fewer doses per day.
- If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.
  - **Pharmacists:** Instruct patients to consult with their prescriber.
- Consider increasing the dose of the around-the-clock opioid medicine used for persistent cancer pain in patients experiencing more than 4 breakthrough cancer pain episodes per day.

# Products\*\* Covered Under this Program:

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is always 100 mcg (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	<p>If adequate analgesia was not obtained with the first 100mcg dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved.</p> <p>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.</p>
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 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 ACTIQ per breakthrough pain episode.</p>	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](http://www.TIRFREMSaccess.com) for further information and resources.

\*\* This includes approved generic equivalents of these products.

# Products\*\* Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Fentora® (fentanyl buccal tablet)	FENTORA is always 100 mcg (unless the patient is being converted from ≥600 mcg ACTIQ - please see Full Prescribing Information).	<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>	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>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 pain 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>

**Note:** This table is also available to print for use as a quick reference guide. Please visit [www.TIRFREMSaccess.com](http://www.TIRFREMSaccess.com) for further information and resources.

\*\* This includes approved generic equivalents of these products.

## Products\*\* Covered Under this Program (cont.):

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Onsolis <sup>®</sup> (fentanyl buccal soluble film)	Always 200 mcg.	<b>ONSOLIS should be used only once per breakthrough cancer pain episode</b> ; 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 <b>200 mcg ONSOLIS film increments</b>.</p> <p>Instruct patients not to use more than 4 films at once. When multiple films are used, <b>films should not be placed on top of each other</b> but may be placed on both sides of the mouth.</p> <p>If adequate pain relief is not achieved after 800 mcg (i.e. <b>four</b> 200 mcg ONSOLIS films), and the patient has tolerated the 800 mcg dose, treat the next episode by using <b>one</b> 1200 mcg ONSOLIS film.</p>
Subsys <sup>®</sup> (fentanyl sublingual spray)	SUBSYS is always 100 mcg (unless the patient is being converted from $\geq$ 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 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](http://www.TIRFREMSaccess.com) for further information and resources.

\*\* This includes approved generic equivalents of these products.

# Patient Counseling

- **Before initiating treatment with a TIRF medicine, review the product-specific Medication Guide with patients and caregivers, and counsel them on TIRF medicine risks and safe use.**
- Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting the TIRF medicine or when the dosage is increased, and that it can occur even at recommended dosages.
- Tell patients exactly how to take the TIRF medicine. Instruct them to take the TIRF medicine strictly as prescribed, with special regard to dosage, dose titration, administration and proper disposal of partially used or unneeded TIRF medicine.

## **Tell the patient:**

- You must be regularly using another opioid pain medicine, around-the-clock, for your constant pain.
- If you stop taking your around-the-clock opioid pain medicine for your constant pain, you must stop taking your TIRF medicine.

# Patient Counseling

## Tell the patient (cont.):

- **Note: Patients have had difficulty comprehending this concept; please emphasize it to your patients.**
- TIRF medicines can cause serious side effects, including life-threatening breathing problems which can lead to death. You must take TIRF medicines exactly as prescribed.
- Contact me or my office if your TIRF medicine does not relieve your pain. Do not change your dose of the TIRF medicine or take the TIRF medicine more often than I have directed.
- Accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.

# Patient Counseling

## Tell the patient (cont.):

- Potentially fatal additive effects may occur if the TIRF medicine is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider.
- The use of the TIRF medicine, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death.
- Opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs.
- Avoid taking their TIRF medicine while using any drugs that inhibit monoamine oxidase.
- Opioids could cause adrenal insufficiency, a potentially life-threatening condition.
- Their TIRF medicine may cause orthostatic hypotension and syncope.

# Patient Counseling

## Tell the patient (cont.):

- Properly dispose of partially used or unneeded TIRF medicine remaining from a prescription. *Refer to the Full Prescribing Information and Medication Guide for each product for specific instructions for disposal.*
- Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated.
- Never give your TIRF medicine to anyone else, even if they have the same symptoms, because it may harm them or even cause death.
- Never sell or give away your TIRF medicine. Doing so is against the law.

# Effective Patient Management & Follow-up

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

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

# Effective Patient Management & Follow-up

- **All patients treated with opioids require careful monitoring. At follow-up visits (cont.):**
  - TIRF medicines, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests as required by state and federal law, is strongly advised.