FDA Briefing Document

Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

August 3, 2018

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

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FDA Briefing Document Contents

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Subject: Risk Evaluation and Mitigation Strategy for the Extended-Release and Long-Acting Opioid Analgesics

1 Introduction

At this joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC), we will be discussing the risk evaluation and mitigation strategy (REMS) for the transmucosal immediate-release fentanyl (TIRF) products. These products include Abstral, Actiq, Fentora, Lazanda, Onsolis, Subsys, and approved generic equivalents of Actiq, Abstral, and Fentora. The TIRF medicines are indicated for the management of breakthrough pain in cancer patients 18 years of age and older (16 years of age and older for Actiq and its generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. The TIRF REMS was approved on December 28, 2011, to address the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors.

Under the TIRF REMS, application holders[1] of TIRF medicines are required to ensure that outpatient prescribers of TIRF medicines are specially certified, that pharmacies that dispense TIRF medicines are specially certified, that distributors only supply TIRF medicines to certified pharmacies, and that patients are enrolled in the REMS. Patients must also sign a patient-prescriber agreement acknowledging their understanding of the risks, safe use, safe storage and disposal of their TIRF medicine, as well as receipt and review of a product-specific Medication Guide by their prescriber. The Medication Guide contains consumer-friendly information on the risks and safe use of the product, including that patients must be opioid tolerant to begin the TIRF medicine and to stop using a TIRF medicine if their around-the-clock opioid pain medicine is stopped.

The FDA has received seven assessments of the TIRF REMS from the application holders of these products. FDA will present the findings from the most recent REMS Assessment at the August 3, 2018 joint meeting of the DSaRM and AADPAC. The goal is to seek comments from the committees as well as the public as to whether the TIRF REMS is meeting its goals, assures safe use, is not unduly burdensome to patient access to these drugs, and to the extent practicable, minimizes the burden to the health care delivery system.

2 Background

2.1 TIRF medicines

TIRF (transmucosal immediate-release fentanyl) medicines contain fentanyl, a potent opioid agonist. They are used to manage breakthrough pain in adults with cancer who are routinely taking other opioid analgesics around-the-clock for persistent cancer pain. All of the TIRF

[1] Application holders refers to all the manufacturers of the new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for transmucosal immediate-release fentanyl products (TIRF) that are subject to the REMS requirements. ANDAs refer to generic drugs. The applicant holders have come together as a consortium and formed the TIRF REMS Industry Group (TRIG). Throughout this background document, the manufacturers may be referred to as application holders or the TRIG.

medicines are Schedule II controlled substances under the Controlled Substance Act. Table 1 includes the approved new drug applications (NDAs) that are TIRF medicines. These TIRF medications are not equivalent and should not be substituted for each other. In addition to the NDAs, FDA has approved four abbreviated new drug applications (ANDAs) that are generic equivalents of Actiq, Abstral, and Fentora.

Table 1. Approved TIRF medicines

Product Name (application number)	Initial Approval	Application Holder	Dosage Forms and Strengths
Actiq (NDA 20747)	11/4/1998	Cephalon, Inc.	Solid oral transmucosal lozenge: 200, 400, 600, 800, 1200, and 1600 mcg
Fentora (NDA 21947)	9/25/2006	Cephalon, Inc.	Buccal tablet: 100, 200, 400, 600, and 800 mcg as fentanyl base
Onsolis†(NDA 22266)	7/16/2009	BioDelivery Sciences International, Inc.	5 strengths: 200, 400, 600, 800, and 1200 mcg of fentanyl base
Abstral (NDA 22510)	1/7/2011	Sentynl Therapeutics Inc.	Sublingual tablets: 100, 200, 300, 400, 600, and 800 mcg as fentanyl base
Lazanda (NDA 22569)	6/30/2011	DepoMed, Inc.	Nasal spray: each spray delivers 100, 300, and 400 mcg fentanyl base
Subsys (NDA 202788)	1/4/2012	Insys Development CO, Inc.	Sublingual spray: 100, 200, 400, 600, and 800 mcg
Fentanyl buccal (ANDA 079075) RLD: Fentora	1/8/2016	Watson Labs	Per Drugs@FDA-discontinued
Fentanyl citrate (ANDA 207338) RLD: Abstral	11/17/2017	Actavis Labs Fl Inc	Sublingual tablets: 100, 200, 300, 400, 600, and 800 mcg
Fentanyl citrate (ANDA 078907) †† RLD: Actiq	10/30/2009	Specgx LLC	Oral transmucosal fentanyl citrate: 200, 400, 600, 800, 1200, and 1600 mcg
Fentanyl citrate (ANDA 077312)†† RLD: Actiq	10/30/2009	Par Pharm	Solid oral transmucosal lozenge: 200, 400, 600, 1200 and 1600 mcg

Source: Agency generated; Fentanyl citrate troche/lozenge (NDA 20195), tradename, Oralet was approved on 10/4/1993 but was withdrawn (Federal Register notice effective January 30, 2017). It is a TIRF product, but is not included in the TIRF REMS because it was withdrawn.
†Onsolis has not been marketed in the US since 2011.
††Approved with a RiskMAP

2.2 Use of the TIRF Medicines in Breakthrough Cancer Pain

Breakthrough cancer pain is defined as a transitory exacerbation of pain that occurs on a background of otherwise stable, persistent pain.[2] Treatments for breakthrough cancer pain

[2] Portenoy RK, Hagen NA: Breakthrough pain: Definition, prevalence, and characteristics. Pain 41:273-281, 1990.

depend upon the underlying etiology. The goals of cancer pain therapy are to find the right dose of around-the-clock medications to control persistent pain and the right dose of supplemental medication to relieve breakthrough pain. Pharmacologic therapy combined with non-pharmacologic measures are frequently used. TIRF medicines, formulated to provide rapid absorption for immediate onset of action, are the only drugs approved for the treatment of breakthrough pain in adult patients with cancer. The safety and efficacy of TIRF medicines was demonstrated in opioid-tolerant adult patients experiencing breakthrough cancer pain.

The approved indication for this group of products, the management of breakthrough cancer pain in adult patients who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain is narrow for two reasons: 1) First, the population identified has a specific need for a treatment to address cancer-associated breakthrough pain, which is characterized by a quick onset, often high severity, and relatively short duration; and 2) These formulations of fentanyl are designed to have a relatively rapid rise to Cmax[3] and a relative short duration of effect. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also reflects the need for patents to be opioid-tolerant, a physiological state in which patients are more tolerant to the central nervous system (CNS) depression and respiratory depression associated with opioids.

2.3 Safety of the TIRF Medicines

All opioids carry serious risks of respiratory depression which could result in death, possible overdose, misuse, and abuse. The TIRF medicines contain fentanyl, a potent opioid agonist that has the potential to cause serious morbidity and death due to respiratory failure if administered to a opioid non-tolerant person. The TIRF product labels contain a class-wide boxed warning for the risk of respiratory depression; accidental ingestion; cytochrome P450 interaction; risks from concomitant use with benzodiazepines or other CNS depressants; risk of medication errors; addiction, abuse, and misuse; REMS requirements; and neonatal opioid withdrawal syndrome. The following information is contained in the boxed warning:

- Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, [TIRF MEDICINE] is contraindicated in opioid non-tolerant patients and in management of acute or postoperative pain, including headache/migraines.
- Accidental ingestion of [TIRF MEDICINE], especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal.
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl.
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom

[3] Cmax is the maximum concentration of the drug achieved in the plasma following dose administration.

alternative treatment options are inadequate; limit dosages and durations to the minimum required and follow patients for signs and symptoms of respiratory depression and sedation.

- When prescribing, do not convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to [TIRF MEDICINE]
- When dispensing, do not substitute with any other fentanyl products.
- [TIRF MEDICINE] exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.
- [TIRF MEDICINE] is available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program.
- Prolonged use of [TIRF MEDICINE] during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

2.4 History of the TIRF medicines

The first formulation of oral transmucosal fentanyl citrate, tradename Oralet, was approved on October 4, 1993, for pre-operative sedation in children. It was for use only in a hospital or a monitored anesthesia setting in an effort to avoid serious hazards associated with off-label use. The product was formulated as a raspberry- flavored lozenge on a stick so that it would be acceptable to the pediatric population. After approval, it became evident that opioid-naïve children who received it could not tolerate the associated adverse events of nausea and vomiting. The application holder ceased marketing Oralet in March, 2001, and more recently withdrew the NDA.[4]

The second TIRF product approved was Actiq (1998), which is a fentanyl lozenge approved for the treatment of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Actiq and Oralet had similarities and differences. In terms of similarities, Actiq was the same formulation as Oralet, a raspberry- flavored lozenge on a stick. In terms of differences, Actiq was available in doses much higher than approved for Oralet, and Actiq was intended for use in the home, whereas Oralet was only for use in the hospital. There was great concern about the appeal of this dosage form to children in the household. During review of the Actiq application, a major concern was how to balance the need for a new analgesic for cancer breakthrough pain with the management of the potential public health risk associated with the marketing of a potent opioid analgesic. This represented an early example of a public health challenge we face regularly with opioids where the population at greatest risk for adverse effects may not be the population that would benefit from approval.

[4] Federal Register/Vol. 81, No. 250/Thursday, December 29, 2016/Notices available at https://www.gpo.gov/fdsys/pkg/FR-2016-12-29/pdf/2016-31625.pdf

This matter was the subject of an Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) meeting in September 1997. The committee voted unanimously that there should be a way found to make Actiq available to those patients who would potentially benefit from it while managing the potential risks to public health. The risks related to the approval of Actiq and its use in an outpatient setting were those common to all high-potency opioids, including misuse (particularly in opioid-naïve patients), abuse, and diversion, and a very important risk of accidental or intentional ingestion of the product by children who have mistaken the lollipop formulation for candy. The potential for partially consumed units left lying around the house was of concern to the Agency.

The Agency issued a non-approval action for Actiq in November 1997, based partly upon the lack of development of an adequate program to protect the safety of those individuals who may accidentally or intentionally ingest the product by mistaking it for candy, use it illicitly, or have it inappropriately prescribed off-label.

Actiq was ultimately approved in 1998 under 21CFR§314.20 (Subpart H) "Approval with restriction to assure safe use" which states: "If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such post-marketing restrictions as are needed to assure safe use of the drug product."

The Agency approved the NDA with a Risk Management Program (RMP)[5] as a condition of approval. The regulations under which this product was approved provided for accelerated withdrawal of the product if the application holder did not adhere to the agreed upon marketing restrictions.

The Actiq Risk Management Program (RMP) was designed to address the following three potential risk situations:

1. Accidental ingestion of Actiq by children
2. Improper patient selection (prescription to and usage by opioid non-tolerant patients)
3. Diversion or abuse

The program included the following key components:

- Strong labeling for professionals, patients, and caregivers
- Product- specific design features to increase child safety
- Redundant child-resistant packaging and storage containers
- Comprehensive professional, patient caregivers, and child educational programs
- Interventions at the point of dispensing

[5] Prior to the 2007 Food and Drug Amendment Acts (FDAAA) that granted the FDA explicit authority to require a REMS when necessary to ensure the benefits outweigh the risks of a drug, the FDA occasionally asked pharmaceutical companies to develop special safety programs to mitigate serious risks for a limited number of drug products that offered substantial therapeutic benefits. These programs were known as Risk Management Programs (RMPs) and Risk Minimization Action Plans (RiskMAPs)

The third TIRF medicine approved was Fentora, a sublingual buccal tablet formulation of fentanyl approved on September 25, 2006 for the management of breakthrough pain in patients with cancer who are already receiving and who are tolerant to opioid therapy for the underlying persistence cancer pain. It was approved with a Risk Minimization Action Plan (RiskMAP)[6] and Medication Guide. The primary components of the RiskMAP were as follows:

- Implementation of a program and distribution of materials to educate prescribers, pharmacists, nurses, and patients about the risks and benefits of Fentora.
- Implementation of a reporting and data collection system for safety surveillance.
- Implementation of a plan to monitor, evaluate, and determine the incidence of use of Fentora by opioid nontolerant individuals, misuse of Fentora, and unintended (accidental) exposure to Fentora.

In 2007, the applicant for Fentora submitted an efficacy supplement for the proposed indication of breakthrough pain in opioid tolerant, non-cancer patients with chronic pain. On May 6, 2008, this supplement was discussed at a joint meeting of the ALSDAC and DSaRM Committee. The committee members heard presentations from the FDA, Substance Abuse and Mental Health Administration (SAMHSA), Cephalon (the application holder for Actiq and Fentora), and the public about the benefits and risks associated with Fentora. Post-marketing information suggested that the RiskMAP in place for Actiq and Fentora was not effective in mitigating the risks of these products. Specifically, Fentora's RiskMAP failed to ensure proper patient selection for patients with cancer or patients that were opioid-tolerant, and failed to provide adequate education of prescribers and dispensers. These failures were demonstrated by reports of deaths of patients being treated for migraine headache and chronic low back pain, increasing numbers of opioid non-tolerant patients being prescribed Fentora, and by medication errors with improper dose titration, improper conversion from dosages of Actiq, and improper substitution for Actiq.

Given these concerns, the committee voted not to expand Fentora's indication (No-17; Yes-3). The committee recommended a more comprehensive program that included patient and physician registration and improved risk communication. Following the advisory committee meeting, the Agency determined that a REMS was necessary to assure the safe use of oral transmucosal fentanyl products.

Onsolis, a transmucosal buccal film fentanyl product formulated as a bioerodible membrane that adheres to the buccal mucosa, was approved in 2009. Onsolis was approved with a REMS. The Onsolis REMS called for dispensing Onsolis via specialty pharmacies. The specialty pharmacies could ship the product by traceable courier to enrolled patients only after all criteria were met.

[6] Prior to the 2007 Food and Drug Amendment Acts (FDAAA) that granted the FDA explicit authority to require a REMS when necessary to ensure the benefits outweigh the risks of a drug, the FDA occasionally asked pharmaceutical companies to develop special safety programs to mitigate serious risks for a limited number of drug products that offered substantial therapeutic benefits. These programs were known as Risk Management Programs (RMPs) and Risk Minimization Action Plans (RiskMAPs).

Abstral, a sublingual fentanyl tablet formulation, and Lazanda, a fentanyl nasal spray, were approved in 2011, with their individual REMS. Subsys, a fentanyl sublingual spray, was approved in 2012 with the class-wide TIRF REMS.

3 Risk Evaluation and Mitigation Strategies (REMS)

3.1 REMS Authority

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), as amended by the Food and Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require a pharmaceutical application holder to develop and comply with a risk evaluation and mitigation strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management program that uses risk minimization strategies beyond the professional labeling. The elements of a REMS may include the following:

A **Medication Guide** provides FDA approved patient- focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

FDA has the authority to determine, based on the risks of a drug and public health concern, whether a Medication Guide should be required as part of a REMS (when the standard for requiring a Medication Guide in 21 CFR part 208 is met), and may decide the Medication Guide should be required as labeling but not part of a REMS if FDA determines that a REMS is not necessary to ensure the benefits of the drug outweigh its risks.

A **Communication Plan** consists of FDA approved materials used to aid an application holder's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) are requirements FDA can impose to help ensure safe use of the drug. In some cases these requirements can place restrictions on prescribing or dispensing the drug to the patient. ETASU can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling – and, for drugs initially approved without ETASU, other elements of a REMS are not sufficient to mitigate the serious risk that is the subject of the REMS. Accordingly, section 505-1(f)(2) of the FDCA specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Considering such risk, cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

A REMS may also include an **Implementation System** to enable the application holder to monitor, evaluate, and improve the implementation of certain elements.[7]

All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a **timetable for submission of assessments** of the REMS. The application holder must conduct assessments on a periodic basis to determine whether the goals of the program are being met and to identify any potential areas for improvement or modification of the REMS. The minimum requirement for REMS assessment submission is 18 months, 3 years and 7 years following approval of the REMS, although the Agency may require more frequent assessments for some programs with ETASU. These assessments are prepared by the application holder and reviewed by FDA.

3.2 TIRF REMS

As noted above, FDA determined following the May 6, 2008 joint meeting of the ALSDAC and the DSaRM advisory committee, that a REMS was necessary to ensure the benefits outweigh the risks of the TIRF medicines.

In October 2010, the Agency met with the application holders (referred to as the TIRF REMS Industry Group or TRIG) of the TIRF medicines and requested they work together to develop a shared system REMS for all TIRF medicines to minimize the burden to healthcare providers and patients. A REMS Notification Letter was sent to the application holders of all innovator and generic TIRF medicines informing them of the REMS requirements that must be implemented across the TIRF class. As the shared system TIRF REMS would take time to develop, the individual application holders were instructed to develop and implement individual product REMS within six months of receiving the notification letter.

The TIRF REMS was approved on December 28, 2011 and includes Abstral, Actiq, Fentora, Lazanda, Onsolis, and generic equivalents of Actiq and Fentora. Subsys joined the TIRF REMS on January 4, 2012 with its approval. The TIRF REMS, also referred to as the TIRF REMS Access Program, was launched on March 12, 2012.

[7] See section 505-1(f)(4) of the Federal Food Drug and Cosmetic Act (FDCA).

The **goals** of the TIRF REMS 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.

The TIRF **REMS elements** include:

- A **Medication Guide** - a product-specific TIRF Medication Guide is dispensed with each TIRF prescription. These medication guides are available on the TIRF REMS Access website (www.TIRFREMSaccess.com).
- **Elements to Assure Safe Use (ETASU)** – details include:
  - Training and certifying providers who prescribe TIRF medicines for outpatient use;
  - Training and certifying pharmacies who dispense TIRF medicines;
  - Assurances that TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions;
  - Patients are enrolled when their first prescription is processed at an outpatient pharmacy;
  - A completed Patient-Prescriber Agreement Form (PPAF) must be sent to the TIRF REMS program by the prescriber within 10 working days from the processing date of the patient's first outpatient prescription;
  - A maximum of three prescriptions are allowed within 10 working days from when the patient had their first prescription filled with no additional dispensings allowed until a completed PPAF is received;
  - Upon receipt of a prescription for a TIRF medicine at an enrolled outpatient pharmacy, the pharmacist enters the prescription details in their pharmacy management system (PMS) and sends the transaction to the TIRF REMS program via a switch to ensure that requirements of the TIRF REMS have been met.
- An **Implementation System** involves training and enrolling wholesalers/distributors who distribute TIRFs. Application holders are required to maintain databases of prescribers, pharmacies, patients, and distributors, as well as developing a TIRF Access System;
- A **Timetable** for submission of REMS assessment reports.

The TIRF REMS was the first program to utilize the pharmacy claims adjudication system i.e., the pharmacy "switch", to verify REMS safe use conditions for TIRF prescriptions prior to dispensing. The switch was implemented in outpatient retail pharmacies and was an attempt to reduce the burden on the healthcare delivery system by integrating REMS authorizations into currently available pharmacy management systems. For closed system outpatient pharmacies[8] that do not utilize the pharmacy claims adjudication system, verification of safe use conditions occurs by contacting the TIRF REMS program by phone or fax, and providing the required information from the TIRF prescription.

[8] The TRIG defines a closed system pharmacy an integrated healthcare systems that dispense for outpatient use.

3.3 Modifications to the TIRF REMS

The TIRF REMS has undergone seven modifications since its original approval in December 2011 (see Attachment 1 for a summary of TIRF modifications). The most significant modification was in November 2013 when the PPAF was modified after receiving feedback from prescribers that believed that the original language was restricting their use of medical judgment in the care of their patients and creating potential barriers to patient access. Table 2 below provides a comparison of the original prescriber and patient attestation statements to the modified attestation statements. Though the modifications to the PPAF did not change program operations or prescriber, pharmacist, or patient responsibilities, it is important to point out this particular modification because it is unclear what impact this may have had on prescribing TIRF medicines to opioid non-tolerant patients.

Table 2: Comparison of original PPAF attestation language at approval (December, 2011) and revised PPAF language following November 2013 REMS modification

Stakeholder	Original attestation	Revised Attestation
Prescriber	My patient is currently using around the clock opioid medication and has been for at least one (1) week.	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. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patient, and know that fatal overdose can occur at any dose
	My patient is opioid tolerant. Patients considered opioid-tolerant are those who are regularly taking 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 opioid for one week or longer	I understand that patients considered opioid tolerant are those who are regularly taking 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 opioid for one week or longer.
Patient	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.	*Attestation removed entirely*
	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	I understand that if I stop taking another opioid pain medicine that I have been taking regularly, around-the-clock for my constant pain, then I must also stop taking my TIRF medicine

3.4 TIRF REMS Assessment Plan

The timetable for submission of assessments is 6 months, 12 months and annually from initial approval of the TIRF REMS on December 28, 2011.

The following is a summary of the TIRF REMS assessment plan elements:

- ***Assessment Element 1***: Enrollment Statistics and TIRF Medicines Utilization Data
  - Patient, prescriber, pharmacy and distributor enrollment in the TIRF REMS
  - TIRF Medicines utilization data
- ***Assessment Element 2***: Dispensing Data
  - Authorizations and rejections of TIRF prescriptions from the TIRF REMS (pharmacy "switch" or other mechanisms) including reasons for rejections and time to authorization for TIRF prescriptions experiencing an initial REMS-related rejection
  - Number of patients with more than 3 prescriptions dispensed during the first 10 days without a PPAF on file
  - Number of prescriptions dispensed after 10 days without a PPAF on file
- ***Assessment Element 3***: Program Infrastructure
  - Use of backup systems to validate prescriptions
  - Unintended system interruptions
  - Summary of contacts to the TIRF REMS call center
- ***Assessment Element 4***: Program Non-compliance
  - Results of yearly audits of at least 3 randomly selected closed pharmacy systems and 5 randomly selected inpatient pharmacies
  - Description of non-compliance events and corrective actions taken to prevent future occurrences
- ***Assessment Element 5***: Surveillance Data
  - Spontaneous adverse event report data and data from surveillance databases focusing on addiction, overdose, death and pediatric exposures.
- ***Assessment Element 6***: Stakeholder Surveys
  - Surveys of patient, prescriber, and pharmacist knowledge on the risks, safe use and safe storage of TIRF medicines.

4 Summary of the TIRF REMS Assessment Reports

The FDA has received and reviewed assessment reports for the TIRF REMS submitted by the application holders at 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, and 72 months. Below is a summary of the key findings based on the *Integrated Review of the 72-Month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for the Transmucosal Immediate-Release Fentanyl (TIRF) REMS* and the *Epidemiology: Review of Risk Evaluation and Mitigation Strategy (REMS) Assessment Report* (both included in the background document.

4.1 Early Assessment Reports

The TIRF REMS assessments at 6 months, 12 months, and 24 months included data from all elements in the original assessment plan included in the December 2011 TIRF REMS approval letter. Comments to the application holders following review of these early assessment reports

were primarily related to presentation of data that summarized how the program was implemented.

FDA had concerns that the TIRF REMS assessments (including the 48-month and 60-month assessments) lacked sufficient data to determine whether the REMS was meeting its goals.

Surveillance Data

Data regarding the adverse events of interest including addiction, overdose, death, and pediatric exposures were limited. The original REMS assessment plan outlined that safety surveillance reporting would occur as follows:

a. TIRF application holders will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the application holder's respective Standard Operating Procedures.
b. Surveillance data from the following sources will be included in the REMS Assessment Reports:
   (1) FDA Adverse Event Reporting System database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion
   (2) Other external databases. The external database used by the TRIG was the American Association of Poison Control Centers (AAPCC) data for TIRF medicines and unknown fentanyl products with inhalation or ingestion as routes of exposure as the external database.

Very few adverse event reports were identified using this strategy. The FDA acknowledged the challenges with the available data sources and limitations of spontaneous reporting of adverse events for such a small patient population. In an attempt to receive more useful information, the REMS assessment plan was revised following the 24-month REMS assessment. The application holders were directed to produce a comprehensive report that includes spontaneous adverse event data from all application holders safety databases as well as data from other surveillance databases. The report was to focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures.

The FDA also had concerns about the evaluation of inappropriate conversion between TIRF medicines, as well as the use of TIRF medicines in patients who are not opioid-tolerant. The TRIG was relying on spontaneous adverse event reports that cite either use of a TIRF medicine in an opioid non-tolerant individual or inappropriate conversions between TIRF medicines to evaluate these issues. In FDA's comments to the TRIG following the 36-month REMS assessment report, the TRIG was asked to conduct an analysis of the use of TIRF medicines in opioid non-tolerant patients using data from a health care database, and to conduct a persistency analysis of TIRF medicine use to identify the occurrence of switching from one TIRF medicine to another.

To address FDA's concerns, the TRIG began submitting data from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) system in addition to the spontaneous event reports. The TRIG also submitted information on utilization of TIRF

medicines in opioid non-tolerant patients and a persistency analysis to inform the degree of switching from one TIRF to another. Though the number of adverse event reports of interest was low, RADARS® system data showed increases in rates of abuse, intentional misuse, unintentional therapeutic errors, emergency department visits and hospitalizations, and deaths/ major medical outcomes, pre-to-post REMS, after adjusting for product utilization. Also concerning was the estimate that as many as 42% of patients initiating TIRF medicines were opioid non-tolerant patients (data from 2012-2015). In addition, the evaluation showed possible inappropriate TIRF medicine switching was occurring in as many as 20% of patients (data from 2012-2015), and FDA reviewers recommended additional follow-up studies to determine the number of these switches that were inappropriate.

Following the review of the 60-month REMS assessment, the FDA concluded that the REMS was only partially meeting its goals because the included surveillance data (spontaneously reported adverse events as well as the multiple RADARS® data sources) appeared to indicate that for most outcomes assessed, event rates for TIRF medicines increased over time per number of prescriptions dispensed. In contrast, utilization-adjusted event rates for the comparator drugs, in most cases either decreased over time or showed smaller increases than those noted for TIRF medicines.[9] Therefore, the FDA determined that the goal to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors was not being met.

Use in Opioid Non-Tolerant Patients

Data regarding the use of TIRF medicines in opioid non-tolerant patients were also limited. In the 48-month assessment report, the TRIG analyzed the IMS Health Longitudinal Prescription Database to describe opioid dispensing patterns preceding a TIRF medicine dispensing to roughly estimate opioid tolerance. They found that as many as 42% of patients may not have been opioid tolerant when they received a prescription for a TIRF medicine. The data for use in opioid non-tolerant patients was provided in aggregate across all TIRF medicines, so FDA directed each application holder to repeat the evaluation for each product for the same timeframe and submit this to the FDA. The FDA was interested in learning whether this trend was occurring for the entire class or being driven by one or two products. The TIRF application holders each provided analyses of individual TIRF medicine use in opioid non-tolerant patients. Regardless of the TIRF medicine analyzed, the proportion of patients receiving a TIRF medicine who were opioid non-tolerant ranged from a low of 34.6% up to 55.4%.

Inappropriate Conversions of TIRF Medicines

Data regarding inappropriate switching between TIRF medicines also had limitations. In the 48-month REMS assessment, the TRIG used data from the TIRF REMS database to describe trends in the switching between TIRF medicines among patients dispensed a TIRF medicine. This initial evaluation was intended to be exploratory in nature to determine whether switching between TIRF medicines was a common occurrence. The analysis revealed that conversion from

[9] Meyer T. Subject: Review of Surveillance Data from the 60-month REMS Assessment Report for TIRF Products. In DARRTS 8/4/2017, Ref ID 4135176.

one TIRF medicine to another is not uncommon, occurring in approximately 20% of patients. However, analyses with greater granularity on dose were needed to inform analyses of the appropriateness of TIRF medicine switching. Additional analysis in the 60-month REMS assessment did not provide further insight into the occurrence of these switches or their consequences. The FDA recommended that the TRIG conduct a chart review within an integrated healthcare system – one that captures patient encounters across inpatient and outpatient settings, as well as prescription drug data with prescriber instructions to determine dose.

Accidental TIRF poisonings in children

FDA determined that the data on accidental TIRF exposures among children in the 48-month TIRF REMS assessment report were difficult to interpret and requested additional surveillance of accidental TIRF poisonings in children. FDA also provided examples of databases that could be used to study accidental TIRF poisonings in children. The TRIG has proposed to evaluate TIRF poisonings in children by using Optum® healthcare claims data linked to electronic medical record data, as well as the Drug Involved Mortality database.

Surveys of prescribers, pharmacists, and patients

Prescribers and pharmacists surveyed had a high level of knowledge across most of the key risk messages, however they were less aware of the correct indication. In addition, pharmacists had low awareness that if a patient stops taking around-the clock opioid pain medicine, they must also stop taking the TIRF medicine. Patients had a high level of knowledge across most of the key risk messages but were less aware of the correct indication for TIRF medicines and unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge rates have consistently been low for both of these questions across assessment periods.

4.2 FDA Summary of the 72-month REMS Assessment Review

The TRIG submitted the 72-month TIRF REMS Assessment Report on February 28, 2018 and additional surveillance data were submitted on April 30, 2018. The timeframe for the assessment period is October 29, 2016 to October 28, 2017. This is the 7th REMS assessment of the TIRF REMS and includes data on all assessment elements. Below is a summary of the key findings based on FDA's review of this assessment report. In addition to the data submitted by the TRIG, FDA reviewers also conducted independent evaluations of drug utilization data, data of abuse from the RADARS® Treatment Center Program Combined and Inflexxion® National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO^{TM}) data, and the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) poison control call data; these have been noted as such.

4.2.1 Assessment Element 1: Enrollment Data and TIRF Medicines Utilization

Enrollment Data

Compared with the 48-month assessment report, the number of active patients[10] in this reporting period has decreased by 52.2% (from 15,922 to 6,984 patients). This is similar to the IQVIA Total Patient Tracker data, which provides estimates of the total number of patients who received prescriptions dispensed for TIRF medicines. That data showed a decrease by 80% from 24,000 patients in 2010 to 5,000 patients in 2017 that were dispensed TIRF medicines.

Additionally, there has been a decrease in prescribers certified in the TIRF REMS. At the end of this reporting period there were 6,606 prescribers currently enrolled (8,151 enrolled last year and 9,096 enrolled the year before). The number of pharmacies enrolled has remained stable; at the end of this reporting period 42,615 pharmacies were enrolled. Nearly all of these were non-closed system pharmacies and included 89% chain pharmacies and 9% independent pharmacies. About 2% of enrolled pharmacies were inpatient pharmacies.

Table 3. Total Number of Enrolled Stakeholders During Reporting Period	
Active patients	6,984
Currently enrolled prescribers	6,606
Enrolled pharmacies	42,615

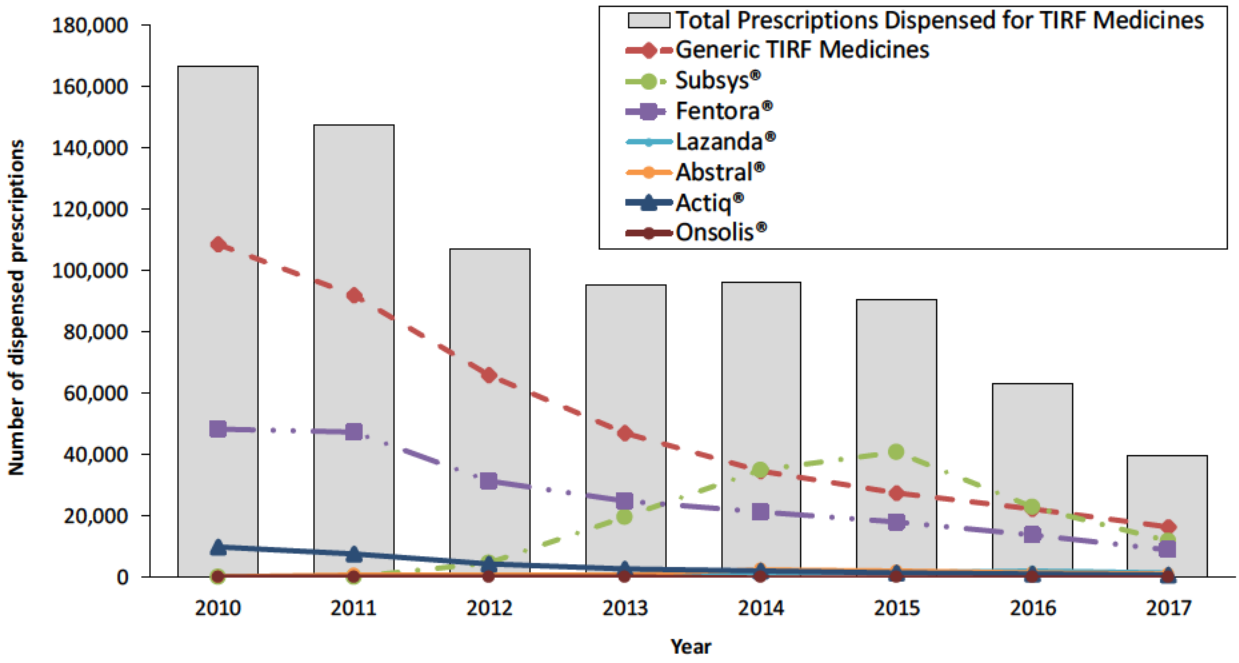
TIRF Utilization Data

Decreases in utilization of the TIRF medicines were noted in the data provided by the TRIG as well as the data from proprietary databases analyzed by the FDA. The FDA's analysis of drug utilization showed that total TIRF prescriptions as shown by the gray bars in Figure 1 below decreased every year from an estimated 167,000 prescriptions dispensed in 2010 to 40,000 prescriptions dispensed in 2017 from U.S outpatient retail pharmacies. Generic equivalents of Actiq and Fentora remained the highest dispensed TIRF medicine each year except from 2014 to 2016 when Subsys matched or exceeded the prescriptions dispensing of other TIRF medicines. TIRF medicines accounted for only 0.02% (40,000 prescriptions) of the estimated 196 million opioid analgesic prescriptions dispensed in 2017 in the outpatient retail setting.[11]

Prescriber specialties accounting for the highest proportion of dispensed prescriptions for TIRF medicines were anesthesiologists (22%), physical medicine and rehabilitation (13%) and pain management specialists (12%). Nurse practitioners (NP) and physician assistants (PA) accounted for 15% of dispensed prescriptions for TIRF medicines. No information is available on whether the NP and PA prescribers were affiliated with specialty practices.

[10] Active patients are those that were enrolled and dispensed a TIRF medicine during the reporting period.
[11] Source: IQVIA National Prescription Audit™. 2017. Data extracted February and May 2018.

Figure 1: Nationally estimated number of prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies, 2010-2017



Source: IQVIA National Prescription Audit™. 2010-2017. Data extracted May 2018.

Though the FDA did not request an extension of the analyses on the use of TIRF medicines in opioid non-tolerant patients to include the 72-month assessment time-period, the TRIG was instructed to undertake a study of the validity of the opioid tolerance algorithm used in the previous analyses and to develop a protocol to study adverse events occurring in opioid non-tolerant patients.

General estimates from a persistency analysis suggested that approximately 20% of patients with two or more TIRF prescriptions changed their index TIRF regimen. To assess whether the REMS is preventing inappropriate product conversions, data are needed on details of the doses and products involved in the index and second regimens, and patient outcomes associated with switching regimens.

4.2.2 Assessment Element 2: TIRF Medicines Dispensing Activity

The TIRF REMS will reject prescriptions that do not fulfill the safe use requirements of the REMS such as a prescription written by a prescriber that isn't certified or when there is a missing or incomplete PPAF. Of the 69,211 unique prescriptions submitted for REMS authorization this reporting period, 90.4% did not encounter any REMS-related rejections (i.e., were authorized for dispensing).

Less than 2% of prescriptions experienced a REMS-related rejection initially but were then authorized for dispensing, and the remaining 8% of prescriptions that encountered at least one

REMS-related rejection were never authorized for dispensing. Overall the reasons for these rejections included an incomplete PPAF or the prescription was written by a non-enrolled prescriber. These data demonstrate that the majority (92.4%) of TIRF prescriptions are eventually authorized by the REMS.

For prescriptions that experience at least one initial REMS-related rejection, mean and median prescription processing times continue to increase over time for both chain and independent stores. The mean time to process a TIRF prescription increased from 2.10 days in the 24-month assessment to 6.95 days in the 72-month assessment; the median increased from 0.01 days to 2.05 days from the same time period. It is unclear what may be impacting these processing times and whether the increase adversely affects patient access to TIRF medicines.

4.2.3 Assessment Element 3: Program Infrastructure and Performance

The evaluation of program infrastructure and performance includes metrics on the use of backup systems to validate prescriptions, unintended system interruptions and information on the contacts to the TIRF REMS call center including a summary of frequently asked questions including REMS-related problems reported to the call center and any corrective actions to address program/system problems. There were no reported instances during the reporting period in which a backup system was used to authorize a prescription (due to pharmacy level problems, switch problems, or REMS database problems). Nor were there any unintended system interruptions reported in the 72-month assessment report.

Of the 137,770 calls received by the TIRF REMS Call Center, the top 5 reported reasons for the calls were: enrollment status inquiry (17.1%); pharmacy claim rejection (16.0%); PPAF inquiry (10.2%), general program questions (6.0%); and Web portal log-on assistance (5.7%).

Results of the assessment indicate that the REMS technical infrastructure appears to be functioning adequately.

4.2.4 Assessment Element 4: TIRF REMS Non-Compliance

Prescriber Non-compliance

The TIRF REMS requires that a PPAF be signed and submitted within 10 days of the patient's first TIRF prescription. The REMS collects information on prescribers who have not completed PPAFs in a timely manner. During the reporting period, 28 prescribers had 5 or more patients enrolled and prescribed a TIRF medicine without a completed PPAF on file. The TRIG has indicated that they plan to lower their threshold for the number of acceptable prescriber non-compliance events from 5 patients without a complete PPAF on file to one patient. A timeline for the implementing this change was not been provided to FDA.

Pharmacy Non-compliance

The TRIG becomes aware of non-closed system pharmacy (a chain or independent outpatient pharmacy) non-compliance through self-reporting. During this reporting period, 6 events were reported where the pharmacy bypassed the REMS authorization process and dispensed the TIRF medicine, and 3 events where a prescription, that was rejected by the REMS, was dispensed by the pharmacy. Additionally, 2 pharmacies that failed to recertify dispensed a total of 7

prescriptions for TIRF medicines. These pharmacies were re-trained in the REMS. The FDA asked the TRIG to develop more proactive mechanisms to capture non-compliance in non-closed system pharmacies and the TRIG has committed to develop an audit.

Though numbers of overall prescriptions dispensed in the closed health care systems are very low, a high proportion of these prescriptions are not authorized by the REMS prior to dispensing. During this reporting period, there were two closed health care systems that dispensed more than 50% (range 54-63%) of TIRF medicines without adjudication through the REMS authorization process.

Inpatient pharmacies audited during the 72-month assessment period passed the audit; however, many of the hospitals contacted for the audit were not eligible as they did not dispense any TIRF medicines during the reporting period.

4.2.5 Assessment Element 5: Safety Surveillance

Evaluation of Spontaneous Adverse Event Report Data

The spontaneous adverse event report data in the 72-month assessment focuses on four categories of adverse events of interest – addiction, overdose, death, and pediatric exposure. The TRIG identified 568 cases of reported adverse events of interest in this reporting period, including 549 cases with an outcome of death. We acknowledge, to some extent, deaths are expected to be captured with a TIRF medication when it is used by their intended population of patients with cancer. In the current reporting period, FDA notes an increase in number of spontaneous adverse event cases reported with an outcome of death and overdose, which is potentially concerning when considered in context of the decreased TIRF medicine utilization described in Section 4.2.1. However, given the paucity of case-level details and large number of cases lacking sufficient information for causal assessment, the interpretability of these data is hampered. Among the 568 cases reporting an adverse event of interest, none involved the following: 1) inappropriate conversion between TIRF medicines, 2) unintentional or accidental exposures, and 3) use of the TIRF medicine by an opioid non-tolerant patient. However, given that these data are only from a subset of all reports (cases of addiction, overdose, death, or pediatric exposure) and due to inherent limitations of spontaneous adverse event data, the absence of information does not provide evidence that TIRF medicines are being appropriately prescribed (e.g., used only by opioid tolerant patients) and that no inappropriate switching of TIRF products or unintentional or accidental exposures occurred. These spontaneous adverse event report data alone are insufficient to inform these safety concerns with TIRF medicines and should be considered in context with other surveillance data.

Evaluation of Surveillance Data

FDA conducted a review of the surveillance data in the 72-month REMS assessment report which compared the pre-to-post REMS rates of adverse events (AE) attributed to TIRF medicines in aggregate to rates of AEs attributed to other opioid analgesics. FDA also conducted product-specific analyses and additional analyses of the aggregated TIRF medicines through FDA contracts.

The purpose of the product-specific analysis was to (1) verify that there was no one product implicated in the increasing prescription-adjusted AE rates that had been observed in the 60-month REMS Assessment report and (2) make pre-versus-post REMS comparisons in AE rates among TIRF medicines that were marketed in both periods. As expected, product-specific case numbers were low in every data source. In the RADARS® Treatment Center Programs Combined, average number of cases per quarter ranged from 7 – 31, depending on the product; in other data sources, quarterly averages were even lower. The available TIRF product-specific data enabled us to make general conclusions for selected outcomes.

TIRF aggregate data from several data streams suggest that the prescription-adjusted rate of TIRF medicine abuse either increased from the pre-to-post REMS period, or that the prescription-adjusted abuse rates post-REMS through 2016 were trending upward, although the abuse rate appeared to decline starting in Q1 2017. These patterns in abuse are concerning given that prescription-adjusted abuse rates of comparators showed either contemporaneous declines or no change. The TIRF product-specific data showed that individual product trends generally tracked with the TIRF medicines aggregate trend, except for Lazanda, which exhibited an apparent decrease in the prescription-adjusted abuse rate pre-to-post REMS. Of note, Lazanda's trend appears to be influenced by extremely high prescription-adjusted abuse rates when it first appeared on the survey, which may have been produced by respondent errors and the low utilization during this period.

Unintentional general TIRF medicine exposure calls to poison centers, overall and among children age <6 years, decreased on both the population-adjusted and prescription-adjusted scales, and to as great an extent or greater than decreases in rates of comparator unintentional general exposures. All told, there were nine exposure calls for children age <6 years in the pre-REMS period and nine in the post-REMS period. Due to the small number of unintentional general TIRF exposure calls, the product-specific data were uninformative. FDA has requested additional data sources from the TRIG to generate a more robust evidence base for accidental poisonings in children, and the process of obtaining these data is ongoing.

Other indicators from the poison center data exhibited pre-to-post REMS increases. TIRF-involved calls resulting in major medical outcomes and deaths increased pre-to-post REMS on both the population-adjusted and prescription-adjusted scales. The increase in the prescription adjusted rate was significant and of larger magnitude relative to that of comparators.

TIRF exposure calls for reasons of intentional misuse and unintentional therapeutic errors decreased from pre-to-post REMS, but there were suggestive increases in the prescription-adjusted rates while the rates of comparators remained constant or decreased. Also, the prescription-adjusted rates of emergency department visits/hospitalizations increased while the rates of comparators remained constant or decreased. In the product-specific data, we noted increases for Actiq/generic lozenge and Fentora, pre-to-post REMS, in the prescription-adjusted rate of ED visits/hospitalizations. Otherwise, the event numbers were too low to produce informative results.

In summary, observed increases in the prescription-adjusted rates of abuse of TIRF medicines and associated major medical outcomes/deaths raised concerns. Also, there were suggestive increases in the prescription-adjusted rates of intentional misuse, unintentional therapeutic errors, and ED visits/hospitalizations, although estimates were imprecise. Based on small numbers pre-and-post REMS, rates of poison center calls for unintentional general TIRF exposures decreased

among adults and children. For all outcomes, making conclusions based on the evaluated data sources was difficult due to the limited number of events and the relatively low utilization of TIRFs. Indeed, in the review of the 60-month REMS Assessment Surveillance Data, DEPI had noted these concerning patterns in the results, and since then, communications with the TRIG about obtaining additional safety data have been ongoing. That process will be explained in an addendum to the DEPI review.

4.2.6 Assessment Element 6: Periodic Surveys of Patients, Healthcare Providers, and Pharmacists

Overall, patients, prescribers, and pharmacists who were surveyed had an adequate understanding of most of the key risk messages related to accidental exposure and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however all groups were less aware of the need to only prescribe and dispense TIRF medicines to appropriate patients (opioid-tolerant) than they were of other components of the TIRF REMS. Although the respondents had adequate understanding of most of the key risk messages, the surveys were not based on probability random samples and had high non-response rate. Results showed a lack of representation of the sample. However, subgroup analyses did not show a systematic bias and standardization of results did not change main conclusions.

4.2.7 Evaluation of Patient Access and Healthcare Provider Burden

The evaluation of the TIRF REMS on patient access and healthcare provider burden is not included in the assessment plan for the TIRF REMS. Several potential indicators of the impact of the TIRF REMS on patient access, however, should be considered in the overall evaluation of the TIRF REMS. These include the decreasing numbers of both patients and prescribers enrolled in the TIRF REMS since original implementation, as well as the decreasing number of prescriptions for TIRF medicines prior to REMS implementation. The initial drop in prescribing may have been reflective of more judicious use of TIRF medicines following the TIRF REMS approval, a delay in prescribers becoming certified in the TIRF REMS due to the new requirements, or the burden of the REMS. It is unclear, however, whether the continued decreases reflect a potential burden on prescribers that, over time, has led them to cease prescribing these products, or whether other factors including insurance are playing a role. Although the assessment does not provide the geographic location of currently enrolled prescribers, the declining numbers of prescribers may signal that patients in some areas may not have access to a prescriber certified in the TIRF REMS thus impacting patient access.

5 Conclusions and Considerations for Modifications to the TIRF REMS

Similar to previous assessments, the review of the 72-month REMS assessment continues to prove challenging when determining whether the goals and objectives of the TIRF REMS are being met.

From an operations perspective, the TIRF REMS program is functioning as intended to ensure that prescribers and pharmacists receive training on the risks and the safe use of TIRF medicines

prior to prescribing or dispensing, and to ensure that patients are informed of the risks and safe use of TIRF medicines before taking them. Using the pharmacy claims adjudication system ("the switch") to ensure that the REMS requirements are met appears to function well with few systems issues identified, although a small number of prescriptions may be dispensed by bypassing this system. Surveys of prescribers, pharmacists and patients, despite their limitations, suggest that they are knowledgeable about these risks. We acknowledge, however, that knowledge may not translate into appropriate prescribing practices.

Of concern are data that suggest a high percentage of use of TIRF medicines in patients who are not opioid tolerant; however, additional analyses may be needed to understand if this represents a change in prescribing patterns since the TIRF REMS was approved. FDA has invited two guest speakers to share their research about TIRF prescribing; we believe their results may contribute greatly to the discussion. It is also unknown if this potential inappropriate prescribing has actually led to poorer patient outcomes. The TRIG was instructed to undertake a study of the validity of the opioid-tolerance algorithm used in the previous analyses and to develop a protocol to study adverse events occurring in opioid non-tolerant patients. Additional analyses should be undertaken to explore potential inappropriate switches between TIRF medicines.

The surveillance data suggest increases in the prescription-adjusted rates of abuse, intentional misuse, unintentional therapeutic errors, and major medical outcomes including ED visits and hospitalizations, although estimates were imprecise. For all outcomes, making conclusions based on the evaluated data sources is difficult due to the limited number of events and the relatively low utilization of TIRFs.

Finally, the declining number of patients receiving prescriptions for TIRF medicines also raises questions, and further investigation is warranted to determine the reason for the decreases (e.g., REMS requirements, insurance coverage changes, or overall concerns with prescribing opioids) and whether this is impacting appropriate patient access for patients with breakthrough cancer pain.

We look forward to the committees' discussion and advice on the best approaches for assessing the effectiveness of the TIRF REMS in meeting its goals as well as any needed modifications to the TIRF REMS program. Modifications to the TIRF REMS program may be considered to reduce the use in opioid non-tolerant patients or strengthen the messages about the use of TIRF medicines only in opioid tolerant patients. Modifications may also be considered to reduce burden to healthcare providers and maintain access to patients who could benefit from these products. Any modifications, particularly with further restrictions, should consider the potential impact on patient access.

6 Discussion topics

1. The intent of the TIRF REMS is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:
   - Ensuring prescribing and dispensing TIRFs only to appropriate patients (e.g., opioid tolerant patients)
   - Preventing inappropriate conversion between TIRF medicines.
   - Preventing accidental exposure to children and others for whom it was not prescribed.
   - Educating prescribers, pharmacists and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

   Discuss whether the approved REMS is adequately designed to achieve its goals and objectives.

2. Assessment data are collected from TIRF REMS utilization statistics, dispensing activity by enrolled pharmacies, the non-compliance plan, safety surveillance by multiple sources, and annual knowledge, attitude, and behavior (KAB) surveys of patients, prescribers, and pharmacies.
   a. Discuss whether the available data are adequate to determine if each of the objectives are being met by the TIRF REMS.
   b. If the available data are not adequate, discuss feasible options for obtaining adequate data

3. The REMS assessment data indicate the outpatient use of TIRF medicines has decreased approximately 75% since 2010.
   a. Discuss any factors you are aware of that may have resulted in the decrease in use of TIRF medicines
   b. Discuss whether the TIRF REMS may be creating barriers to access to these products for patients who could benefit from them, and if so, what can be done to reduce these barriers.
   c. Discuss whether there are additional mechanisms to reduce burden to the healthcare system associated with the TIRF REMS.

4. Based on the data presented and discussed today, should the TIRF REMS remain the same or modified. If you think it should be modified, discuss how the REMS should be modified.

Attachment 1 – Summary of TIRF REMS Modifications (initially approved on 12/11/2011)

Date	Major Changes Made
06/05/2012	Modified to: 1. Edit the Patient-Prescriber Agreement Form, add the Closed System Pharmacy Enrollment Form, add newly approved TIRF medicines, , and make minor editorial changes. 2. Update the TIRF REMS Access Program "go-live" placeholder date to the actual "go-live" date of March 12, 2012.
11/07/2013	Modified to: 1. Revise terminology, processes, and definitions for outpatient pharmacies. 2. Revise attestations for physicians and patients to address concerns regarding patient access. 3. Revise Program Overview and Frequently Asked Questions to improve clarity and content. 4. Reflect the completion of the transition phase for the TIRF REMS Access Program in the REMS materials.
11/04/2014	Modified to add the Abstral product to the shared system REMS.
12/24/2014	Modified to: 1. Remove NDC Numbers from the Independent Outpatient Pharmacy Enrollment Form, Chain Outpatient Pharmacy Enrollment Form, and TIRF REMS Website. 2. Remove reference to generic equivalents of specific products and replacement with a footnote in the Education Program for Prescribers and Pharmacists and TIRF REMS Website. 3. Remove "Attachment 1: List of TIRF Medicines Available Only through the TIRF REMS Access Program," and replacement with a hyperlink to the new TIRF REMS Webpage in the TIRF REMS Document, Overview for Prescribers, Prescriber Enrollment Form, Overview for Patients and Caregivers, Independent Outpatient Pharmacy Overview, Chain Outpatient Pharmacy Overview, Closed System Outpatient Pharmacy Overview, Independent Outpatient Pharmacy Enrollment Form, Chain Outpatient Pharmacy Enrollment Form, Closed System Outpatient Enrollment Form, Inpatient Pharmacy Enrollment Form, Distributor Enrollment Form, and TIRF REMS Website and Website Landing Page. 4. Revise criteria for inactivation of Patient-Prescriber Agreement Form (PPAF) in the TIRF REMS Document. 5. Revise to enhance knowledge about conversion of TIRF Medicines in the Education Program for Prescribers and Pharmacists and TIRF REMS Website. 6. Add information clarifying the process to electronically transmit TIRF REMS Cash Claims in the TIRF REMS Document, TIRF REMS Access Program Frequently Asked Questions (FAQ), Independent Outpatient Pharmacy Overview, Chain Outpatient Pharmacy Overview, Closed System Outpatient Pharmacy Overview.
12/21/2015	Modified to include the new strength of 300 mcg per spray in the Medication Guide.
04/11/2017	Modified to add the authorized generic and a Medication Guide that is identical to that of the branded product, except that only the authorized generic (fentanyl buccal tablets) is listed as the product name.
09/07/2017	Modified to make changes to the REMS document, and appended materials consistent with the safety label changes approved on December 16, 2016, as well as additional minor modifications.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Integrated Review of the 72-Month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for the Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Date: July 12, 2018

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OND Review Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Therapeutic Class:	Opioid Analgesics
	Transmucosal immediate-release fentanyl (TIRF) medicine
Drug Names:	See chart below
Dosage and Route:	See chart below
Application Type/Number:	See chart below
Submission Type/ Number:	See chart below
Applicant/sponsor:	See chart below
OSE RCM #:	2018-450
Submission Date:	February 28, 2018

TIRF Medicines

Drug Name	Dosage and Route	NDA/ ANDA	Applicant	Submission Date
Abstral	Sublingual Tablet	NDA 022510	Sentynl Therapeutics, Inc	February 28, 2018 to DMF (b) (4)
Actiq	Oral Transmucosal Lozenge	NDA 020747	Teva Pharmaceuticals USA, Inc.	
Fentora	Buccal Tablet	NDA 021947	Teva Pharmaceuticals USA, Inc.	
Lazanda	Nasal Spray	NDA 022569	Elefsee Pharms Intl	
Onsolis	Buccal Soluble Film	NDA 022266	BioDelivery Sciences International, Inc	
Subsys	Sublingual Spray	NDA 202788	Insys Therapeutics, Inc	
fentanyl citrate	Sublingual Tablet	ANDA 207338	Teva Pharmaceuticals USA, Inc.	
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 077312	Par Pharmaceutical, Inc	
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 078907	SPECGX, LLC	
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 079075	Watson Labs	

Table of Contents

Table of Tables

Table of Figures

1. EXECUTIVE SUMMARY

This review by the Office of Surveillance and Epidemiology, Division of Risk Management (DRISK), the Division of Epidemiology II (DEPI II), the Division of Pharmacovigilance II (DPV II), and the Office of Translational Sciences, Division of Biostatistics VII (DB7) evaluates the 72-month risk evaluation and mitigation strategy (REMS) assessment report for the transmucosal immediate release fentanyl products (TIRF) REMS. The shared system[12] TIRF REMS was approved in December 2011 to ensure the benefits of TIRF medicines outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. All of the TIRF application holders have formed a consortium known as the TIRF REMS Industry Group (TRIG). The REMS assessment report was submitted two months after the due date, on February 28, 2018, as requested by the FDA due to the number and magnitude of changes to the data requested by the FDA based on the 60-month assessment report. Part of the surveillance data component of the 72-month report was submitted on February 28; the rest was submitted on April 30, 2018.

The goals of the REMS 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; and
4) Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

The 72-month assessment report for the TIRF REMS includes data on certification/enrollment, distribution/dispensing, programmatic/infrastructure functioning and compliance, patient, prescriber, and pharmacist knowledge and behavior (KAB) surveys, and surveillance data. Surveillance data came from multiple data streams and included information on adverse events involving TIRF medicines—i.e., abuse, addiction, misuse, unintentional therapeutic error, overdose, death, and pediatric exposure—as well as persistency with a TIRF regimen. The FDA has conducted additional analyses of drug utilization using proprietary data sources available to the Agency to supplement the REMS assessment and results of these analyses are included in this review. Similarly, the FDA has also conducted additional analyses of surveillance data using proprietary data sources available to the Agency. A detailed review of the surveillance data submitted by the TRIG is included in a separate review by the OSE Division of Epidemiology II (DEPI II). A summary of that DEPI II review is included in this review and will also help inform us whether the REMS is meeting its goals.

Key observations of the 72-month REMS assessment report and analyses by the FDA include:

[12] A shared system REMS encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants.

- Decreases in the utilization of the TIRF medicines, noted in the data provided by the in the REMS assessment report as well as FDA analyses of drug utilization data obtained from proprietary databases available to the FDA. The FDA's evaluation of drug utilization data from 2010 to 2017 indicated there has been a decrease in utilization by 76% from dispensed prescription data and by 80% from patient data. An estimated 5,000 patients received prescriptions dispensed for TIRF medicines in 2017, with generic TIRF medicines, Subsys, and Fentora accounting for the majority of prescriptions dispensed from U.S. outpatient retail pharmacies.
- TIRF medicines accounted for only 0.02% (40,000 prescriptions) of the estimated 196 million prescriptions dispensed in 2017 for opioid analgesic products in the U.S. outpatient retail setting.
- The top prescriber specialties accounting for the highest proportion of prescriptions dispensed for TIRF medicines were anesthesiologists (22%), nurse practitioners /physician assistants (15%), physical medicine and rehabilitation specialists (13%), and pain management specialists (12%).
- In the report submitted by the TRIG, over 92% of TIRF prescriptions are eventually authorized by the REMS.

- Governmental closed systems have significant numbers of prescriptions not routed through the REMS authorization process: during this reporting period, 63% of Defense Logistics Agency (DLA) Troop Support and 54% of Department of Veterans Affairs (VA) TIRF dispensations were not adjudicated through the REMS authorization process.
- The TRIG states that they will be changing the criteria for a non-compliance event from five patients without a complete Patient-Prescriber Agreement Form (PPAF) on file, (with each patient having greater than ten working days lapse from the initial enrollment date) to one patient. The TRIG also states that their non-compliance protocol will clearly articulate the non-compliance pathway to deactivation from the program, which will now be a "three strike" process. However, the TRIG does not provide a timeline for implementing either change.
- The spontaneous adverse event report data provided in the 72-month assessment report focuses on four categories of adverse events of interest (addiction, overdose, death, and pediatric exposure). The TRIG identified 568 cases of adverse events of interest associated with a TIRF medicine, including 549 cases with an outcome of death. In the current reporting period, FDA notes there is an increase in cases with an outcome of death and overdose, in comparison to previous reporting periods, that is potentially concerning, especially given the decreased drug utilization data. However, given the minimal case level details provided and large number of cases that the TRIG determined lacked sufficient information for causality assessment, the interpretability of these data is hampered. Among the 568 reported cases of adverse events of interest, the TRIG also assessed for the following: 1) inappropriate conversion between TIRF medicines, 2) unintentional or accidental exposures, and 3) use of the TIRF medicine by an opioid non-tolerant patient and did not identify any cases for this reporting period. Given that these metrics were assessed from a subset of cases (addiction, overdose, death, and pediatric exposure) rather than all adverse event reports and due to inherent limitations of spontaneous adverse event report data, the absence of information does not provide evidence that TIRF medicines are: appropriately converted, only used by opioid-tolerant patients, or that no unintentional or accidental exposures occurred. These spontaneous

adverse event report data alone are insufficient to inform these safety concerns with TIRF medicines and should be considered only in context with other surveillance data.

- Based on FDA review of several data streams provided in the 72-month report surveillance data as well as analyses conducted by the FDA, we observed increases in the prescription-adjusted rates of abuse and major medical outcomes/deaths that raised concerns. Also, there were suggestive increases in the prescription-adjusted rates of intentional misuse, unintentional therapeutic errors, and emergency department visits/hospitalizations, although estimates were imprecise. Based on small numbers pre- and post-REMS, rates of poison center calls for unintentional general TIRF exposures decreased among adults and children. For all outcomes, making conclusions based on the evaluated data sources difficult due to the limited number of events and the relatively low utilization of TIRF medicines. FDA has requested additional sources of safety data from the TRIG, and the process of obtaining these data is ongoing.
- Findings from individual NDA and ANDA submissions of opioid tolerance data indicate that regardless of the type of analysis, the proportion of opioid non-tolerant patients receiving a TIRF medicine ranged from 34.6% to 55.4%. The proportion of opioid non-tolerant patients receiving a TIRF medicine, as calculated by these analyses, is concerning. Additional analyses are needed to understand if this represents a change in prescribing patterns since the TIRF REMS was approved.
- General estimates from a persistency analysis suggest that approximately 20% of patients with two or more TIRF prescriptions changed their index TIRF regimen. To assess whether the REMS is preventing inappropriate TIRF medicine conversions, additional data are needed on the doses and products involved in the TIRF medicine index and second regimens, as well as patient outcomes associated with switching regimens.
- The data provided by the TRIG regarding prevention of accidental exposure are limited and difficult to interpret; therefore, additional safety data has been requested from the TRIG.
- Overall, patients, prescribers, and pharmacists who were surveyed had adequate understanding of most of the key risk messages related to accidental exposure and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however, all groups were less aware of the need to only prescribe and dispense TIRF medicines to appropriate patients (opioid-tolerant) than they were of other components of the TIRF REMS program. Although the respondents had adequate understanding of most of the key risk messages, the surveys were not based on probability random samples and had high non-response rate. Results showed a lack of representation of the sample. However, subgroup analyses did not show a systematic bias and standardization of results did not change main conclusions. The surveys suggest that prescribers, pharmacists and patients are knowledgeable about these risks; however, we acknowledge, that knowledge may not translate into appropriate prescribing practices.

Similar to previous assessments, the review of the 72-month REMS assessment continues to prove challenging when determining whether the goals and objectives of the TIRF REMS are being met.

On August 3, 2018, the TIRF REMS will be the topic of discussion at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The Committees will be asked to discuss whether the

approved REMS is designed to achieve the goals and objectives, whether the available data are adequate to determine if each of the objectives are being met and if they are not adequate, to discuss feasible options for obtaining adequate data. In addition, they will be asked to discuss any factors they are aware of that may have resulted in the decrease in use of TIRF medicines, whether the REMS may be creating barriers to access to these products for patients who could benefit from them and if there are mechanisms that may reduce the burden associated with the REMS. Lastly, they will be asked their advice on if the TIRF REMS should be modified or remain the same.

2. INTRODUCTION

This review evaluates the 72-month REMS assessment report for the transmucosal immediate-release fentanyl (TIRF) risk evaluation and mitigation strategy (REMS). The assessment period covers October 29, 2016 to October 28, 2017. This 7th REMS assessment report for the TIRF REMS was submitted to the FDA on February 28, 2018. In FDA's email communication of November 8, 2017 as well as the 60-Month FDA REMS Assessment Acknowledgement Letter (RAAL) of December 11, 2017, the FDA extended the due date for the 72-Month REMS Assessment report from December 28, 2017 to February 28, 2018 in order to allow the TRIG to address changes FDA requested. Part of the surveillance data component of the 72-month report was submitted on February 28; the rest was submitted on April 30, 2018.

The 72-month REMS assessment report includes data on certification/enrollment, distribution/dispensing, programmatic/infrastructure functioning and compliance, patient, prescriber, and pharmacist knowledge and behavior (KAB) surveys, and surveillance data. Surveillance data came from multiple data streams and included information on adverse events involving TIRF medicines—i.e., abuse, addiction, misuse, unintentional therapeutic error, overdose, death, and pediatric exposure—as well as persistency with TIRF regimen. Results from the surveillance data submission within the 72-month report, and from additional analyses of surveillance data sources conducted by the FDA, are summarized in this review and described in detail in a separate review.[13]

FDA also conducted an analysis of the utilization of TIRF medicines in the U.S. to supplement the review of the REMS assessment and to provide context for the Advisory Committee meeting discussion on August 3, 2018.

3. BACKGROUND

TIRF medicines are short-acting, high-potency opioid analgesics indicated in the management of breakthrough pain in cancer patients. A primary safety concern with all the TIRF medicines is their use in opioid non-tolerant patients due to the potential of life-threatening respiratory depression in patients not already taking and tolerant to chronic opioid analgesics. In addition, cases of diversion, abuse, overdose, misuse, and prescribing to opioid-non-tolerant patients have led to serious adverse events or fatalities, further demonstrating that these products can pose a serious and significant public health concern. Thus, FDA determined that a REMS was necessary

[13] Radin R, Karami S. Epidemiology: Review of the 72-month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for the Transmucosal Immediate-release Fentanyl Shared REMS. 2018.

to ensure the benefits outweigh the risks of misuse, abuse, addiction, overdose, and serious complications associated with the use of TIRF medicines.

In 2010, the FDA also determined that, in the interest of public health and to minimize the burden on the healthcare system, *a shared system* REMS should be implemented for all members of the TIRF medicine class and on December 28, 2011, the "TIRF REMS" was approved for Abstral, Actiq, Fentora, Lazanda, Onsolis, and generic versions of these TIRF medicines. On January 4, 2012, the FDA approved Subsys, as well as its inclusion into the TIRF REMS program. The TIRF REMS also referred to as the TIRF REMS Access program was launched on March 12, 2012, approximately 11 weeks after REMS approval. One of the key aspects of the TIRF REMS is the use of the claims adjudication system to ensure that REMS requirements are met prior to dispensing. Any prescription for a TIRF medicine presented to an outpatient pharmacy must first pass through an electronic pharmacy software (*switch*) to adjudicate prescriptions through the TIRF REMS prior to any insurance adjudication. Pharmacies that do not utilize electronic claims processing cannot be processed in this manner, requiring pharmacies to call or fax the TIRF REMS for verification that safe use conditions have been met prior to TIRF dispensing. Implementation of the TIRF REMS for these closed system pharmacies[14] was launched on June 30, 2012.

The TIRF REMS Industry Group (TRIG) is composed of the following Sponsors: BioDelivery Sciences International, Inc., Depomed, Inc., Insys Therapeutics, Inc., SpecGX LLC [a wholly owned subsidiary of Mallinckrodt Inc.], Mylan, Inc., Par Pharmaceutical, Inc., Sentynl Therapeutics, Inc., and Teva Pharmaceuticals USA, Inc. During this reporting period, Actavis Laboratories FL, Inc. and Cephalon, Inc. ceased to participate separately in the TRIG and each of their NDAs/ANDAs have been consolidated under participation by Teva Pharmaceuticals USA, Inc. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. The 72-month report was prepared by United BioSource Corporation (UBC).

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

3.1 REMS ELEMENTS

The TIRF **REMS elements** include:

- A **Medication Guide** - a product-specific TIRF Medication Guide will be dispensed with each TIRF prescription. These Medication Guides are available on the TIRF REMS Access website (www.TIRFREMSaccess.com).

[14] Closed systems are defined as "integrated healthcare systems that dispense for outpatient use with pharmacy management systems unable to support the process of electronically transmitting the validation and claim information required."

- **Elements to Assure Safe Use (ETASU)** – details include:
    - (ETASU A) training and certifying outpatient TIRF prescribers;
    - (ETASU B) training and certifying pharmacies who dispense TIRFs;
    - (ETASU C) assurances that TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions;
        i. patients are enrolled when their first prescription is processed at a pharmacy;
        ii. a completed Patient-Prescriber Agreement Form (PPAF) must be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription;
        iii. a maximum of three prescriptions are allowed within 10 working days from when the patient had their first prescription filled with no additional TIRF dispensing allowed until a completed PPAF is received;
        iv. upon receipt of a prescription for a TIRF medicine at an enrolled outpatient pharmacy, the pharmacist enters the prescription details into the pharmacy management system (PMS) which sends the transaction to the TIRF REMS Access program via a "switch" provider to ensure that all elements meet the safe use requirements of the TIRF REMS Access program
        v. Since closed-system pharmacies do not electronically transmit the validation and claim information required by the REMS (and thus do not use a switch provider), these pharmacies must instead call or FAX the TIRF REMS to ensure that safe use conditions have been met prior to dispensing.
- An **Implementation System** involves training and enrolling wholesalers/distributors who distribute TIRFs. The TRIG is required to maintain databases of prescribers, pharmacies, patients, and distributors, as well as develop a TIRF Access System;
- The **Timetable** for submission of REMS Assessment Reports was at 6 and 12 months for the first year then annually thereafter to be submitted on or before December 28th of each year.

The REMS Assessment Plan (approved December 11, 2017) **Appendix A.**

4. METHODS AND MATERIALS

4.1 REMS MATERIALS REVIEWED (SUBMITTED BY TRIG)

- September 7, 2017, sNDA and REMS Modification approval letter from DAAAP (S. Hertz)
- December 11, 2017, 60-month REMS Assessment Acknowledgement Letter (RAAL) from DAAAP (J. Racoosin)
- February 28, 2018, 72-month TIRF REMS Assessment Report submitted by the TRIG

- April 6, 2018, TRIG response to a March 31, 2018 FDA Information Request
- April 30, 2018, surveillance data addendum to the 72-month TIRF REMS Assessment Report submitted by the TRIG
- May 16, 2018, TRIG response to a May 9, 2018 FDA Information Request
- June 6, 2018, TRIG response to a May 2, 2018 FDA Information Request

4.2 FDA'S DRUG UTILIZATION ANALYSES

The FDA's **Office of Surveillance and Epidemiology (OSE)** performed analyses of the national utilization of TIRF medicines to supplement the review of the REMS assessment and to provide context for the Advisory Committee meeting discussion on August 3, 2018. Proprietary databases available to the FDA were used to conduct the drug utilization analyses (see **Appendix B** for full database descriptions).

4.2.1 SALES DISTRIBUTION DATA FROM MANUFACTURERS

The IQVIA National Sales Perspectives™ (NSP) database was used to provide the nationally estimated number of bottles/packages of TIRF medicines sold from manufacturers, stratified by setting of care, for years 2010 through 2017, annually. The sales distribution data were examined to determine the setting of care where TIRF medicines were primarily used. These data do not provide a direct estimate of TIRF use but do provide a national estimate of bottles/packages of TIRF medicines sold from manufacturers to various U.S. channels of distribution such as retail, mail-order/specialty, and hospital settings. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

4.2.2 PRESCRIPTION DATA

The IQVIA National Prescription Audit™ (NPA) database was used to provide the nationally estimated number of prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies from 2010 through 2017, annually. The top 10 prescriber specialties based on the volume of prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies in 2017 were also analyzed using the IQVIA NPA database.

4.2.3 PATIENT DATA

The IQVIA Total Patient Tracker™ (TPT) database was used to provide the nationally estimated number of patients who received prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies from 2010 through 2017, annually.

4.2.4 OFFICE-BASED PHYSICIAN SURVEY DATA

The Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel database was used to provide the diagnoses associated with the use of TIRF medicines, stratified by prescriber specialty, as reported by U.S. office-based physician surveys during 2017.

4.3 FDA'S SURVEILLANCE DATA ANALYSES

This integrated review summarizes the findings of the review conducted by DEPI II. The findings are based on surveillance data submitted by the TRIG and the following additional materials:

- Researched Abuse, Diversion, and Addiction Related Surveillance (RADARS®) Treatment Center Programs Combined report requested by the FDA through a contract with RADARS®
- National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) report requested by the FDA through a contract with Inflexxion®
- National Poison Data System (NPDS) report requested by the FDA through a contract with the American Association of Poison Control Centers (AAPCC). FDA reviewers conducted statistical analyses of these NPDS data.

5. RESULTS

The data in this section are primarily from the TRIG's 72-month assessment report; however, in some cases the FDA has provided additional data analyses, and these will be clearly identified as such.

The TRIG's surveillance data analyses describing adverse events involving TIRFs—i.e., abuse, addiction, misuse, unintentional therapeutic error, overdose, death, and pediatric exposure—as well as persistency with TIRF regimen are discussed, in detail, in a separate review by FDA's Division of Epidemiology (DEPI) II.

5.1. ASSESSMENT ELEMENTS 1 AND 2: UTILIZATION & DISPENSING DATA

5.1.1. FDA'S DRUG UTILIZATION ANALYSES

5.1.1.1. FDA'S ANALYSIS OF SALES DISTRIBUTION DATA FROM MANUFACTURERS[15]

Throughout the study period from 2010 through 2017, TIRF medicines were primarily sold from manufacturers to the outpatient retail setting, which accounted for approximately 84% of total bottles/packages of TIRF medicines sold in 2017. Non-federal hospitals and other non-retail settings such as clinics accounted for approximately 1% and 15%, respectively, of total bottles/packages of TIRF medicines sold from manufacturers in 2017. Therefore, we examined the utilization of TIRF medicines from outpatient retail pharmacies from 2010 through 2017.

5.1.1.2. FDA'S ANALYSIS OF OUTPATIENT RETAIL UTILIZATION DATA

PRESCRIPTION DATA:

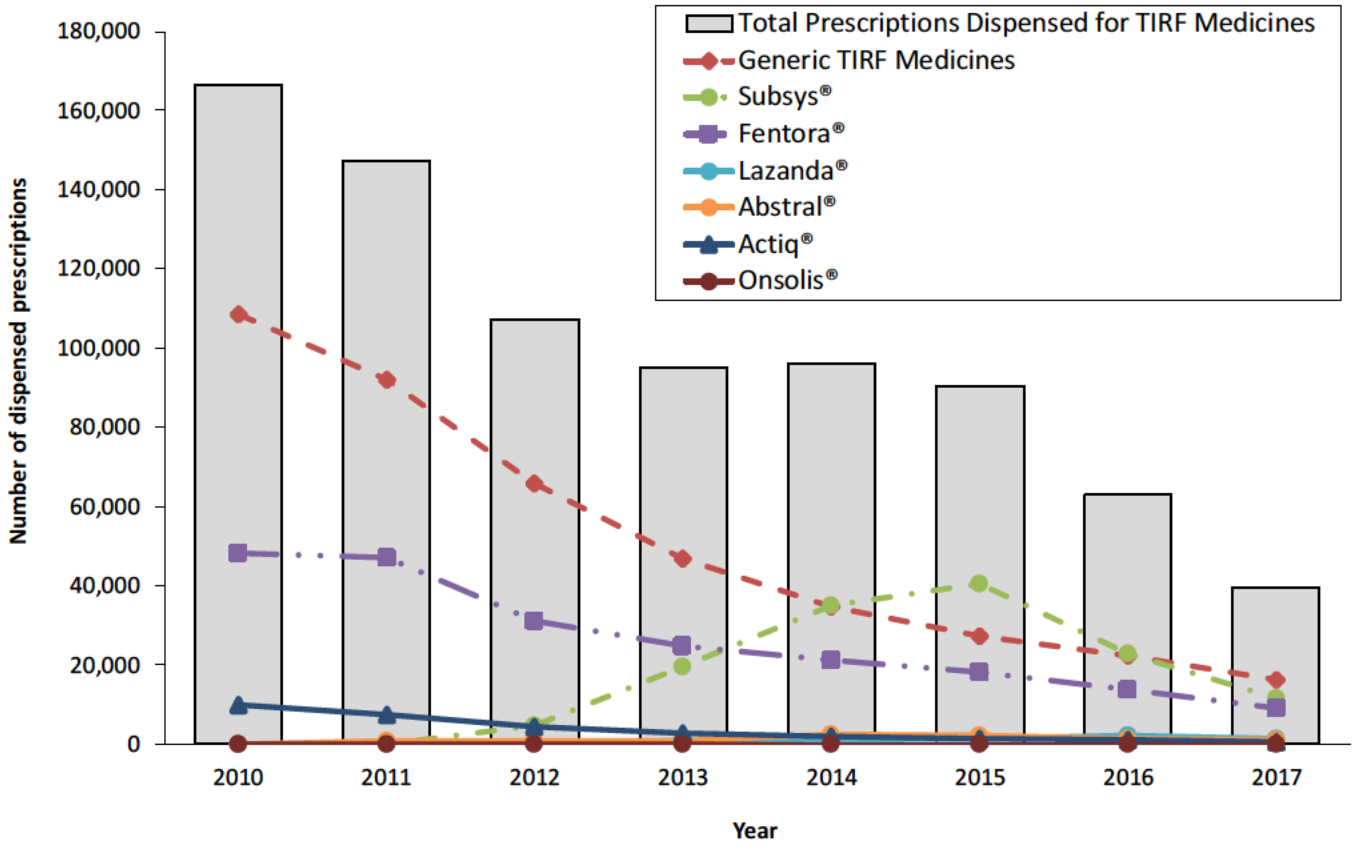
Figure 1 below and **Table A** in **Appendix C** provide FDA's analysis of the nationally estimated number of prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies. Overall, the total number of prescriptions dispensed for TIRF medicines decreased by 76% from 167,000 prescriptions in 2010 to 40,000 prescriptions in 2017 (see Figure 1 below). TIRF medicines accounted for 0.02% (40,000 prescriptions) of the estimated 196 million prescriptions

[15] Source: IQVIA National Sales Perspectives™, 2010-2017. Data extracted April 2018.

dispensed in 2017 for opioid analgesic medicines in the outpatient retail setting (see Figure 2 below).

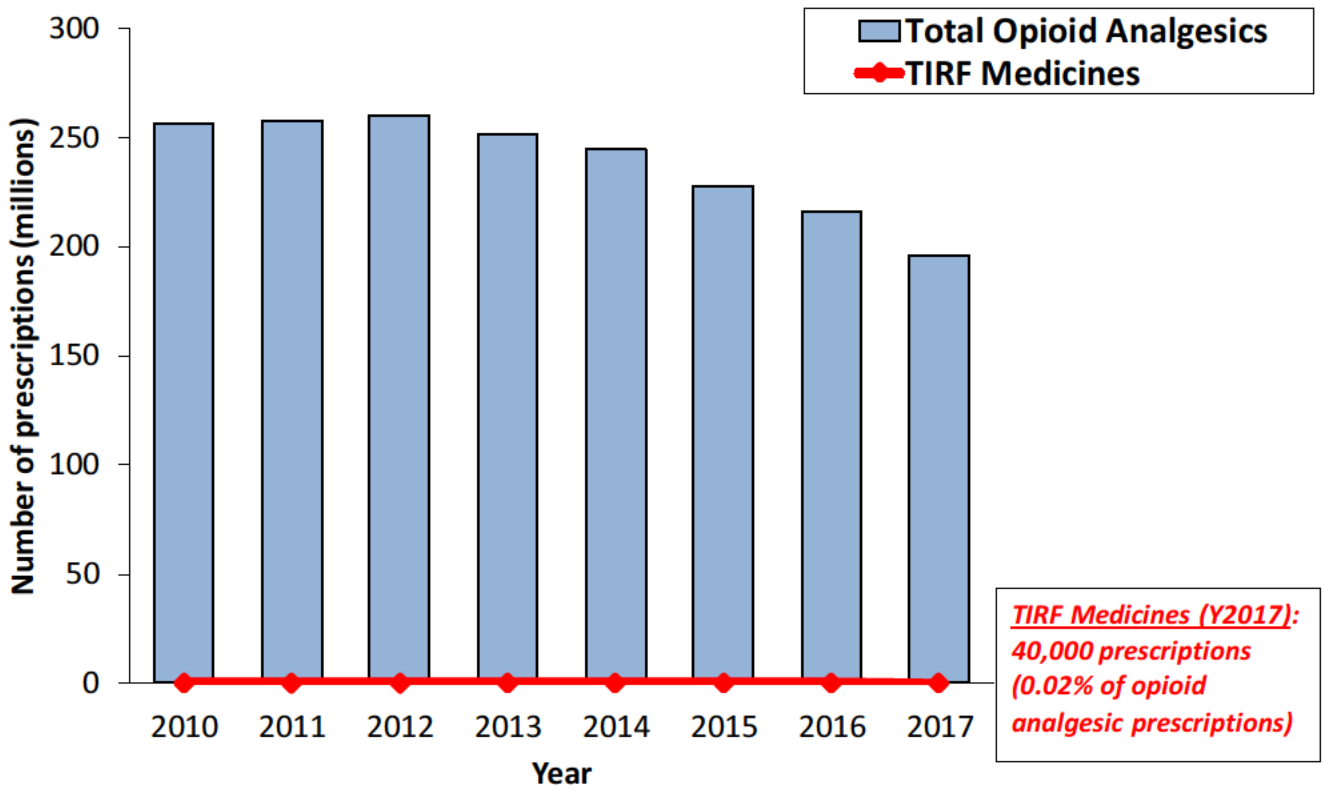
Prior to 2014, the highest proportion of prescriptions for TIRF medicines were dispensed for generic TIRF medicines and Fentora®. By 2017, generic TIRF medicines accounted for 41% (16,000 prescriptions) of total dispensed prescriptions, followed by Subsys® at 29% (12,000 prescriptions) and Fentora® at 22.5% (9,000 prescriptions) of total dispensed prescriptions.

Figure 1: Nationally estimated number of prescriptions dispensed for transmucosal immediate release fentanyl medicines from U.S. outpatient retail pharmacies, 2010-2017



Source: IQVIA National Prescription Audit™. 2010-2017. Data extracted May 2018.

Figure 2: Nationally estimated number of prescriptions dispensed for opioid analgesic medicines from U.S. outpatient retail pharmacies, 2010-2017

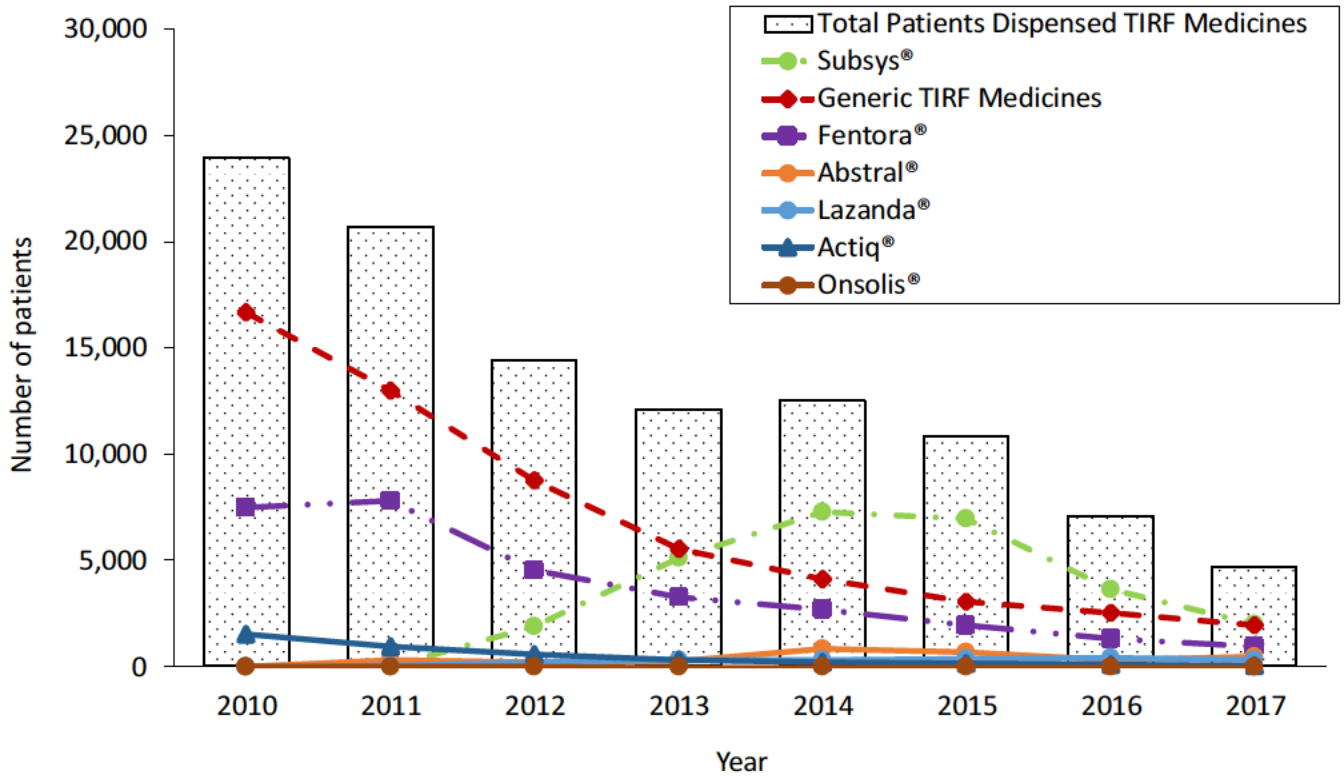


Source: IQVIA National Prescription Audit™ (NPA) and static data 2006-2011 (Extracted March 2017) and data 2012-2017 (Extracted February 2018). Time Period: January 2006- December 2017.

PATIENT DATA:

Figure 3 below and **Table B** in **Appendix C** provides the nationally estimated number of patients who received prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies. Similar to dispensed prescription data, the total number of patients who received prescriptions dispensed for TIRF medicines decreased by 80% from 24,000 patients in 2010 to 5,000 patients in 2017. Subsys® and generic TIRF medicines each accounted for approximately 42% (2,000 patients) of total patients who received TIRF prescriptions dispensed in 2017, respectively, followed by Fentora® at 20% (928 patients).

Figure 3: Nationally estimated number of patients who received prescriptions dispensed for transmucosal immediate release fentanyl medicines from U.S. outpatient retail pharmacies, 2010-2017



Source: IQVIA Total Patient Tracker™. 2010-2017. Data extracted May 2018.

Prescriber Specialties:

Table C in **Appendix C** provides the top 10 prescriber specialties based on the nationally estimated number of prescriptions dispensed for TIRF medicines from U.S. outpatient retail pharmacies in 2017. Anesthesiologists were the top prescriber specialty, accounting for approximately 22% of total TIRF dispensed prescriptions in 2017. Nurse practitioners and physician assistants, physical medicine and rehab specialists, and pain medicine specialists followed at 15%, 13%, and 12%, respectively, of TIRF dispensed prescriptions.

5.1.1.3. FDA's Analysis of Office-Based Physician Survey Data

Table D in **Appendix C** provides the nationally estimated number of drug use mentions[16] associated with the use of TIRF medicines, stratified by prescriber specialty, as reported by U.S. office-based physician survey database. In 2017, the use of TIRF medicines was mainly

[16]Syneos Health Research & Insights LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

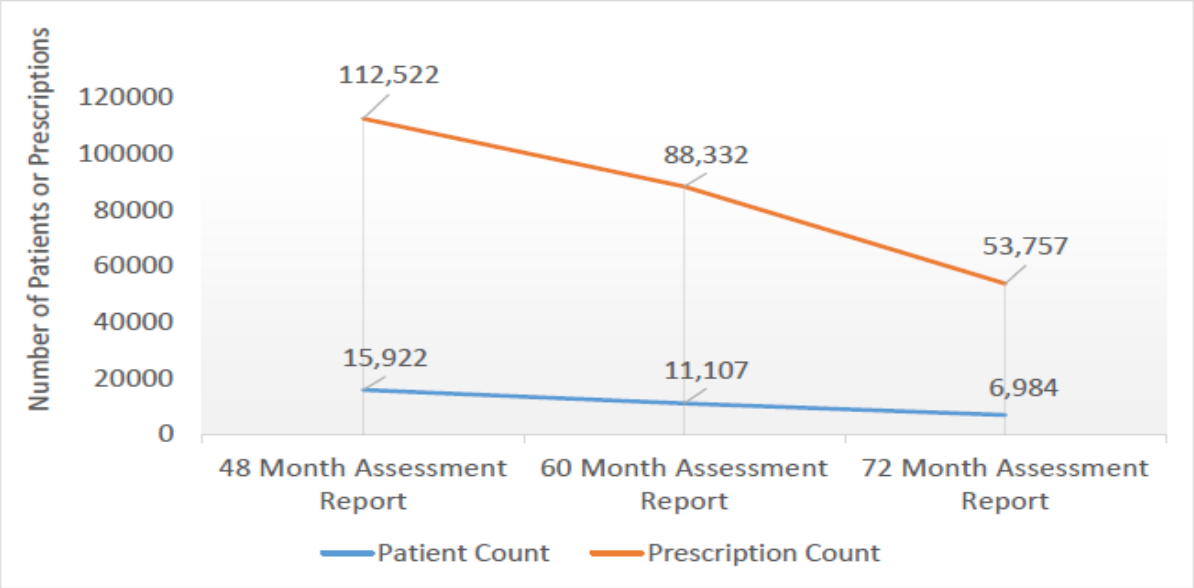
mentioned by pain specialists in the office-based setting for the diagnoses of pain, not elsewhere classified (ICD-10 code G89) at 38% of total TIRF mentions. Cancer-related conditions (ICD-10 codes C00-D49), and abdominal and pelvic pain (ICD-10 code R10) each followed at 31% of total TIRF mentions. However, the estimated number of drug use mentions for TIRF medicines were too low (<100,000 use mentions) to provide reliable national estimates of use.

5.1.2. THE TRIG'S UTILIZATION AND DISPENSING DATA

Patients:

The TRIG notes that there has been a substantial decrease in both the reported number of active patients in the TIRF REMS program (active is defined as the number of patients dispensed a TIRF 'during the timeframe') and the number of TIRF prescriptions dispensed (claims paid and not reversed) since the 48-month assessment report. Compared with the 48-month report, the number of active patients in this reporting period has decreased by 52.2% (from 15,922 to 6,984 patients) and the respective number of prescriptions dispensed has decreased by 56.1% (from 112,522 to 53,757 prescriptions). **Figure 4** below (taken from the TRIG's report) depicts this graphically.

Figure 4: Changes in Active Patients and Prescriptions Over Time



During the current reporting period, there were **2,570 newly enrolled patients** (compared to 4,225 in the 60-month report, and 8,740 in the 48-month report), resulting in a cumulative total of 44,724 patients enrolled in the TIRF REMS. Only 6,371 unique patients were dispensed a TIRF medicines during this reporting period based on paid claims as of the end of the reporting period (data on file with the TRIG).

Prescribers:

At the end of this reporting period there were **6,606 prescribers currently enrolled** (8,151 enrolled last year and 9,096 enrolled the year before). This current total of 6,606 includes 894

newly enrolled prescribers, 1,775 prescribers who re-enrolled and 3,937 who remain active from a previous period.

Pharmacies:

At the end of this reporting period, **42,615 pharmacies were currently enrolled** in this REMS and 42,386 (99.5%) were non-closed system pharmacies. Of these non-closed system pharmacies:

- 88.8% (37,837) were chain pharmacy stores
- 8.8% (3,769) were independent outpatient pharmacies
- 1.7% (706) were inpatient pharmacies

Overall the number of pharmacies in the REMS program has remained fairly constant over time.

In the TRIG's May 30, 2017 response to the Agency's April 28, 2017 Information Request, the TRIG states that: "*The TIRF REMS Access program defines independent outpatient pharmacies as "retail, mail order, or institutional outpatient pharmacies*". In the 60-Month RAAL, DRISK requested that the TRIG research and report what proportion of prescriptions come from each one of the 3 sub-types of the independent pharmacy category. In the current assessment report, the TRIG stated that their current enrollment form does not allow for the collection of such data. The TRIG stated that the enrollment form needs to be changed to enable them to collect these data and that will be done in conjunction with any future REMS modifications.

Prescriber and pharmacy inactivations are summarized in **Appendix Section D.1**., including Appendix D, **Table A.** The reason why 92% of prescribers/pharmacies did not re-enroll was due to "Change in Prescribing/Dispensing Data."

TIRF REMS Prescription dispensation/rejections

The TIRF REMS will reject prescriptions that do not fulfill all of the requirements of the REMS such as a prescription written by an unenrolled prescriber, a prescription being filled at an unenrolled pharmacy, or a missing/incomplete/incorrect Patient-Prescriber Agreement Form (PPAF). Of the 69,211 unique prescriptions (closed and non-closed systems) submitted for REMS authorization this reporting period, 90.4% met REMS requirements and were authorized for dispensing. Of these 90.4%, 63.0% were filled at independent pharmacies versus 36.4% from chains. Recall that independent pharmacies comprised only 8.8% of pharmacies enrolled in this REMS this reporting period

The TRIG also presents data regarding prescriptions that either encountered at least one REMS-related rejection or were totally rejected due to REMS criteria

- For this reporting period, 1.6% of prescriptions experienced a REMS-related rejection but were subsequently authorized for dispensing. The reasons for initial rejection involved either an incomplete PPAF and/or a prescription written by a non-registered prescriber
- Also during this reporting period, 7.9% of TIRF prescriptions encountered at least one REMS-related rejection and were never authorized for dispensing. Overall the reasons for these rejections were similar to those rejections noted in the preceding paragraph but also now include "Prescriber is terminated"**.**

In the 60-Month RAAL, the FDA requested data for when a TIRF prescription experiences a REMS-related rejection due to a missing or incomplete PPAF, the number of instances the prescriber ceased to attempt to rectify the situation with the TIRF prescription and instead prescribed an alternative therapy. In the assessment report, the TRIG states that data to confirm whether the prescriber pursued an alternative therapy are not available through the REMS.

Table 1 *below (taken in part from the TRIG's 72-month REMS Assessment Report, Table 17) presents the mean and median times to eventual prescription authorization after the prescription experienced at least one REMS-related rejection per pharmacy type.* Data in the table indicate that the mean and median prescription processing time for a prescription that experienced at least one initial REMS-related rejection continue to increase over time for both chain and independent stores.

Table 1: Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection

	72 month Reporting Period 29OCT2016 to 28OCT2017	**60 month** Reporting Period 29OCT2015 to 28OCT2016	**48 month** Reporting Period 29OCT2014 to 28OCT2015	**36 month** Reporting Period 29OCT2013 to 28OCT2014	**24 month** Reporting Period 29OCT2012 through 28 OCT2013	**Cumulative** 28DEC2011 to 28OCT2017
Total Mean Time For Prescription to be Authorized[a] (Days)[b]	6.95	6.30	6.68	4.90	2.10	**4.15**
Inpatient Pharmacies	--	--	--	--		--
Chain Pharmacy Stores	7.78	7.14	7.81	5.10		**5.11**
Independent Outpatient Pharmacies	6.38	5.46	6.25	4.82		**3.73**
Closed System Pharmacies	--	56.86[c]	--	10.04		**7.16**
Total Median Time For Prescription to be Authorized[a] (Days)[b]	2.05	2.03	1.32	1.06	0.01	**0.76**
Inpatient Pharmacies	--	--	--	--		--
Chain Pharmacy Stores	2.85	2.80	2.17	1.73		**1.23**
Independent Outpatient Pharmacies	1.88	1.68	1.03	0.98		**0.18**
Closed System Pharmacies	--	56.86[c]	--	2.48		**1.16**

a Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.
b Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process.

In the 36-month, 48-Month, and 60-month RAALs, the FDA requested that the TRIG investigate the cause of increasing delays in prescription processing since these may be potential indicators of access barriers. Previous responses to this request of FDA's have not included an investigation as to the reasons for these increasing delays.

In the current report, the TRIG states that over the period of 29 October 2014 through 28 October 2017, an analysis of prescription processing times for prescriptions that encountered at least one REMS-related rejection was conducted to evaluate trends over time. The TRIG reports that the number of prescription transactions completed in less than 25 days has gone down significantly over time while the number of prescription transactions completed in more than 25 days has generally remained the same and that this has resulted in an increase in average and median prescription processing time. The TRIG then states that "*Some of the possible reasons that can contribute to the number of prescriptions transactions completed in more than 25 days are:*

- *Patient drops the prescription at the pharmacy but does not pick up the drug for a while because they may be admitted to the hospital and may be receiving the drug from hospital;*
- *Patient drops the prescription at the pharmacy and realizes that they don't need the drug for a while; and*
- *Based on the patient request, pharmacist runs the prescription transaction to check the copay but then patient may not pick the drug."*

In the FDA's December 11, 2017 RAAL, the TRIG was asked to clarify whether the term "authorization" used by the TRIG is limited to REMS authorizations or insurance authorizations. In the current assessment report, the TRIG confirmed that the term "authorization" is limited to only REMS authorizations.

PPAF Data:

The REMS is to monitor prescribers' compliance with the requirement to complete a PPAF with each TIRF patient, and to submit the PPAF to the REMS within ten (10) working days. A maximum of three prescriptions are allowed within 10 working days from when the patient has their first prescription filled. No further prescriptions will be dispensed after the 10 working day window until a completed PPAF is received. The TRIG also points out that a patient can receive prescriptions both without and then with a PPAF in the first 10 days depending on when the PPAF was filled out and thus data regarding dispensing with and without a PPAF likely contains some patients that appear in both categories.

For this reporting period:

- 1,739 prescriptions (1,735 from non-closed systems) were dispensed to 1,505 patients within the first 10 days after patient enrollment
- 533 patients received 1 prescription fill within 10 days without a PPAF on file
- 31 patients received 2 prescription fills within 10 days without a PPAF on file.
- No patients received 3 or more prescription fills within 10 days without a PPAF**.**

From the inception of this REMS through the current reporting period, 798 prescriptions have been dispensed beyond the first 10 days without a PPAF across all pharmacies (closed and non-closed); however, during the current reporting period, and across all pharmacies, no prescriptions were dispensed beyond 10 days after enrollment without a PPAF.

FDA COMMENTS RE: UTILIZATION & DISPENSING:

1. The number of newly enrolled patients & currently enrolled prescribers in the REMS continues to decrease over time as does the number of prescriptions dispensed (those with claims paid & not reversed). FDA's utilization analysis also showed a 76% decrease in prescriptions dispensed for TIRF medicines from the U.S. outpatient retail setting.
2. Of the 69,211 unique prescriptions (closed and non-closed systems) submitted for REMS authorization this reporting period, it is only a minority of prescriptions

(7.9%) that incur at least one REMS-related rejection and are never authorized for dispensing. Thus 92% of TIRF prescriptions are eventually authorized by the REMS.

3. Chain pharmacies make up the majority (88.8%) of pharmacies in the TIRF REMS program, while independent pharmacies comprise only 8.8%. The TRIG reports that their category of independent pharmacies is composed of retail, mail order and institutional outpatient pharmacies. However, the TRIG is not able to provide the proportion of prescriptions that come from each one of the 3 sub-types since the current pharmacy enrollment form does not allow for the collection of such data. Upon any subsequent modificaction of this REMS, the pharmacy enrollment form should be modified to include collection of data regarding the three independent pharmacy subtypes.
4. Since the implementation of this REMS, of the prescriptions submitted for REMS authorization that did not encounter any REMS-related rejections, 65.2% were filled at independent pharmacies versus 34.3% from chains.
5. Of the 7,180 chains that inactivated, 12% remained inactivated; of the 617 independent outpatient pharmacies that inactivated, 85% remained inactivated. This pattern of a greater number of independent pharmacies versus chains not re-enrolling was noted in both the 48-month and 60-month reports and, the FDA asked the TRIG to investigate this finding. In the current report, the TRIG states that they were not able to determine the reason for this discrepancy. However, the TRIG speculates that independent pharmacies are typically more likely to have changes in their dispensing activity as well as may be subject to acquisitions by chain pharmacies. These reasons may or may not be related to this observation but in either case, no substantiating data are provided for either rationale.
6. For prescriptions that experience at least one initial REMS-related rejection, mean and median prescription processing times continue to increase over time for both chain and independent stores. The TRIG's investigation into this steady increase indicates that: "*The number of prescription transactions completed in less than 25 days has gone down significantly over the years while the number of prescription transactions completed in more than 25 days has generally remained the same resulting in an increase in average and median time*."

   The TRIG then provides "*…possible reasons that can contribute to the number of prescriptions transactions completed in* more than 25 days:

   - *Patient drops the prescription at the pharmacy but does not pick up the drug for a while because they may be admitted to the hospital and may be receiving the drug from hospital;*
   - *Patient drops the prescription at the pharmacy and realizes that they don't need the drug for a while; and*
   - *Based on the patient request, pharmacist runs the prescription transaction to check the copay but then patient may not pick up the drug."*

   The TRIG did not provide their rationale or their methodology for selecting 25 days as demarcation for increased processing in time. Twenty-five days would seem to be a very long period of time to wait for a drug used for breakthrough pain. For example, a point of demarcation of 2 days might be more reasonable. In addition, the reasons

provided for this increase in processing times noted over the years remain speculative. The TRIG is once again encouraged to do a root cause analysis to determine the cause of these increasing delays.

7. In future REMS assessments, the TRIG should conduct an analysis as to whether upon receiving a complete REMS rejection of a prescription, what proportion of prescribers instead pursue an alternative therapy.

5.2. ASSESSMENT ELEMENT 3: PROGRAM INFRASTRUCTURE (ASSESSMENT REPORT DATA)

During this reporting period there were no instances in which a backup system was used to validate a prescription due to pharmacy level problems, switch problems, or REMS database problems. There were no unintended system interruptions during this reporting period as well as no reports of program/system problems that occurred in this reporting period.

Of the 137,770 calls received by the TIRF REMS Call Center, the top 5 reported reasons for the calls were: enrollment status inquiry (17.1%); pharmacy claim rejection (16.0%); PPAF inquiry (10.2%), general program questions (6.0%); and Web portal log-on assistance (5.7%).

5.3. ASSESSMENT ELEMENT 4: PROGRAM NON-COMPLIANCE (ASSESSMENT REPORT DATA)

In the 72-month report, the TRIG states that non-compliance is reported via solitary (1 or 2) or repeated non-compliance events; via the closed-system pharmacy audits; and via inpatient hospital pharmacy audits, and that events from all of these sources are additive. **Table 7** in **Appendix Section D.2** summarizes the solitary non-compliance events.

5.3.1. PRESCRIBER REMS NON-COMPLIANCE:

Currently, the TRIG defines a single non-compliant event involving PPAFs to involve "***5 or more patients*** *enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date*." The TRIG reports 28 instances of PPAF non-compliance events. Given that there were 28 such instances with at least 5 or more patients involved, we estimate that there were a minimum of 140 patients affected by PPAF non-compliance with the REMS. Of the 28 events, the TRIG did not include reasons for 13 of them; for 7 events, the reason was that the prescriber was not aware of the PPAF requirement; for 5 events, the reason was due to the prescriber being aware of the PPAF requirement but not completing one; and in 3 events, the prescriber was aware of the PPAF requirement, completed the PPAFs, but failed to send the PPAFs to the REMS.

In both the 48-month and 60-month RAALs, the FDA expressed concerns about the TRIG's threshold of noncompliance (at least 5 patients without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date) before a formal non-compliance event is triggered. FDA expressed concern about underreporting of PPAF noncompliance and the TRIG was directed to capture lower levels of non-compliance. After discussions with FDA on October 4, 2017, the TRIG states in the 72-month report that they will "*…reduce the threshold of patients enrolled without a PPAF from 5 patients to 1 patient before the trigger for a non-compliance event."* The TRIG does not provide a timeframe for this change.

In response to a previous request by the FDA (the 48-month RAAL) in the TRIG conducted outreach to 64 prescribers who failed to submit PPAFs in a timely manner to solicit their reasons for non-compliance. The main findings of this outreach were as follows:

- 31 (48%) - prescriber could not be reached
- 10 (16%) - prescriber reported issues with staff/training gaps among staff
- 8 (~13%) - prescriber could not recall the reason for non-compliance
- 8 (~13%) - prescriber not aware of the PPAF requirements

There were 2 prescribers who had multiple PPAF non-compliance events over many years:

- In the first case, PPAFs were not submitted to the REMS for 18 patients spanning September 2014 to December 2016. The TRIG began trying to initiate contact with the prescriber in December 2016, issued a Warning Letter, suspended, and then deactivated August 2017.
- In the second case, PPAFs were not submitted to the REMS for 16 patients spanning March 2013 to July 2017. The TRIG initiated contact with the prescriber in July 2017, issued a Warning Letter August 2017, and after multiple deficient corrective action plans (CAP) were submitted, a CAP was approved November 2017.

In the 60-month RAAL, the FDA pointed out to the TRIG that the 60-month assessment report "*… continues to include cases of prescribers who receive numerous Notices of Violation, Warning Letters, and then file several CAPs before one is accepted. Yet, these prescribers are rarely suspended and apparently never deactivated from the program."* The TRIG was encouraged to add more specificity to their non-compliance protocol. Following discussions between the FDA and the TRIG, the 72-month report contained the compliance process suggested by the FDA as follows:

- *A first offense of non-compliance will result in a Warning*
- *A second offense of non-compliance will result in a Suspension*
- *A third offense of non-compliance will result in a Deactivation (3 yrs)]*

In the current report, the TRIG states their concern that "*…these changes in combination* [including setting 1 PPAF not on file as noncompliance] *could result in a prescriber becoming inactivated from the program upon enrollment of their third patient without a PPAF*."

5.3.2. PHARMACY NON-COMPLIANCE

Non-closed system pharmacies reported 11 solitary (1-2) non-compliant events. Of these, 9 involved either bypassing the REMS authorization process (6 events) or receiving a REMS rejection notice, but proceeding to dispense the drug (3 events). One additional case involved altering prescription details in order to obtain REMS authorization, and one case of an inpatient pharmacy not complying with the REMS (details not provided).

Additionally, during the reporting period, two non-closed system pharmacies dispensed a TIRF prescription a total of three times after receiving a REMS rejection. The prescriptions were rejected by the REMS because they were written by non-enrolled prescribers. Both pharmacies were re-educated by the REMS and one pharmacy was issued a first notice of noncompliance.

Also during this reporting period, two non-enrolled pharmacies dispensed a total of 7 prescriptions. Both pharmacies were re-educated about the REMS (both pharmacies had been previously enrolled in the REMS) and were issued notices of non-compliance.

Lastly, there were three pharmacies that had 210 TIRF prescriptions impacted by inadvertent non-configuration with REMS validation routing logic. Once the issue was realized, of the 210 prescriptions dispensed, 38 would have been rejected based on REMS requirements (e.g.., prescriber enrollment, passive patient enrollment). All three pharmacies were issued a notice of non-compliance.

Since all of the aforementioned pharmacy non-compliance events have been self-reported, the FDA urged the TRIG (in both the 48-month and 60-month RAALs) to develop proactive mechanisms to capture these events. In the 72-month report, the TRIG states that they "…*will develop an audit process to identify non-compliance events where a non-closed–system pharmacy dispenses a TIRF product after receiving a REMS rejection*."

Miscellaneous

The TRIG states from the pharmacy noncompliance data, there were no reports of TIRF medicines being prescribed to an opioid non-tolerant patient and no cases of inappropriate conversions between TIRF products during this reporting period.

5.3.3. Closed System Audits

The six closed-system pharmacies enrolled in the TIRF REMS during this reporting period as well as the overall numbers/percent of prescriptions dispensed are featured below in **Table 2:**

Table 2: Number of Prescription Authorizations per Closed System Pharmacy Cumulatively

	Cumulative 28DEC2011 to 28OCT2016
Total Number of Closed System Pharmacy Prescriptions Authorizations	3,118
Kaiser Permanente	1,170 (37.5%)
CVS Caremark	1,076 (34.5%)
ESI Mail Pharmacy Services Inc Dba Express Scripts	448 (14.4%)
Veterans Affairs	279 (8.9%)
DLA Troop Support	133 (4.3%)
Landmark Medical Center	8 (0.3%)
National Institutes Of Health	4 (0.1%)

(Reproduced from the TIRG's 72 month REMS assessment report) for the TIRFs)

Kaiser Permanente and CVS Caremark account for 72% (3,118) of the cumulative total of closed system prescriptions authorized. The aforementioned governmental entities account for a cumulative total of 13.6% of the closed system prescriptions authorized.

Previous audits of closed system have indicated that the governmental closed systems (the VA and DLA) had the highest percentage of prescriptions that were dispensed without a REMS authorization. In the 60-Month RAAL, the FDA agreed with the TRIG that it may not be practical to convert the two governmental closed pharmacies to a switch system as used by non-closed–system pharmacies. The FDA suggested that the TRIG request that the VA and DLA

- build in system alerts reminding pharmacists of REMS requirements;
- develop two-person check when any TIRF is dispensed to ensure that REMS processes are followed.

In the current assessment report, the TRIG reports that they sent a Warning Letter to both governmental entities asking them for a CAP and citing the 2 suggestions above. Both entities were also told that failure to provide a complete response within 15 business days from the date of this letter may result in suspension or deactivation of their enrollment in the TIRF REMS. The TRIG stated that they will report an update on this in the Assessment Report due December 2018.

For the current audit, the TRIG included all closed-system pharmacies in the audit with a request to provide dispensing records from May 1, 2016 through June 30, 2017. There was a total of 6 closed-system pharmacies audited during this reporting period. The audit process used is described in **Appendix D.3.** Three closed-system pharmacies were found to be non-compliant with the TIRF REMS requirements:

- Defense Logistics Agency (DLA) Troop Support where 63% (17/27) of TIRF dispensations were not adjudicated through the REMS authorization process
- Department of Veterans Affairs (VA) where 54% (43/79) of TIRF dispensations were not adjudicated through the REMS authorization process
- Kaiser Permanente where 4% (4/105) of TIRF dispensations were not run through the REMS authorization process

Both DLA and the VA were issued a request for a CAP after each audit period (both entities had three audit periods) and both were issued a Warning Letter regarding their non-compliance over all 3 monitoring periods. Kaiser Permanente was issued a Warning Letter after their one audit period which also requested that they submit a CAP.

5.3.4. INPATIENT PHARMACY AUDIT

The inpatient hospital pharmacy audit process starts with an audit questionnaire invitation that is faxed to authorized inpatient pharmacist(s) of pharmacies that are enrolled in the TIRF REMS requesting their participation. Once the authorized inpatient pharmacist agrees to participate, they receive the audit questionnaire. If the authorized pharmacist confirms that they are a hospital pharmacy and have dispensed a TIRF in the previous 12 months, they are then asked the following:

1. *Provide the number of units dispensed within <insert date range>. (See NDC list for a current listing of TIRF NDCs) _____units of use of TIRFs dispensed to inpatients.*

2. *Did all pharmacists who dispensed TIRF medicines complete training on the TIRF REMS Access program prior to dispensing these products? Yes/No*
3. *Do you have procedures in place such as order sets/protocols to assure compliance with the TIRF REMS program requirements? Yes/No.*
    a. *If yes, are you willing to provide examples of an order set or protocol?*

During this reporting period:

- 29 enrolled inpatient locations were solicited for participation in the audit.
    - 9 did not respond.
- The remaining 20 agreed to participate
- Of the 20 pharmacies, 15 pharmacies answered no to at least one of the qualifying questions (not a hospital inpatient pharmacy facility or hadn't dispensed TIRFs in the previous 12 months).
    - The remaining 5 proceeded with answering the 3 remaining audit questions and their responses to these 3 questions indicated that they passed the audit.

In FDA's 48 month RAAL, the FDA communicated that it was considering revisions to the pharmacy enrollment form to inform inpatient pharmacies that as a condition of enrollment into the REMS, they are audited about the REMS. In addition, to better inform inpatient pharmacies of their responsibilities in the REMS, such a change could also increase the potential pool of inpatient pharmacies in the audit. In the 60-month assessment report the TRIG indicated that they were considering this change. In the current assessment report, the TRIG stated that the "*TRIG acknowledges that this revision needs to be made to the enrollment form and this will be done in conjunction with any REMS modifications*."

5.3.5. FDA COMMENTS RE: TRIG'S NON-COMPLIANCE DATA

1. Regarding the Closed-System Pharmacy audits, the Federal pharmacy entities (DLA and the VA) continue to struggle with their processes for obtaining dispensing authorization from the REMS. We have previously asked the TRIG to suggest process improvements to the two closed systems. The effects of such changes will be reported upon in the TRIG's 84-month assessment report due to the Agency on December 28, 2018.

2. Regarding the Inpatient Pharmacy audits:
    a. In the 48-month assessment report, 6 inpatient pharmacies either did not respond to the audit request or decided not to participate. In the 60-month assessment report, 3 pharmacies did not respond to an audit request. In the current report, of the 29 invitations send to enrolled inpatient pharmacies, 9 did not respond. Upon enrolling into the REMS program, the inpatient pharmacy enrollment form makes no mention that as a condition of enrollment, pharmacies may be asked to participate in an audit. The inpatient enrollment form should be modified as soon as feasible to stipulate to inpatient pharmacies that as a condition of enrollment, they may be subject to an audit by the REMS.
    b. Of the 20 enrolled inpatient pharmacies that responded to the audit request, 15 (75%) were either not a hospital inpatient pharmacy facility or hadn't dispensed TIRFs in the previous 12 months. These data seem to further support the need for the inpatient

enrollment form to be modified so that these pharmacies are aware that they may be audited.

3. The TRIG has stated in the current assessment report that they will be changing the criteria for one non-compliance event from 5 patients without a complete PPAF on file, (with each patient having greater than 10 working days lapse from the initial enrollment date) to one patient. The TRIG also states that their non-compliance protocol will clearly articulate the non-compliance pathway to deactivation from the program, which will now be a "three strike" process. However, the TRIG does not provide a timeline for either change to occur. The FDA looks forward to assessing the impact of these changes.

4. As in previous reports, the current assessment report states that there were no reports of TIRFs being prescribed to an opioid non-tolerant individual or cases of inappropriate conversions between TIRF products. The Agency has repeatedly commented that spontaneous reports are not suitable to assess the extent of TIRF use in opioid non-tolerant patients or the extent inappropriate interchanges between TIRF products.

5.4. SURVEILLANCE DATA

The TRIG's surveillance data came from internal and external databases that focus on events of misuse, abuse, addiction, overdose, death, unintentional therapeutic error, and pediatric cases—as well as persistency with TIRF regimen. Spontaneous adverse event reports included in the TRIG assessment report are reviewed below. Other results from the TRIG's external surveillance data are discussed in detail in a separate review by FDA's Division of Epidemiology (DEPI) II[13] and are described here, in brief.

5.4.1 SPONTANEOUS ADVERSE EVENT REPORT DATA (ASSESSMENT REPORT DATA)

The spontaneous adverse event report data focuses on four categories of adverse events of interest – addiction, overdose, death, and pediatric exposure – retrieved primarily by utilizing specific Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) outlined in the assessment report. Within this reporting period, the TRIG reported a total of 568 cases of reported adverse events of interest associated with a TIRF medicine. Of these, 549 (96.7%) had an outcome of death, 34 (6.0%) were cases of overdose, 10 (1.8%) were cases of addiction, and there was 1 (0.2%) pediatric exposure. A case may report more than one adverse event of interest; hence, the categories are not mutually exclusive. In the 60-month RAAL, the Agency requested assessment of the spontaneous adverse event data to be reported separately by TIRF medicine in the 72-month report; however, this was not provided in the 72-month report.

Additionally, the TRIG identified 55 adverse event cases that were not included in previous REMS assessments. Of the 55 new cases, 43 reported an outcome of death, five included cases of overdose, five cases noted addiction, and three cases noted pediatric exposures. One case of overdose also had an outcome of death.

Table 3 (adapted from TRIG's 72-month REMS assessment report, Table 27) presents the number of cases of adverse events of interest for the 72-month reporting period as well as the updated number of cases for the 60-month, 48-month, and 36-month reporting periods.

Table 3: Number of Cases of Adverse Events of Interest by Reporting Period

	Current (72-Month) Reporting Period 29AUG2016-28AUG2017 **Number of AEs (N)***	**60-Month Reporting Period** 29AUG2015-28AUG2016 **Number of AEs (N)*,†**	**48-Month Reporting Period** 29AUG2014-28AUG2015 **Number of AEs (N)*,†**	**36-Month Reporting Period** 29AUG2013-28AUG-2014 **Number of AEs (N)*,†**
Addiction	10	6	16	6
Death	549	359	305	414
Overdose	34	5	10	2
Pediatric Exposure	1	5	5	2

* Cases may* Cases may have more than one adverse event of interest.
† Reflects updates from additional cases the TRIG identified during the 72-month reporting period

Of the 549 cases reporting an outcome of death in the 72-month reporting period, the TRIG assessed 5 cases as possibly causally-related to the TIRF medicine and two as related (physician confirmed inappropriate use of the TIRF medicine; further information on the inappropriate use was not provided). Of the five possibly related cases, three reported the MedDRA PT *Respiratory arrest* or PT *Respiratory depression*. The reported indications for these three cases were prostate cancer, [unspecified] cancer, and breakthrough cancer pain. The TRIG's summary analysis did not provide additional details (e.g., clinical course preceding the event, opioid tolerance) on these three cases that may provide further clarity on the TRIG's causal assessment. Of the remaining 542 cases, the TRIG assessed 187 deaths as not related to the TIRF medicine and 355 as lacking sufficient information for causality assessment.

The 72-month assessment report provided two notable descriptive characteristics for the 549 cases reporting an outcome of death. First, in 261 of the deaths the indication for the TIRF medicine was related to [unspecified] breakthrough pain/breakthrough cancer pain and/or a cancer diagnosis. Second, in more than 130 cases, hospice care was noted. Among the 288 death cases that did not report an indication for breakthrough pain/breakthrough cancer pain and/or a cancer diagnosis, FDA notes there are 257 cases with an unknown indication, 20 reporting pain (including chronic and severe pain), 5 with a non-cancer/back-related pain indication, and 6 with other non-cancer indications.

The one pediatric exposure case from the 72-month reporting period included the PT *Product use in unapproved indication* and PT *Drug administered to patient of inappropriate age*. No additional information, such as indication for TIRF use, was provided. Similarly, the line listings from the three new pediatric exposures from previous reporting periods, included the *PT Drug administered to patient of inappropriate age* and no additional information was provided in the summary analysis.

The TRIG assessed the 568 adverse events of interest cases for the following metrics: 1) inappropriate conversions between TIRF medicines, 2) unintentional or accidental exposures, and 3) use of the TIRF medicine by an opioid non-tolerant patient. Within this subset of cases (cases of addiction, overdose, death, or pediatric exposure), the TRIG's report states they did not identify any cases meeting any of these three metrics of interest.

5.4.2 FDA'S COMMENTS ON THE TRIG'S SPONTANEOUS ADVERSE EVENT REPORT DATA

The spontaneous adverse event report data in the TRIG's 72-month assessment report is insufficient to determine whether there are new safety signals related to the four adverse events of interest with the use of TIRF medicines. The adverse events of interest are known risks with the use of TIRF medicines and are prominently labeled to communicate these risks in current product labeling. **Table 3** shows an increase in the number of cases reporting death or overdose in the past reporting periods. Given the decrease in utilization of TIRF medicines **(See Figure 1 and Appendix C, Tables A and B)**, this increase in the number of spontaneous adverse event cases for death and overdose is potentially concerning, however, these data should be interpreted with caution. Reporting rates were provided by the TRIG and show a notable increase for death and overdose in this reporting period. However, given the minimal case level details provided in the assessment report and large number of cases that the TRIG determined lacked sufficient information for causality assessment, the interpretability is hampered. More specifically, among the death cases, 65% (355/549) were assessed by the TRIG as having insufficient information for causal assessment and 47% (257/549) reported an unknown indication. We acknowledge, to some extent, deaths are expected to be captured with a TIRF medicine when it is used by their intended population of patients with cancer.

The number of cases for each adverse event of interest by reporting period should be interpreted with caution. Many factors can influence the reporting of an adverse event. The increase in cases with an outcome of death and overdose may be the result of stimulated reporting from news media coverage of the current opioid epidemic. Further, the TRIG reports some included cases reference fentanyl, without providing specific information on product formulation (fentanyl patch, illicit fentanyl). On the other hand, the FDA or sponsors do not receive a report for every adverse event that occurs with a product in the postmarketing setting. Given the aforementioned, these data should not be interpreted as the incidence rate of the adverse events of interest with TIRF medicines.

Limited information was provided for the pediatric exposure case other than the PT *Drug administered to patient of inappropriate age*. It is unknown if other information was available in the case narrative to understand this important issue. Our assessment was limited to the TRIG's summary analysis of the adverse events of interest and the line listing because individual case narratives or MedWatch forms for the 568 cases were not required nor provided in the 72-month assessment report. Further, the TRIG utilized a third-party vendor, UBC, for data analysis. To maintain blinding of cases from the various sponsors, UBC's case identification numbers are used as the identifying case number in the line listings. The Agency relies on the sponsor's manufacturer control numbers as the identifying case number, thus using the UBC's case identification number hinders the Agency's ability to readily verify details or obtain additional information on these cases from the FDA's Adverse Event Reporting System (FAERS) database.

The 55 new cases of adverse events of interest, identified from previous reporting periods, were reported as line listings. A summary analysis was not provided separately or within the analysis of this reporting period. FDA is unable to make clinically meaningful assessments from the provided line listings.

It is important to note the other metrics of interest: inappropriate conversions between TIRF medicines, unintentional or accidental exposures, and use of the TIRF medicine by an opioid non-tolerant patient were assessed from the subset of cases identified as having at least one of the

four adverse events of interest and not from all adverse event reports in the Sponsors' safety databases. Given these data are only from a subset of the reports and due to inherent limitations of spontaneous report data, the absence of information does not provide evidence that TIRF medicines are being appropriately converted, used by opioid tolerant patients, as defined in the TIRF labeling, or that no unintentional or accidental exposures occurred. The data previously submitted by the TRIG in the June 15, 2017 individual NDA/ANDA submissions of opioid tolerance data suggest increasing use by opioid non-tolerant patients. The lack of spontaneous adverse event reports for opioid non-tolerant patients is concerning, and these findings raise additional questions such as, what adverse events are occurring in this population? And, what factors are driving the lack of spontaneous adverse event reports for these three metrics of interest? Regarding accidental exposure, in the poison control center data for unintentional general exposures to TIRF medicines (summarized in the DEPI Review Conclusion section below) the overall numbers were small and there was a decrease in the rate of exposure calls, which provides additional context to the spontaneous adverse event surveillance data in the TRIG's 72-month report. Overall, these spontaneous adverse event data alone are insufficient to inform these safety concerns with TIRF medicines and should be considered in context with other surveillance data.

5.4.3 FDA'S DEPI REVIEW SUMMARY

This section summarizes the Division of Epidemiology (DEPI) review of the surveillance data in the 72-month TIRF REMS Assessment report. The full review is included in a separate document.[13]

SUMMARY OF RESULTS

In reviewing the prior, i.e., 60-month, TIRF REMS assessment report, DEPI had recommended that the 72-month assessment report present TIRF product-specific data, noting that (1) not all TIRF medicines were marketed in the pre-REMS period, and (2) from pre- to post-REMS, the TIRF aggregate data suggested there were increases in the prescription-adjusted rates of certain AEs attributed to TIRFs, while the opioid comparator data showed these AE rates either increased to a lesser extent, or decreased. Specifically, these AEs were abuse, unintentional therapeutic errors, emergency department visits/hospitalizations, and major medical outcomes. The TRIG declined to provide product-specific data, citing small numbers of events per product. DEPI therefore obtained product-specific data through FDA contracts, so this review evaluates TIRF product-specific data alongside the TIRF aggregated data from the TIRF REMS Assessment report. FDA conducted analyses of the aggregated TIRFs alongside the product-specific analyses since the extra resources required was negligible and allowed us to present results in a consistent manner for TIRF aggregate and product-specific results.

The purpose of the product-specific analysis was to (1) verify that there was no one TIRF medicine implicated in the increasing prescription-adjusted AE rates that had been observed in the 60-month REMS Assessment report and (2) make pre- versus post-REMS comparisons in AE rates among TIRF medicines that were marketed in both periods. The available TIRF product-specific data enabled us to make general conclusions for selected outcomes. As expected, product-specific case numbers were low. In the RADARS® Treatment Center Programs Combined, average number of abuse cases per quarter ranged from 7 – 31, depending on the TIRF medicine; in other data sources, quarterly case counts were even lower.

TIRF aggregate data collected from poison control center calls and from surveys conducted in two populations of patients presenting for substance use disorder evaluation or treatment suggested that the prescription-adjusted rate of TIRF abuse increased following TIRF REMS implementation. Findings from these various sources suggested that the prescription-adjusted rate of TIRF abuse either increased from the pre- to post-REMS period, or, that there was a positive trend in the prescription-adjusted abuse rate post-REMS through 2016, although the abuse rate appeared to decline starting in Q1 2017. Prescription-adjusted abuse rates of comparators showed either contemporaneous declines or no change. The TIRF product-specific data showed that individual TIRF medicine trends tracked with the TIRF aggregate trend, except for Lazanda, which exhibited an apparent decrease in the prescription-adjusted abuse rate pre- to post-REMS. Of note, Lazanda's trend appears to be influenced by extremely high prescription-adjusted abuse rates when it first appeared on the survey, which may have been produced by respondent errors and the low utilization during this period.

Poison control center data suggested that unintentional general TIRF medicine exposure calls, overall and among children age <6 years, decreased on both the population-adjusted and prescription-adjusted scales, and to as great an extent or greater than decreases in rates of comparator unintentional general exposures. All told, there were nine exposure calls for children age <6 years in the pre-REMS period and nine in the post-REMS period. Due to the small number of unintentional general TIRF medicine exposure calls, the product-specific data were uninformative.

Other indicators from the poison control center data suggested pre- to post-REMS increases. TIRF-involved calls resulting in major medical outcomes/ deaths increased pre- to post-REMS on both the population-adjusted and prescription-adjusted scales. The increase in the prescription-adjusted rate was significant and of larger magnitude relative to that of comparators. TIRF medicine exposure calls for reasons of intentional misuse and unintentional therapeutic errors decreased from pre- to post-REMS, but there were suggestive increases in the prescription-adjusted rates while the rates of comparators remained constant or decreased. Also, the prescription-adjusted rates of emergency department (ED) visits/ hospitalizations increased while the rates of comparators remained constant or decreased. In the product-specific data, it was feasible to estimate increases for Actiq/generic lozenge and Fentora, pre- to post-REMS, in the prescription-adjusted rate of ED visits/hospitalizations. Otherwise, the event numbers were too low to produce informative results.

Finally, an analysis of persistency with index TIRF regimen suggested that approximately 20% of patients with two or more TIRF prescriptions changed their index TIRF regimen.

DEPI REVIEW CONCLUSIONS

Observed increases in the prescription-adjusted rates of abuse suggested that the TIRF REMS may not be achieving its overarching goal of mitigating abuse. TIRF aggregate data from several data streams suggested that the prescription-adjusted rate of TIRF abuse increased from the pre- to post-REMS period, or, that there was a positive trend in the prescription-adjusted abuse rate post-REMS through 2016, although the abuse rate appeared to decline starting in the first quarter (Q1) of 2017. These patterns in abuse are concerning giving that prescription-adjusted abuse rates of comparators showed either contemporaneous declines or no change. The TIRF product-specific data generally showed that individual TIRF medicine trends mainly tracked with the TIRF aggregate trend.

Rates of major medical outcomes/ deaths attributed to TIRF exposure in poison control center data also increased, further suggesting that the TIRF REMS may not be achieving its goal of mitigating the risk of overdose. There were no data to assess whether the rise in major medical outcomes/deaths was linked to the rise in abuse, and further data are needed on the reason for these major medical outcomes/deaths.

The results of other adverse outcomes are difficult to interpret due to low numbers of events. Prescription-adjusted rates of unintentional therapeutic errors, intentional misuse, and ED visits and hospitalizations increased from pre- to post-REMS, although estimates were imprecise. Product-specific analyses of poison control center calls involving Fentora or Actiq/generic oral transmucosal lozenge also suggested their respective prescription-adjusted rates of ED visits and hospitalizations increased from pre- to post-REMS. In contrast, rates of poison center calls for unintentional general TIRF exposures decreased among adults and children, but these events were extremely rare pre-REMS and post-REMS. FDA has requested additional data sources from the TRIG to generate a more robust evidence base, and the process of obtaining these data is ongoing.

Finally, we conclude that TIRF product-specific data are useful for understanding potential contributing factors to trends in aggregated TIRF data and limitations of the data.

5.5. ASSESSMENT ELEMENT 6: STAKEHOLDER KAB SURVEYS (ASSESSMENT REPORT DATA)

The sixth element of the Assessment Plan States*:*

> *Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages.*

5.5.1 PATIENT SURVEY

The purpose of the patient survey was to assess patients' and caregivers' knowledge, attitudes, and behavior in terms of the safe use of TIRF medicines as described in the REMS educational materials. Patients/caregivers were eligible to participate if they were age 18 or older and had a prescription filled for a TIRF medicine within 120 days (four months) prior to the survey launch date. Respondents were recruited through the TIRF REMS Access Program database and a Pharmacy Benefits Manager (PBM) via direct mail. The target sample size was 300 patients or caregivers. The survey was conducted from August 2, 2017 to October 18, 2017. Survey invitations were sent to 3,842 potential respondents with 209 returned as undeliverable. A total of 429 respondents accessed the survey 320 were eligible, and 310 completed the survey. The majority of respondents completed the survey via the internet (73%) followed by telephone (27%). According to patient reports, most respondents were between the ages of 50-69 (69%), female (60%), White (83.5%), and had some college/Associate's degree or higher (80%). The most commonly reported prescription was for Subsys (36.5%), followed by Actiq (35.5%), and Fentora (18%). A larger proportion of respondents were from the South (38%), followed by the West (34%), Midwest (13.5%), and the Northeast (14.5%).

The TRIG compared survey respondents (n=310) with the general population of patients who have received a TIRF prescription in the last four months (obtained from IQVIA data) (n=3,117). The populations were compared in the areas of TIRF products used, age, gender, race, ethnicity,

geographic distribution, level of education, and main language spoken at home. The TRIG noted statistically significant differences between the two groups for highest level of education (<.0001), main language spoken at home (0.0251), and ethnicity (0.0326).

In terms of education, the level of education on average was statistically significant higher for survey respondents than for the general population of TIRF patients. There were more survey respondents with some college versus the general patient population (41% versus 28%) and fewer survey respondents with high school (17% versus 28%) or less than high school diploma (2% versus 5.5%) than the general population. In terms of ethnicity, survey respondent were less likely to report being Hispanic or Latino as compared to the general population of patients (4% versus 8%).

Key Risk Messages Results

The survey contained questions about six key risk messages:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death;

2) Patients should not take TIRF medicines if they are not opioid tolerant;

3) TIRF medicines should be taken exactly as prescribed by the healthcare provider;

4) Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider;

5) Patients should not give the TIRF medicines to anyone else even if they have the same symptoms;

6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The following sections will provide key findings from the patient survey. Detailed tables about the patient participants' responses to each individual key risk message as well as their understanding of additional safe use questions are in **Appendix E.1.**

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.

This key risk message included questions about patients' and caregivers' knowledge of the life-threatening breathing problems that TIRF medicines can cause. The majority of respondents answered the question correctly for this key risk message (93%). The average adjusted knowledge score was 92%. In general, respondents who received and read the Medication Guide (MG) scored higher than respondents who did not received or read the MG (94.5% vs. 83%).

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicines should not be taken if they are opioid tolerant and understanding of what opioid tolerance is. The majority of respondents were aware that opioid tolerance means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines (85%) and TIRF medicines should only be taken by patients that are opioid tolerant (87%). Overall, 78% of respondents answered both questions correctly for this key risk message and 15% answered one out of two correctly. The average adjusted knowledge score was 84%.

Respondents who received or read the MG scored significantly higher on both questions than those who did not receive or read the MG. Similarly, scores were higher for respondents who completed a BA/BS or MA/MS versus respondents who completed a GED or less.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.

This key risk message included nine questions about patients' and caregivers' knowledge that TIRF medicines should be taken exactly as prescribed, the correct indication for TIRF medicines, knowledge that headache pain is not an appropriate indication for use of TIRF medicines, to stop taking TIRF medicines if they stop taking around-the clock opioid pain medicine, and it is not okay to take TIRF for short-term pain. All respondents were aware that TIRF medicines should be taken exactly as prescribed. The majority of respondents were aware that it is not okay to take TIRF medicine for short-term pain (83%) while fewer correctly answered the following statement as false, "It is okay for patients to take TIRF medicines for headache pain" (73%). Only 43% of respondents were aware that they should stop taking their TIRF medicine if they stop their around-the-clock opioid pain medicine; 28% answered incorrectly and 28% didn't know). When asked for which of the following conditions should you use a TIRF medicine, most respondents were aware that TIRF medicine should not be used for headache pain (83.5%) or dental pain (91%). Respondents were less aware that TIRF medicines should not be used for long-lasting painful conditions not caused by cancer (48%) or pain after surgery (68%). Most respondents were aware of the correct indication of breakthrough pain from cancer (80%). Overall, 15.5% of respondents answered all nine questions correctly for this key risk message and 24% answered eight out of nine correctly. The average adjusted knowledge score was 74.5%.

Respondents who received or read the MG had a higher awareness of the need to stop taking their TIRF medicine if they stop their around-the-clock opioid pain medicine compared to those who did not receive of read the MG.

Key Risk Message 4: Patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

This key risk message included questions about patients' and caregivers' knowledge that they should not switch to another medicine that contains fentanyl without talking to a healthcare provider. The majority of respondents were aware that is not safe to switch to another medicine that contains fentanyl without discussing with a healthcare provider first (96%). The average adjusted knowledge score was 96%.

Key Risk Message 5: Patients should not give the TIRF medicines to anyone else even if they have the same symptoms.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicine should not be given away and selling or giving them away was against the law. The majority of respondents were aware that TIRF medicines should not be given to another person if they have the same symptoms as the patient (99%) and that selling or giving away TIRF medicines is against the law (99%). Respondents were also aware that a side effect of TIRF medicines is the chance of abuse or addiction (95%) and that TIRF medicines can be misused by people who abuse prescription medicines or street drugs (97%). All respondents were aware that TIRF medicines should be kept in a safe place to prevent them from being stolen. Overall,

92% of respondents answered all five questions correctly for this key risk message. The average adjusted knowledge score was 84%.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.

This key risk message included questions about patients' and caregivers' knowledge that TIRF medicines should be stored in a safe place out of reach of children, disposed of as described in the specific product's Medication Guide (MG), can cause an overdose and death in any child who takes it, and what to do if an adult takes TIRF medicines that have not been prescribed. All respondents were aware that TIRF medicines should be stored in a safe place out of the reach of children. Most respondents were aware that TIRF medication must be disposed of as described in the specific product's MG (96.5%), that a TIRF medicine can cause an overdose and death in any child who takes it (95.5%), and if an adult who has not been prescribed a TIRF medicine takes it they should get emergency help right away (85.5%). Overall, 80% of respondents answered all four questions correctly for this key risk message. The average adjusted knowledge score was 94.5%.

In general, respondents who received and read the Medication Guide (MG) scored higher than respondents who did not received or read the MG.

Additional Safe Use Questions

The survey included five additional questions about the safe use of TIRF medicines and patient-reported prescriber behaviors related to use of TIRF medicines. Most respondents reported that their healthcare provider talked to them about the risks and possible side effects of TIRF medicines (89%), told them how to use the TIRF medicine (96%), told them how to store or keep the TIRF medicine (83%), told them not to share the TIRF medicine (88%), and told them to keep TIRF medicines out of reach of children to prevent accidental exposure (84%). Knowledge scores have been consistent across the assessment periods. The majority of respondents were also aware that TIRF medicines are only available through a pharmacy enrolled in a special program called the TIRF REMS Access Program (78%). Only 64% of respondents reported that a healthcare provider ever asked them about the presence of children in the home and only 75.5% reported being counseled that accidental exposure to TIRF medicines by a child may be fatal.

Questions about REMS Educational Materials

The survey included questions about patients and caregivers' awareness of the TIRF educational materials including the MG and the Patient-Prescriber Agreement Form. The majority of respondents reported ever receiving the MG (94.5%). Most respondents reported receiving it from the pharmacy (82%) each time a prescription was filled (92%). Over half of respondents reported receiving the MG from their prescribing doctor or someone in the doctor's office (59%), most at the first appointment (82%). The majority of respondents reported reading the MG (95%) with 92% reporting reading all or most of the MG. Most of the respondents (91%) reported understanding all or most of the MG. While most patients/caregivers reported that they did sign a Patient-Prescriber Agreement Form (79%), a smaller number reported receiving a copy of the form (62%). For respondents who reported not signing a form (n=15; 5%), all reported that they were never given a form to sign. Respondents also reported that their healthcare provider offered to explain the form (78%) and they understood all or most of the explanation (97%).

Respondents were asked if signing a form was barrier to obtaining a TIRF medicine. Less than half reported "No" (45.5%), while the remaining respondents selected "Yes" (27%), or "I don't know" (27%).

Additional Findings

The TRIG noted 89 reports of a potential adverse event or product complaint associated with the use of TIRF medicines during telephone interviews or telephone calls to activate gift cards. Forty adverse events were reports of a patient death. The TRIG stated that all reports were provided to the applicable TIRF sponsor.

Subgroup Analysis by Education Level and Adjusted Knowledge Scores

The subgroup analysis shows that the correct response rate for the key risk message was generally higher in the respondents with higher education level. For Key Risk Messages 1, 3, 4, 5, and 6, the differences of the response rate among different education level were small and the adjusted knowledge scores were close to the unadjusted scores (**Table 4**). For Key Risk Message 2, the difference of the response rate was relatively large (**Table 5**), and the adjusted knowledge score was lower than the unadjusted score about 2% (not statistically significant).

Table 4: Patient Survey: Responses to Questions linked to Key Risk message #2 by Highest Level of Education - Completed Surveys.

Question	Highest Level of Education			
	GED or less (N=62) n (%) [95% CI][1]	College (N=128) n (%) [95% CI][1]	BA/BS or MS/MA (N=100) n (%) [95% CI][1]	Professional or Doctoral Degree (N=20) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	46 (74.2) [61.5 - 84.5]	114 (89.1) [82.3 - 93.9]	90 (90.0) [82.4 - 95.1]	20 (100.0) [83.2 - 100.0]
False	3 (4.8)	4 (3.1)	2 (2.0)	0
I don't know	13 (21.0)	10 (7.8)	8 (8.0)	0
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	44 (71.0) [58.1 - 81.8]	108 (84.4) [76.9 - 90.2]	93 (93.0) [86.1 - 97.1]	18 (90.0) [68.3 - 98.8]
False	6 (9.7)	8 (6.3)	3 (3.0)	2 (10.0)
I don't know	12 (19.4)	12 (9.4)	4 (4.0)	0

Source: Appendix B: Survey Tables, Table 7.1.3
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

(Reproduced from TRIG's 72 month REMS assessment report, Table 7.1.3)

Table 5 : Patient Survey: Average and Adjusted Knowledge Scores by Key Risk Message

	Score [95% CI][1]	Adjusted Knowledge Score [95% CI][2]
KRM #1	92.6 [89.6, 95.5]	92.1 [88.7, 95.4]
KRM #2	86.0 [82.7, 89.2]	83.9 [80.2, 87.6]
KRM #3	74.4 [72.3, 76.6]	74.5 [72.3, 76.6]
KRM #4	96.1 [94.0, 98.3]	95.6 [92.9, 98.2]
KRM #5	98.1 [97.3, 98.8]	98.1 [97.4, 98.9]
KRM #6	94.4 [93.0, 95.7]	94.5 [92.9, 96.0]
Overall Knowledge Score	86.3 [85.1, 87.5]	86.1 [84.8, 87.4]

Source: Appendix B: Survey Tables, Table 12
[1] 95% CIs are constructed based on normal distribution function.
[2] Adjusted knowledge scores are standardized based on highest level of education. Only responses with corresponding categories in the IQVIA data are included in this analysis.

(Reproduced from the TRIG's 72 month REMS assessment report for the TIRFs, Table 12)

FDA Patient Survey Comments

1. Respondents were unaware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine, with only 43% selecting the correct answer. Knowledge rates have consistently been low with this questions across assessment periods. The TRIG has proposed that revisions will be made to the prescriber training to increase knowledge in this area.
2. Since the survey respondents had a significantly higher education level than all users in the general population of TIRF patients, FDA suspected the knowledge rate in the survey overestimated the knowledge rate for all TIRF patients, and requested that the TRIG provide subgroup analyses stratified by education level, to quantify the impact of education on knowledge in the survey, and conduct a sensitivity analysis to predict the knowledge rate in all users adjusting for education. The subgroup analyses did not show a systematic bias and standardization of results did not change main conclusions in patients' survey.

5.5.2 PRESCRIBER SURVEY

The purpose of the prescriber survey was to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines. Prescribers were eligible to participate if they were enrolled in the TIRF REMS Access Program and had prescribed a TIRF medicine in the last six months. A target sample size of 300 was proposed. The survey was conducted from August 2, 2017 to October 29, 2017. Prescribers were recruited via mail. Approximately 2,221 prescribers were invited to participate and 47 invitations were returned as undeliverable. A total of 8,013 reminder letters were sent to non-responders; from those 272 were returned as undeliverable. From these, 273 respondents agreed to participate and were screened, 178 prescribers were eligible and 154 completed the survey. The majority of

respondents completed the survey via the internet (98%) followed by telephone (2%). Most respondents were male (63%), were medical doctors or DOs (73%), and over half had been practicing medicine for 11 to more than 15 years (56%). Most respondents had prescribed TIRF medicines about one to two times per month (72%) followed by 19% prescribing between three to more than five times per month. The main medical specialty was pain management (54%) followed by "Other" (23%), oncology (16%), and primary care (6%). Actiq or generic Actiq were most commonly prescribed (58%) followed by Subsys (55%), and Fentora (31%). Respondents represented all geographic regions with 35% from the South, 31% from the West, 17% from the Northeast, and 17% from the Midwest. Only three percent of respondents reported that they practiced in a closed healthcare system.

The TRIG compared prescriber survey respondent self-reported data (n=154) with prescriber survey respondent data from the REMS switch provider (n=154) and the general population of prescribers that had prescribed a TIRF medicine in the last six months (REMS switch provider (n=2,221)) for average times per month TIRF medicines have been prescribed within the past six months, TIRF medicines prescribed within the last six months, and geographic region. A comparison was also completed between self-reported data from the prescriber survey respondents (n=154) and prescribers of TIRF medicines in the past six months (IQVIA data) (n=2,060) on average times per month TIRF medicines have been prescribed within the past six months, TIRF medicines prescribed within the last six months, geographic region of practice location, gender, medical profession, number of years practicing medicine, and medical specialty.

There was a difference between survey respondent's self-reported data and data provided from the REMS switch provider in average times per month TIRF medicines have been prescribed within the last six months, but it was not statistically significant. There were statistically significant differences between the survey respondents and the general population of prescribers from IQVIA data for on average times per month they prescribed TIRF medicines within the past six months (p=<.0001),TIRF medicines prescribed within the last six months, gender (p=0.0096), medical profession (p=<.0031), number of years practicing medicine (p=<.0001), and medical specialty (p=<.0001). Survey respondents were less likely to prescribe one to two times a month (72% versus 90%) and more likely to prescribe three to five times per month (14% versus 6%) as compared to prescribers from IQVIA data. Survey respondents were also less likely to be male (63% versus 73%), less likely to be MDs (67% versus 72%), more likely to have practiced medicine for a shorter timeframe (46% practiced for more than 15 years as compared to 67% IQVIA data), and more likely to have the specialty of pain management as compared to IQVIA data prescribers (40% versus 19%).

Key Risk Messages Results

The survey contained questions about five key risk messages: 1) TIRF medicines are contraindicated in opioid-non tolerant patients; 2) TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 or older for Actiq and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain; 3) TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics; 4) TIRF medicines are not interchangeable with each other, regardless of route of administration; 5) Patients and their caregivers must be instructed that TIRF medicines

contain a medicine in an amount that can be fatal to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The following sections will provide key findings from the prescriber survey. Detailed tables about prescriber participants' responses to each individual key risk message, their understanding of additional safe use questions, and their reported activities when prescribing TIRFs are in **Appendix E.2.**

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients

This key risk message included questions about prescribers' understanding of who is considered an opioid tolerant patient and that TIRF medicines are contraindicated in opioid non-tolerant patients because of the problems of respiratory depression and death. The majority of respondents were aware that TIRF medicines should only be taken by patients who are opioid tolerant (97%). Most respondents knew that cancer patients who are considered opioid tolerant are those who are taking around-the clock opioid therapy for underlying persistent cancer pain for one week or longer (93%). The majority of respondents were also aware that the statements, "patients with cancer who are considered opioid tolerant are those who are not currently taking opioid therapy, but have taken opioid therapy before" (94%) and "patients with cancer who are considered opioid tolerant who have no known contraindications to the drug fentanyl, but are not currently taking around the clock opioids" (89%) were false. Most respondents also knew that TIRF medicines were contraindicated in opioid non-tolerant patients because they can cause life-threatening respiratory depression at any dose (91%) and death (94%). Respondents were also aware that TIRF medicines should not be used to treat opioid non-tolerant patients (90%) and that all prescribers should begin with titration from the lowest dose available for all new patients even if the patient has taken another TIRF medicine before (86%). Overall, respondents were aware of the specific medication/dose for opioid tolerant patients: 60 mg oral morphine (96%), 30 mg oral oxycodone/day (83%), 25 mg oral oxymorphone/day (79%) and 25 mcg transdermal fentanyl/hour (89%). Respondents were less aware of the other regimens for opioid-tolerance (8 mg oral hydromorphone/day (77%), and an equianalgesic dose of another oral opioid (70%). Overall, 40% of respondents answered all fourteen questions correctly and the average knowledge score was 88%.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 years of age or older for Actiq) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

This key risk message included questions about prescribers' knowledge of the correct indication for TIRF medicines and understanding of timing of administration of TIRF medicines. Most respondents were aware that breakthrough pain from cancer was the correct indication for TIRF medicines (99%) and stated that before initiating treatment with a TIRF medicine, they inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraines, or any other short-term pain (94%). In addition, most respondents were aware of incorrect indications for TIRF medicines (acute or postoperative pain (91%); headache or migraine pain (96%); dental pain (97%)); however less respondents (79%) were aware that chronic non-cancer pain was not a correct indication. For respondents that indicated that chronic non-cancer pain was a correct indication (n=23), there was a follow-up question about what types of chronic pain conditions that they prescribed TIRF medicines for. Back pain was the top

reported condition (26%), followed by failed back surgery syndrome (17%), and chronic pain (13%). Respondents were also asked why a TIRF medicine was selected to treat these chronic pain conditions. The top responses were I do not treat non-cancer pain (30%), efficacy (26%), and other types of treatments have failed (17%). Most respondents (82.5%) were able to identify the patient that should not use a TIRF medicine based on the provided patient scenarios. In terms of awareness of the timing of administration of TIRF medicines, 82% of respondents were aware that a cancer patient cannot start taking a TIRF medicine for breakthrough pain after one day on an around the clock opioid, 79% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time, and 74% of respondents were aware that it is incorrect to instruct patients to continue taking their TIRF medicine if they stop taking their around the clock opioid medicine. Overall, 36% of respondents answered all ten questions correctly for this key risk message and the average knowledge score was 87%.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a schedule II controlled substance, with abuse liability similar to other opioid analgesics.

This key risk message included questions about prescribers' knowledge of the risk factors and signs and symptoms of opioid abuse and the importance of monitoring patients taking TIRF medicines. Most respondents were aware that a personal history of past or current alcohol or drug abuse or a family history of illicit drug use or alcohol abuse was a risk factor for opioid abuse (98%) and that a personal history of psychiatric illness was also a risk factor (90%). In addition, respondents were aware that it was important to monitor for signs of abuse and addiction in patients who take TIRF medicines (99%) and that TIRF medicines can be abused in a manner similar to other opioid agonists (97%). Respondents were aware that misuse (99%), abuse (99%), addiction (99%), and overdose (99%) were all risks associated with the use of TIRF medicines. Overall, 60% of respondents answered all ten questions correctly for this key risk message and the average knowledge score was 94%.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

This key risk message included questions about prescribers' knowledge that TIRF medicines are not interchangeable regardless of the route of administration. The majority of respondents were aware that TIRF medicines are not interchangeable (95.5%), that conversion of one TIRF medicine to another may result in a fatal overdose (96%), and the dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (94%). A total of 81% of respondents selected the appropriate course of action in a proposed scenario converting a patient from one TIRF medicine to another. Overall, 75% of respondents answered all four questions for this key risk message and the average knowledge score was 92%.

Subgroup Analysis and Adjusted Knowledge Scores

No uniform trend was seen for the key risk message in the respondents in the subgroup analysis, given the sample sizes for the prescribers' survey. The adjusted knowledge rate for each key risk message were close to the unadjusted rate (**Table 6**).

Table 6 : Prescriber Survey: Average and Adjusted Knowledge Scores for Each Key Risk Message

	Average Knowledge Score [95% CI][1]	Adjusted Knowledge Score [95% CI][2]
KRM #1	87.8 [85.3, 90.2]	87.0 [82.9, 91.1]
KRM #2	87.4 [85.1, 89.7]	85.8 [81.4, 90.1]
KRM #3	93.7 [92.2, 95.2]	93.6 [91.3, 95.8]
KRM #4	91.7 [89.0, 94.4]	90.5 [86.6, 94.4]
Overall Knowledge Score	89.6 [88.0, 91.3]	88.8 [86.1, 91.4]

Source: Appendix B: Survey Tables, Table 11
[1] 95% CIs are constructed based on normal distribution function.
[2] Adjusted knowledge scores are standardized based on the average times per month TIRF medicines were prescribed within the past 6 months, gender, medical profession, number of years practicing medicine, and medical specialty. Only responses with corresponding categories in the IQVIA data are included in this analysis.

(Reproduced from the TRIG's 72 month REMS assessment report, Table 11)

Additional Safe Use Questions

The survey included additional questions about the safe use of TIRF medicines and prescriber-reported activities performed related to use of TIRF medicines. For a scenario presented of a patient who started on the lowest dose of a TIRF medicine, and after 30 minutes breakthrough pain had not been sufficiently relieved, only 66% of respondents selected the appropriate action (to follow the guidance presented in the product-specific MG because the instructions are not the same for all TIRF medicines). In another scenario, a patient is taking a TIRF medicine and the doctor wants to prescribe a CYP3A4 inhibitor. A total of 74% of respondents identified the appropriate response, that use of TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment, to carefully monitor the patient for opioid toxicity, and combined use can cause fatal respiratory depression. Respondents were aware that if a patient is starting titration with a TIRF medicine, they should start with the lowest available dose (93%). In addition, almost all respondents were aware that TIRF medicine contains fentanyl which can be fatal to children (99%) and most respondents knew to instruct patients never to share their TIRF medicine (98%).

In terms of prescriber-reported activities, most respondents reported always instructing patients not to share TIRF medicines (86%) while 10% did this only with the first prescription:

Responses were relatively low with respondents reported always performing the following activities or performing them only with the first prescription:

- Asking patients (or caregivers) about the presence of children in the home (58%; only with first prescription (27%))
- Counseling patients or caregivers that accidental exposure to TIRF medicines by a child may be fatal (67%; only with first prescription (21%))
- Instructing patients to keep TIRF medicines out of reach of children (79%; only with first prescription (16%))

- Instructing patients about proper disposal of any unused or partially used TIRF medicines (64%; only with first prescription (22%))
- Giving patients the MG for their TIRF medicine (44%; only with first prescription (42%)).
- Talk to the patient about the risks and possible side effects of the TIRF medicine (77%; only with first prescription (15%)).
- Instruct the patient on how to use the TIRF medicine that was most recently prescribed (75%; only with first prescription (17.5%)).
- Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed (55%; only with first prescription (32%)).

Questions about TIRF Medicine REMS Educational Materials

The survey included questions about prescribers' access to educational materials for TIRF medicines. Almost all prescribers reported receiving or having access to the Prescribing Information (97%), and the majority of those reported reading the Prescribing Information (87%). The majority reported receiving or having access to the Medication Guide (MG) (95%) and 91% of those reported reading it. Most respondents reported reviewing the Patient-Prescriber Agreement Form with each patient prescribed TIRF medicines (92%). Of those the majority reported signing the Patient-Prescriber Agreement Form (94%), and giving a copy of the Patient-Prescriber Agreement Form to the patient or caregiver (85%).

FDA Prescriber Survey Comments

1. The survey only had 154 respondents, instead of the proposed 300. The sponsor should make efforts to reach the target sample size for respondents. The decreasing numbers of prescriptions and prescribers of TIRFs may have an impact on recruiting survey participants.
2. A total of 79% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, 74% of respondents were aware that it is incorrect to instruct patients to continue taking their TIRF medicine if they stop taking their around the clock opioid medicine. Knowledge has consistently been lower in this area across assessment periods, and FDA asked the TRIG to propose ways to improve knowledge in this area. The TRIG proposed revisions to the prescriber and pharmacist Knowledge Assessment to increase knowledge in this area. A score of 100% on the Knowledge Assessment is required to enroll in the REMS program. The TRIG believes that this modification will strengthen understanding among prescribers, pharmacists, and patients.
3. Since the survey respondents had significantly different distributions from the general population by "average times per month TIRF medicine and have been prescribed within the last 6 months", "gender", "medical degrees", "number of years practicing medicine", and "medical specialty", FDA requested that the TRIG provide subgroup analyses stratified by these characteristics, and conduct a sensitivity analysis to predict the knowledge rate in all users adjusting for these characteristics.
4. Given the available data from survey sample and general population, it is difficult to assess the simultaneous impact of multiple factors. When computing weights for the

adjusted knowledge scores, the sponsor calculated the weights for each characteristic independently and then multiplied all these weights together. We are evaluating the adequacy of this approach and whether an alternative approach is better.

5.5.3 PHARMACIST SURVEY

The purpose of the pharmacist survey was to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines. Pharmacists were eligible to participate if they dispensed TIRF products in the past six months. Respondents were recruited from a random sample of pharmacists from pharmacies that were enrolled in the TIRF REMS Access Program as of July, 2017. Any pharmacist who worked at an enrolled pharmacy was eligible to participate. The survey was conducted from August 2, 2017 to October 18, 2017. Pharmacists were recruited via mail or fax. Three categories of pharmacies were sampled: Closed System Pharmacies (CSP), Inpatient Pharmacies, and Outpatient Pharmacies. Approximately 20,088 invitation letters were sent to pharmacists from 3,348 enrolled pharmacies. A total of 105 were returned as undeliverable. An additional 15,756 reminder letters were sent and 31 were returned as undeliverable. From these, 676 pharmacists accessed the survey, 325 (48%) met the eligibility criteria, and 308 pharmacists completed the survey. The majority of respondents completed the survey via the internet (98%) followed by telephone (2%). A little over half of respondents were male (53%) and had been practicing pharmacy for 11 or more years (50%). Fifteen percent (15%) of respondents had never dispensed a TIRF medicine while 50% had dispensed a TIRF medicine one to two times per month. Actiq was most commonly dispensed (67%) followed by Subsys (40%), and Fentora (31%), and. Most respondents were from the South (37%), followed by the West (30%), the Northeast (22%), and the Midwest (11%). The majority of respondents (80%) were not the pharmacist-in-charge. For the chain/independent pharmacies, there were 118 unique pharmacies with one completer; 46 with two completers, 16 with three completers, four with four completers, and one each with five and six completers. For the inpatient pharmacies, there were nine unique pharmacies with one completer, three with two completers, and three with one completers. For the closed system pharmacies, there were three pharmacies with one completer and one with two completers.

The TRIG compared pharmacist survey respondents (n=203) with the general population of pharmacists that have dispensed a TIRF prescription in the last six months (REMS switch provider data) (n=3,136) for region, type of pharmacy, and number of orders by type of pharmacy.

There were statistically significant differences between the two groups for “type of pharmacy” (p=<.0001). Most of the survey respondents represented independent outpatient pharmacies (75%) while a higher proportion of the general population of TIRF pharmacists was from chain outpatient pharmacies (44%).

Key Risk Messages Results

The survey contained questions about five key risk messages: 1) TIRF medicines are contraindicated in opioid-non tolerant patients; 2) TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 or older for Actiq and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain; 3) TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to

other opioid analgesics; 4) TIRF medicines are not interchangeable with each other, regardless of route of administration; 5) Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal to children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The following sections will provide key findings from the pharmacist survey. Detailed tables about the pharmacist participants' responses to each individual key risk message, their understanding of additional safe use questions, and reported activities when dispensing TIRFs are in **Appendix E.3.**

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients

This key risk message included questions about pharmacists' understanding of who is considered an opioid tolerant patient and that TIRF medicines are contraindicated in opioid non-tolerant patients because of the problems that can occur such as respiratory depression and death. The majority of respondents were aware that TIRF medicines should only be taken by patients who are opioid tolerant (95%). Most respondents knew that cancer patients who are considered opioid tolerant are those who are taking around-the clock opioid therapy for underlying persistent cancer pain for one week or longer (91%). Respondents also identified patients who were not considered opioid-tolerant: patients who are not currently taking opioid therapy, but have taken opioid therapy before (82.5%) and patients who have no known contraindications to fentanyl, but are not currently taking around the clock opioid therapy (78%). Most respondents also knew that TIRF medicines can cause life-threatening respiratory depression (92.5%) or death (97%) if used in opioid non-tolerant patients and that all prescribers should begin with titration from the lowest dose available for all new patients even if the patient has taken another TIRF medicine before (86%). Overall, awareness was low in terms of the specific medication/dose that a patient would need to be taking for a patient to be opioid-tolerant. While most respondents were aware that patients who are taking 60 mg oral morphine/day for one week or longer (86%) were considered opioid-tolerant, respondents were less aware of the other regimens for opioid-tolerance (25 mcg transdermal fentanyl/hour (78%), 8 mg oral hydromorphone/day (75%), 30 mg oral oxycodone/day (76%), 25 mg oral oxymorphone/day (71%), and an equianalgesic dose of another oral opioid (64%)). Overall, 27% of respondents answered all fourteen questions correctly and the average knowledge score was 83%.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age or older (16 years of age or older for Actiq) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

This key risk message included questions about pharmacists' knowledge of the correct indication for TIRF medicines and understanding of timing of administration of TIRF medicines. Most respondents were aware that breakthrough pain from cancer was the correct indication for TIRF medicines (91%). In addition, most respondents were aware of incorrect indications for TIRF medicines with the exception that only 54% were aware that chronic non-cancer pain was not a correct indication. While 79% of respondents were aware that a cancer patient cannot start taking a TIRF medicine after one day on an around the clock opioid, only 67% of respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. Only 48% of respondents were aware that a patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine. Overall, 25% of

respondents answered all eight questions correctly for this key risk message and the average knowledge score was 77%.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a schedule II controlled substance, with abuse liability similar to other opioid analgesics.

This key risk message included questions about pharmacists' knowledge of the risk factors and signs and symptoms of opioid abuse in patient taking TIRF medicines. Almost all respondents were aware that a personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse was a risk factor for opioid abuse (98%) although only 79% were aware that a personal history of psychiatric illness was also a risk factor. Pharmacists were aware that it was important to monitor for signs of abuse and addiction in patients who take TIRF medicines (97%) and that TIRF medicines can be abused in a manner similar to other opioid agonists (93%). In addition, respondents were aware of the risks associated with TIRF medicines: misuse (98%), abuse (99%), addiction (99%), and overdose (99%). Overall, 52% of respondents answered all ten questions correctly for this key risk message and the average knowledge score was 91%.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.

This key risk message included questions about pharmacists' knowledge that TIRF medicines are not interchangeable regardless of the route of administration. The majority of respondents were aware that TIRF medicines are not interchangeable (93%), that conversion of one TIRF medicine to another may result in a fatal overdose (93.5%), the dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (90%), and TIRF medicines with the same route of administration cannot be substituted with each other if the pharmacy is out of stock for one product (95.5%). Overall, 80% of respondents answered all four questions for this key risk message and the average knowledge score was 93%.

Subgroup Analysis and Adjusted Knowledge Scores

No uniform trend were seen for the key risk message in the respondents in the subgroup analysis, except that a trend favoring respondents from independent/outpatient pharmacies related to respondents from inpatients pharmacies in some questions under Key Risk Message 1 (TIRF medicines are contraindicated in opioid non-tolerant patients). The adjusted knowledge rate for each key risk message were close to the unadjusted rate (**Table 7**).

Table 7: Pharmacists: Average and Adjusted Knowledge Score by Key Risk Message

	Average Knowledge Score [95% CI][1]	Adjusted Knowledge Score [95% CI][2]
KRM #1	82.8 [80.7, 84.9]	81.2 [77.7, 84.6]
KRM #2	76.6 [74.3, 79.0]	78.6 [75.1, 82.1]
KRM #3	91.3 [90.0, 92.6]	91.1 [89.6, 92.7]
KRM #4	92.9 [91.1, 94.8]	93.6 [91.2, 96.0]
Overall Knowledge Score	84.9 [83.4, 86.4]	84.8 [82.7, 86.8]

Source: Appendix B: Survey Tables, Table 10
[1] 95% CIs are constructed based on normal distribution function.
[2] Adjusted knowledge scores are standardized based on pharmacy type.

(Reproduced from the TRIG's 72 month REMS assessment report, Table 10)

Additional Safe Use Questions

The survey included additional questions about the safe use of TIRF medicines and pharmacist-reported activities performed related to use of TIRF medicines. Respondents were aware that TIRF medicines should not be sold, loaned, or transferred to another pharmacy (89%), that pharmacy staff must be educated about the TIRF REMS Access Program (94%), and that the use of TIRF medicines with a CYP3A4 inhibitor may require dosage adjustment and monitoring (92%). Most inpatient pharmacist respondents were aware that it is not OK to dispense TIRF medicines from the inpatient inventory to outpatients (83%) although the sample size was small (n=18).

In terms of pharmacist-reported activities, most respondents reported always performing the following activities or performing them only with the first prescription:

- Giving patients the MG for their TIRF medicine (90%; only with first prescription (7%)).

Responses were relatively low with respondents reported always performing the following activities or performing them only with the first prescription:

- Instructing patients on how to store or keep the TIRF medicines (56.5% only with first prescription (34%))
- Talk to patients about the risks and possible side effects of the TIRF medicines (60%; only with first prescription (31.5%))
- Instructing patients not to share TIRF medicines (72%; only with first prescription (18%))
- Asking patients about the presence of children in the home (58%; only with first prescription (25%))
- Instruct the patient on how to use the TIRF medicines (63%; only with first prescription (30%))
- Instructing patients about proper disposal of any unused or partially used TIRF medicines (68.5% only with first prescription (21%))
- Counseling patients that accidental exposure to TIRF medicines by a child may be fatal (69% only with first prescription (21%))
- Instructing patients to keep TIRF medicines out of reach of children (71%; only with first prescription (19%))

Only 13 (72%) of inpatient pharmacists reported having an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the REMS program. Most outpatient pharmacists (82.5%) reported processing all TIRF medicine prescriptions regardless of method of payment, through the pharmacy management system.

Questions about TIRF Medicine REMS Educational Materials

The survey included questions about pharmacists' access to educational materials for TIRF medicines. Almost all pharmacists reported receiving or having access to the Prescribing Information (96%), and the majority of those reported reading it (84%). Most respondents

reported receiving or having access to the MG (98%) and 88% of those reported reading it. In addition, 90% of respondents reported always giving patients the MG.

FDA Pharmacist Survey Comments

1. Only 67% of pharmacist respondents were aware that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. In addition, only 48% of respondents were aware that a patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine. FDA asked the TRIG to propose ways to improve knowledge in this area. The TRIG proposed revisions to the prescriber and pharmacist Knowledge Assessment to increase knowledge in this area. A score of 100% on the Knowledge Assessment is required to enroll in the REMS program. The TRIG believes that this modification will strengthen understanding among prescribers, pharmacists, and patients.
2. Since the survey respondents had significantly different distributions from the general population by type of pharmacy, FDA requested that the TRIG provide subgroup analyses stratified by type of pharmacy, and conduct a sensitivity analysis to predict the knowledge rate in all users adjusting for type of pharmacy. The subgroup analyses did not show a systematic bias and standardization of results did not change main conclusions.

FDA'S OVERALL SURVEY CONCLUSIONS

Patients surveyed had a high level of knowledge (≥80%) across most of the key risk messages. Respondents were less aware of the correct indication for TIRFs, and only 43% were aware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge rates have consistently been low with both of these questions across assessment periods.

Prescribers surveyed had a high level of knowledge (≥80%) across most of the key risk message questions as in previous assessments. However, as in previous assessments, fewer correctly stated that chronic non-cancer pain was not an approved indication. Respondents that answered incorrectly stated that they prescribe TIRF medicines for conditions including back pain, neuropathic pain, and post-operative pain. Similar to patients and pharmacists respondents, prescribers surveyed were less aware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine and that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time.

Pharmacists surveyed also had a high level of knowledge (≥80%) across most of the key risk messages as in previous assessments. However, 54% correctly stated that chronic non-cancer pain was not an approved indication, and pharmacist respondents were less aware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine and that a cancer patient cannot start a TIRF medicine and an around the clock opioid at the same time. Knowledge has consistently been low in this area across assessment periods.

FDA asked the TRIG to propose ways to improve knowledge in this area. The TRIG proposed revisions to the prescriber and pharmacist Knowledge Assessment to increase knowledge in this area. A score of 100% on the Knowledge Assessment is required to enroll in the REMS program. The TRIG believes that this modification will strengthen understanding among prescribers, pharmacists, and patients.

One main review issue with the surveys was the inadequate representation and possible lack of generalizability of results. The surveys responses were from a sample of patients, prescribers, and pharmacists who used, prescribed and dispensed TIRFs, respectively. There was evidence that knowledge observed in these samples was not always representative of knowledge of everyone who uses, prescribers or dispenses a TIRF.

The TIRF surveys designed by the sponsor were not probability random samples but rather convenience samples with very low response rates. The response rates in the 72-month KAB surveys of patients, prescribers and pharmacists were 11.8%, 12.6% and 3.4%, respectively. To evaluate potential bias and lack of generalizability of results, the FDA requested from the sponsor multiple analyses. In each survey, we requested the sponsors compare characteristics of survey respondents to those in the general population. When differences were found, we requested subgroup analyses and standardization to evaluate any potential response bias on observed knowledge rates. Although these analyses were informative, we note that characteristics that could be compared between the sample and the population was low. Additionally, when multiple characteristics were different between the sample and the population, the current analyses did not guarantee that multiple characteristics were simultaneously standardized in the sample.

The 72-month report showed a lack of representation of the sample. However, subgroup analyses did not show a systematic bias and standardization of results did not change main conclusions.

5.6. APPLICANT'S OVERALL CONCLUSION OF WHETHER THE REMS IS MEETING THE GOALS

The TRIG's report states: "*Based on the data available in this TIRF REMS Access program assessment report (program and product utilization statistics, dispensing activity, program infrastructure and performance, noncompliance reporting, and safety surveillance data), the TRIG concludes that there is no indication that the REMS is not meeting its goals. However, the TRIG acknowledges that the data are limited and that FDA has requested further evaluation, as described in the 60-Month FDA REMS Assessment Report Acknowledgement Letter, to determine whether the REMS is meeting its goals. The TRIG looks forward to discussing and collaborating with the FDA on updates to evaluate and improve upon the REMS.*"

6. CONCLUSIONS

6.1. COMPLETENESS OF REPORT

As this juncture, prior to the upcoming Advisory Committee meeting, the assessment report is technically complete and addresses all issues outlined in the approved REMS assessment plan.

6.2. ACHIEVEMENT OF THE GOALS OF THE REMS

The goals of the REMS 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; and

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

Surveillance data (spontaneously reported adverse events as well as data from poison control centers and substance abuse treatment centers) appear to indicate that utilization-adjusted rates of abuse and major medical outcomes/deaths involving TIRF medicines have increased from pre- to post-REMS or within the post-REMS period. In contrast, utilization-adjusted event rates for the comparator drugs in most cases indicated either contemporaneous decreases or much smaller increases than those noted for TIRF medicines. As for the other adverse events monitored, our conclusions are limited by the small numbers of poison center calls pre- and post-REMS. Calls for unintentional therapeutic errors, intentional misuse, and ED visits and hospitalizations involving TIRF medicines increased from pre- to post-REMS, although estimates were imprecise, while calls for unintentional general exposures to TIRF medicines decreased among adults and children. There continues to be ongoing communications with the TRIG about obtaining additional safety data.

Findings from the June 15, 2017 individual NDA/ANDA submissions of opioid tolerance data indicate that regardless of the type of analysis, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from 34.6% to 55.4%. The proportion of patients receiving TIRFs as calculated by these analyses remains concerning, therefore additional analyses are needed to understand if this represents a change in prescribing patterns since the TIRF REMS was approved.

General estimates from a persistency analysis of utilization suggested that approximately 20% of patients with two or more TIRF prescriptions changed their index TIRF regimen. Data on the doses and products involved in the index and subsequent regimens, is needed to better understand issues around inappropriate TIRF conversions.

The data provided by the TRIG regarding the prevention of accidental exposure are limited and thus difficult to interpret and therefore, the FDA has requested additional safety data from the TRIG.

Patients surveyed had a high level of knowledge (≥80%) across most of the key risk messages. Respondents were less aware of the correct indication for TIRFs, and only 43% were aware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge rates have consistently been low with both of these questions across assessment periods.

Pharmacists surveyed had a high level of knowledge (≥80%) across most of the key risk messages as in previous assessments. However, fewer than 50% correctly stated that chronic non-cancer pain was not an approved indication, and pharmacist respondents were less aware that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine. Knowledge has consistently been low in this area across assessment periods.

Prescribers surveyed also had a high level of knowledge (≥80%) across most of the key risk message questions as in previous assessments. However, as in previous assessments, only 65% correctly stated that chronic non-cancer pain was not an approved indication. Respondents that answered incorrectly stated that they prescribe TIRF medicines for conditions including back pain, neuropathic pain, and post-operative pain.

Surveys of prescribers, pharmacists and patients, despite their limitations, suggest that they are knowledgeable about these risks; however, we acknowledge the knowledge may not translate into appropriate prescribing practices.

The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goal(s). Similar to previous assessments, the review of the 72-month REMS assessment continues to prove challenging when determining whether the goals and objectives of the TIRF REMS are being met.

On August 3, 2018, the TIRF REMS will be the topic of discussion at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. The Committees will be asked to discuss whether the approved REMS is designed to achieve the goals and objectives, whether the available data are adequate to determine if each of the objectives are being met and if they are not adequate, discuss feasible options for obtaining adequate data. In addition, they will be asked to discuss the any factors they are aware of that may have resulted in the decrease in use of TIRF medicines, whether the REMS may be creating barriers to access to these products for patients who could benefit from them and it there are mechanisms to reduce the burden associated with the REMS. Lastly, they will be asked their advice on if the TIRF REMS should be modified or remain the same.

APPENDIX A – CURRENT TIRF REMS ASSESSMENT PLAN (APPROVED 12/11/2017)

1. TIRF REMS Access Program Utilization Statistics (data presented per reporting period and cumulatively):
   a. Patient Enrollment:
      i. Number of unique patients enrolled
      ii. Number of patients inactivated
      iii. Number of unique patients dispensed a prescription for a TIRF during this reporting period
   b. Prescriber Enrollment:
      i. Number of prescribers enrolled
      ii. Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending;
      iii. Number of prescribers inactivated
   c. Pharmacy Enrollment:
      i. Number of pharmacies enrolled by type (inpatient, chain, independent, mail order, institutional outpatient, and closed system; provide identity of closed system entities);
      ii. Number of pharmacies that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type);
      iii. Number of pharmacies inactivated by type (inpatient, chain, independent, closed system);
   d. Distributor enrollment:
      i. Number of distributors enrolled;
      ii. Number of distributors inactivated;

2. Dispensing activity for enrolled pharmacies - metrics stratified by pharmacy type (open vs. closed system)
   a. Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription transactions per closed system entity;
   b. Number of prescriptions/transactions denied and reasons for denial. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken);
   c. Number of prescriptions/transactions rejected for other reasons (e.g., prescriber not enrolled) with a description of these specific other reasons;

d. Mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized

e. Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF;

f. Number of prescriptions dispensed after ten days without a PPAF in place

3. Program Infrastructure and Performance: The following metrics on program infrastructure performance will be collected (per reporting period):

a. Number of times a backup system was used to validate a prescription, with reasons for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described;

b. Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions;

c. Call center report with:

i. Overall number of contacts;

ii. Summary of frequently asked questions;

iii. Summary of REMS-related problems reported

d. Description of corrective actions taken to address program/system problems.

4. TIRF REMS Access Non-Compliance Plan: The TIRF TRIGs should provide the following data regarding non-compliance in each assessment report (per reporting period):

a. Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products;

ii. Numbers of prescription authorizations per closed system;

iii. Reconciliation of data describing TIRF product received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS program. Include details on how the reconciliation is conducted (e.g., electronic vs. manual process).

iv. Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance

b. Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12 month period These reports are to include:

i. Verification of training for all pharmacists dispensing TIRF products

ii. Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program

iii. Describe any corrective actions taken for any non-compliance with i and ii identified above during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events

c. Description of number, specialties, and affiliations of the personnel that constitute the Non-Compliance Review Team (NCRT) as well as:

i. Description of how the NCRT defines a non-compliance event

ii. Description of how non-compliance information is collected and tracked

iii. Criteria and processes the Team uses to make decisions

iv. Summary of decisions the Team has made during the reporting period

v. How the Team determines when the compliance plan should be modified

d. Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action

e. Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrence

f. Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

g. Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified

h. Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified

i. Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified.

8. Safety Surveillance (data collected per reporting period):

a. TIRF TRIGs will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the TRIG's respective Standard Operating Procedures

b. TIRF TRIGs will produce one comprehensive report that presents spontaneous adverse event data from all TRIGs of the TIRF REMS Access Program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of adverse events of interest: addiction, overdose, death, and pediatric exposures. This report should include the following:

i. Line listings under each category of adverse events of interest as listed above

ii. Line listings should provide at a minimum the following information (see sample table provided):

- Identifying case number
- Age and Gender of the patient
- Date of the event as well as of the report
- The Preferred Terms
- Indication of TIRF use
- Duration of TIRF therapy
- Concomitant medications
- Event Outcome

iii. Other metrics of interest include:

1. Number of event reports in each event category of interest
2. Counts of adverse events related to inappropriate conversions between TIRF products
3. Counts of adverse events related to accidental and unintentional exposures
4. Counts of adverse events that are associated with use of TIRF medicines in non-opioid tolerant patients

iv. Duplicate cases are identified and eliminated

v. Case reports with adverse events in multiple categories will be listed in each category of interest, and will be noted as such

vi. For each adverse event category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events. Rate of each adverse event of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Section 5.b. directly above:

i. Non-medical use of prescription drugs

ii. Surveys conducted at substance abuse treatment programs

iii. College surveys

iv. Poison control center data

v. Drug-related hospital emergency department visits

vi. Drug-related deaths

vii. Other databases as relevant

Table 1. Report Template

Manuf. Reporting Number(s)	Patient		Date		Preferred Term(s)	Indication	TIRF Duration	Concomitant Medications	Event Outcome
	Age	Gender	Event	Report					

6. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies: Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access Program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacists, and patients. Surveys will assess understanding of key messages.

APPENDIX B – FDA DRUG UTILIZATION DATABASE DESCRIPTIONS

IQVIA National Sales Perspectives™ (NSP)

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

The distribution data do not provide a direct estimate of TIRF medicine use but do provide a nationally estimated number of bottles/packages of TIRF medicines sold from manufacturers to various U.S. retail and non-retail channels of distribution. The amount of product purchased by these channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

IQVIA National Prescription Audit™ (NPA)

The IQVIA National Prescription Audit (NPA) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.7 billion prescription claims per year, captured from a sample of the universe of approximately 58,900 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 92% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 60 – 86% (varies by class and geography) of mail service pharmacies and approximately 75 – 83% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

IQVIA Total Patient Tracker™ (TPT)

The IQVIA Total Patient Tracker (TPT) is a national-level projected service designed to estimate the total number of unique (non-duplicated) patients across all drugs and therapeutic classes in the retail outpatient setting from U.S. retail pharmacies. Data are available back to January 2002 and are available 20 days after the close of the month. TPT uses prescription activity as part of its projection and integrates information from pharmacies and payers to eliminate duplicate patients and multiple prescription fills, producing quick and reliable unique patient counts. IQVIA has 92% coverage and a sample of ~58,900 retail pharmacies. IQVIA captures about 3.8 billion transactions annually. TPT is projected to the known universe of retail pharmacies.

The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in patient counts due to rounding attributable to the projection methodology utilized as well as double counting of patients across time or products.

Syneos Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Due to the small sample sizes captured with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

APPENDIX C - FDA DRUG UTILIZATION TABLES

Table A: Nationally estimated number of prescriptions dispensed for transmucosal immediate release fentanyl medicines from U.S. outpatient retail pharmacies, 2010-2017

	Year															
	2010		2011		2012		2013		2014		2015		2016		2017	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Prescriptions Dispensed for TIRF Medicines	166,576	*100.0%*	147,322	*100.0%*	107,191	*100.0%*	95,170	*100.0%*	95,992	*100.0%*	90,556	*100.0%*	62,892	*100.0%*	39,555	*100.0%*
Generic TIRF Medicines	108,631	*65.2%*	91,985	*62.4%*	65,914	*61.5%*	46,799	*49.2%*	34,535	*36.0%*	27,210	*30.1%*	22,218	*35.3%*	16,197	*41.0%*
Subsys®	--	--	--	--	4,485	*4.2%*	19,481	*20.5%*	34,885	*36.3%*	40,539	*44.8%*	22,656	*36.0%*	11,567	*29.2%*
Fentora®	48,138	*28.9%*	47,120	*32.0%*	31,141	*29.1%*	24,591	*25.8%*	21,236	*22.1%*	17,995	*19.9%*	13,709	*21.8%*	8,907	*22.5%*
Lazanda®	--	--	46	*<0.5%*	510	*0.5%*	870	*0.9%*	991	*1.0%*	1,373	*1.5%*	2,089	*3.3%*	1,363	*3.5%*
Abstral®	--	--	849	*0.6%*	820	*0.8%*	796	*0.8%*	2,519	*2.6%*	2,054	*2.3%*	1,287	*2.1%*	944	*2.4%*
Actiq®	9,805	*5.9%*	7,317	*5.0%*	4,317	*4.0%*	2,632	*2.8%*	1,826	*1.9%*	1,385	*1.5%*	933	*1.5%*	577	*1.5%*
Onsolis®	2	*<0.5%*	5	*<0.5%*	4	*<0.5%*	1	*<0.5%*	--	--	--	--	--	--	--	--

Source: IQVIA National Prescription Audit™. 2010-2017. Data extracted May 2018. File: NPA 2018-452 TIRFs REMS AC product MD 3-14-2018 and 5-16-2018 and 6-13-2018.xlsx

Table B: Nationally estimated number of patients who received prescriptions dispensed for transmucosal immediate release fentanyl medicines from U.S. outpatient retail pharmacies, 2010-2017

	Year															
	2010		2011		2012		2013		2014		2015		2016		2017	
	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%	Patients	%
Total Patients Dispensed TIRF Medicines	23,948	*100.0%*	20,682	*100.0%*	14,446	*100.0%*	12,080	*100.0%*	12,537	*100.0%*	10,853	*100.0%*	7,114	*100.0%*	4,722	*100.0%*
Subsys®	--	--	--	--	1,885	*13.1%*	5,106	*42.3%*	7,252	*57.8%*	6,964	*64.2%*	3,628	*51.0%*	1,985	*42.0%*
Generic TIRF Medicines	16,662	*69.6%*	13,000	*62.9%*	8,768	*60.7%*	5,544	*45.9%*	4,133	*33.0%*	3,073	*28.3%*	2,527	*35.5%*	1,967	*41.6%*
Fentora®	7,480	*31.2%*	7,784	*37.6%*	4,546	*31.5%*	3,279	*27.1%*	2,678	*21.4%*	1,968	*18.1%*	1,338	*18.8%*	928	*19.6%*
Abstral®	--	--	314	*1.5%*	213	*1.5%*	268	*2.2%*	854	*6.8%*	675	*6.2%*	315	*4.4%*	464	*9.8%*
Lazanda®	--	--	32	*0.2%*	229	*1.6%*	319	*2.6%*	311	*2.5%*	375	*3.5%*	421	*5.9%*	292	*6.2%*
Actiq®	1,533	*6.4%*	947	*4.6%*	578	*4.0%*	309	*2.6%*	228	*1.8%*	157	*1.4%*	100	*1.4%*	73	*1.5%*
Onsolis®	1	*<0.1%*	5	*<0.1%*	5	*<0.1%*	--	--	--	--	--	--	--	--	--	--

Source: IQVIA Total Patient Tracker™. 2010-2017. Data extracted May 2018. File: TPTS 2018-452 generic T RFs PFS age no vet 5-11-2018.xlsx

*The patient estimates are nationally projected based on a sample of prescriptions claims from retail pharmacies. Summarization of these projected estimates across time periods and/or products may lead to differences in patient counts due to rounding attributable to the projection methodology utilized as well as double counting of patients across time or products.

Table C: Nationally estimated number of prescriptions dispensed for transmucosal immediate release fentanyl medicines from U.S. outpatient retail pharmacies, stratified by prescriber specialty, 2017

	Year 2017	
	TRxs	**%**
Total TIRF Dispensed Prescriptions	**39,555**	***100.0%***
Anesthesiology	8,748	*22.1%*
Nurse Practitioner/Physician Assistant	5,914	*15.0%*
Physical Medicine & Rehab	5,232	*13.2%*
Pain Medicine	4,575	*11.6%*
Family Practice/General Practitice/Internal Medicine	4,492	*11.4%*
Osteopathic Medicine	3,067	*7.8%*
Oncology	2,594	*6.6%*
Unspecified	1,758	*4.4%*
Neurology	1,489	*3.8%*
Psychiatry	470	*1.2%*
All Others	1,216	*3.1%*

Source: IQVIA National Prescription Audit™. 2017. Data extracted March 2018. File: NPA 2018-452 TIRFs REMS AC MD 3-14-2018.xlsx

Table D: Diagnoses associated with the use of transmucosal immediate release fentanyl medicines, stratified by prescriber specialty, as reported by U.S. office-based physician surveys, 2017

	Year 2017		
	Uses	**95% CI**	**%**
Total TIRF Mentions	**9,000**	**<500 - 28,000**	***100.0%***
Pain Specialist	**9,000**	**<500 - 28,000**	***100.0%***
G89 Pain, not elsewhere classified	**4,000**	**<500 - 15,000**	***37.9%***
R10 Abdominal and pelvic pain	**3,000**	**<500 - 13,000**	***31.1%***
C00-D49 Neoplasm	**3,000**	**<500 - 13,000**	***31.1%***

Source: Syneos Health Research & Insights LLC., TreatmentAnswers™. 2017. Data extracted May 2018. File: PDDA_2018-452_TIRF_REMS_AC_ICD10_dx3_ungroup_2017_5-17-2018.xls

*Diagnosis data are not directly linked to dispensed prescriptions, but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

APPENDIX D - ADDITIONAL PROGRAMMATIC AND COMPLIANCE DATA

D.1. PRESCRIBER AND PHARMACY INACTIVATIONS

A total of 3,241 prescribers were inactivated at some point during the current reporting period, 99.3% (3,217) due to expiration of enrollment (prescribers are required to re-enroll every 2 years in the REMS). Of those 3,217 prescribers whose enrollment expired at some point during the current reporting period, 2,756 (85.7%) remained expired at the end of the reporting period.

In the FDA's 36-month RAAL (August 3, 2015), the TRIG was asked to "*Conduct an outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report.*" However, since the TRIG did not conduct such an outreach in their 48-month assessment report, they were asked again to conduct such an outreach for the 60-month report. In the 60-month assessment report, the TRIG stated that the results of such an outreach would be available in the 72-month assessment report.

The TRIG submitted the results of this outreach in the 72-month report. The TRIG reports that calls were made to 5,630 prescribers and 1,458 pharmacies [1,432 independent outpatient pharmacies and 26 chain pharmacies]) with a minimum of three call attempts per stakeholder to ascertain the reason why they did not re-enroll in the TIRF REMS Access program. Reason for not re-enrolling were categorized into one of the seven pre-established reasons: Change in Prescribing/Dispensing Data; Never Prescribed/Dispensed TIRFs; No Longer Prescribes/Dispenses; Unaware of Re-enrollment Requirement; Deceased; Retired; and Other.

A total of 3,980 stakeholders were successfully contacted (56% of all target stakeholders): 3,369 prescribers and 611 pharmacies that opted not to re-enroll in the REMS. The reasons stated by 91.6% was "Change in Prescribing/Dispensing Data." The 72-month report did not define the term "Change in Prescribing/Dispensing Data." However, in a May 16, 2018 response to a May 9, 2018 Information Request (IR), the TRIG stated that this term "… *was used to categorize those who no longer required enrollment based on their prescribing/dispensing activities (e.g. a prescriber who changed from prescribing in an outpatient setting to prescribing in an inpatient setting or a pharmacy that dispenses both inpatient and outpatient, who no longer have the need to dispense outpatient).*" The TRIG further clarified that only "*… 'No Longer Prescribing/Dispensing' was used for those who no longer had a need to prescribe or dispense (e.g. a prescriber that no longer writes prescriptions for TIRF products or a pharmacy that no longer dispenses TIRF products).*" For prescribers, the second most common reason (affecting 7.1%) was unawareness of the need to re-enroll.

Presumably, those stakeholders who decided that they no longer wished to prescribe or dispense TIRFs were captured under the "No Longer Prescribing/Dispensing" category and not the "Change in Prescribing/Dispensing Data" category. These results are noted in **Table A** below:

Table A : Summary of Reasons Prescribers and Pharmacies Did Not Re-Enroll in the TIRF REMS Program

Reason for Not Re-Enrolling[a]	Prescribers (N=3,369)	Independent Pharmacies (N=602)	Chain Pharmacies (N=9)	Total (N=3,980)
Change in Prescribing/Dispensing Data	3,059	584	5	3,648
Never Prescribed/Dispensed TIRFs	12	1	0	13
No Longer Prescribes/Dispenses	8	1	2	11
Unaware of Re-Enrollment Requirement	238	10	2	250
Deceased	49	1	0	50
Retired	3	5	0	8

[a] No reported reason of 'Other' was collected from any stakeholder.

D.2. NON-COMPLIANCE EVENTS

Table B below (taken in its entirety from the assessment report's Table 23) summarizes non-compliance reports by either prescriber or pharmacy during the current reporting period:

Table B: Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period

Stakeholder	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	No. of Events	No. of Stakeholders
Prescriber	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date)	Aware of PPAF requirements but failed to complete PPAF	5	No w/1 report: 1 No w/3 reports: 2
		Completed PPAF with patient but failed to send PPAF to TIRF	3	No w/1 report: 3
		Not aware of PPAF requirement	7	No w/1 report: 7
		No reason provided	13	No w/1 report: 13
	Prescriber no longer has a valid, schedule II DEA.	No reason provided	1	No w/1 report: 1
		Total Prescriber Reports	29	
Non-Closed System Pharmacy	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF PMS that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Received reject but dispensed drug	3	No w/1 report: 3
		Dispensed drug without obtaining an authorization	4	No w/1 report: 2 No w/2 report: 1
		Not aware of requirements to process cash claims	2	No w/1 report: 2
	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS Access program.	No reason provided	1	No w/1 report: 1
	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Altered prescription details for a REMS authorization	1	No w/1 report: 1
		Total Non-Closed System Pharmacy Cases	**11**	
		Total Number of Reports During This Reporting Period	40	

D.3. CLOSED SYSTEM AUDIT PROCESS

The REMS Assessment Plan includes the following three components for closed system pharmacy audits:

1. Verification of training for all pharmacists dispensing TIRF products
2. Numbers of prescription authorizations per closed system
3. Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program

The first component of the closed system pharmacy audit requirement is accomplished through the enrollment process where the authorized representatives must attest that all pharmacy staff that participate in dispensing TIRF products will be trained on the TIRF REMS Access program requirements.

The second component is done through the closed system pharmacy prescription authorization process. Closed system pharmacists are required to validate the enrollment status of the prescriber and patient prior to dispensing a TIRF product by calling or faxing the prescription details to the TIRF REMS Access program.

Regarding the third component, the TRIG describes that the process of reconciliation between the closed system pharmacy's dispensing data and the REMS program's authorizations necessitates the TRIG requesting dispensing records from the closed system pharmacies and compares these records to the TRIG's authorization data. Specific data requested include:

- RX number for each prescription dispensed
- DEA number or NPI number of the facility that dispensed each prescription
- DEA number or NPI number of the prescriber that issued each prescription
- Date and time of each prescription transaction
- REMS Authorization code obtained for each prescription dispensed

APPENDIX E. SURVEY TABLES

E.1. PATIENT SURVEY TABLES

Table A: Patients'/Caregivers' Understanding of Key Risk Message 1

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310	72 Month Survey N=310
TIRF medicines can cause life-threatening breathing problems that can lead to death.	**True: 173 (90%)** False: 5 (3%) I don't know: 14 (7%)	**True: 272 (90%)** False: 0 (0%) I don't know: 30 (10%)	**True: 209 (91%)** False: 1 (0.4%) I don't know: 19 (8%)	**True: 285 (92%)** False: 3 (1%) I don't know: 22 (7%)	**True: 284 (92%)** False: 8 (3%) I don't know: 18 (6%)	**True: 287 (93%)** False: 2 (1%) I don't know: 21 (7%)
Composite Score*	**90%**	**90%**	**91%**	**92%**	**92%**	**93%**

**Composite score is 1/1 correct answer

Table B: Patients'/Caregivers' Understanding of Key Risk Message 2

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310	72 Month Survey N=310
TIRF medicines should only be taken by patients who are opioid tolerant. *Changed to TIRF medicines should only be taken by cancer patients who are opioid tolerant. (48 month)	**True: 174 (91%)** False: 5 (3%) I don't know: 13 (7%)	**True: 277 (92%)** False: 5 (2%) I don't know: 20 (7%)	**True: 195 (85%)** False: 6 (3%) I don't know: 28 (12%)	***True: 135 (44%)** False: 122 (39%) I don't know: 53 (17%)	**True: 277 (89%)** False: 8 (3%) I don't know: 25 (8%)	**True: 270 (87%)** False: 9 (3%) I don't know: 31 (10%)
Opioid	**True: 176**	**True: 267**	**True: 187**	**True: 280**	**True: 273**	**True: 263**

tolerant means that a patient is already taking other opioid pain medicines around the clock and their body is used to these medicines.	**(90%)** False: 7 (4%) I don't know: 9 (5%)	**(88%)** False: 12 (4%) I don't know: 23 (8%)	**(82%)** False: 19 (8%) I don't know: 23 (10%)	**(90%)** False: 14 (5%) I don't know: 16 (5%)	**(88%)** False: 14 (5%) I don't know: 23 (7%)	**(85%)** False: 19 (6%) I don't know: 28 (9%)
Composite Score*	**61.5%**	**60%**	**54%**	**42%**	**83%**	**78%**

**Composite score is 2/2 correct answers

Table C:Patients'/Caregivers' Understanding of Key Risk Message 3

Question	**12 Month Survey** **N=192**	**24 Month Survey** **N=302**	**36 Month Survey** **N=229**	**48 Month Survey** **N=310**	**60 Month Survey** **N=310**	**72 Month Survey** **N=310**
For which of the following conditions should you use a TIRF medicine?						
Headache or migraine pain	Yes: 29 (15%) **No: 140 (73%)** I don't know: 23 (12%)	Yes: 25 (8%) **No: 234 (77.5%)** I don't know: 43 (14%)	Yes: 25 (11%) **No: 179 (78%)** I don't know: 25 (11%)	Yes: 32 (10%) **No: 250 (81%)** I don't know: 28 (9%)	Yes: 34 (11%) **No: 242 (78%)** I don't know: 34 (11%)	Yes: 30 (10%) **No: 259 (83.5%)** I don't know: 21 (7%)
Breakthrough pain from cancer	**Yes: 134 (70%)** No: 52 (27%) I don't know: 6 (9%)	**Yes: 194 (64%)** No: 90 (30%) I don't know: 18 (6%)	**Yes: 151 (66%)** No: 71 (31%) I don't know: 7 (3%)	**Yes: 212 (68%)** No: 80 (26%) I don't know: 18 (6%)	**Yes: 225 (73%)** No: 81 (26%) I don't know: 4 (1%)	**Yes: 248 (80%)** No: 55 (18%) I don't know: 7 (2%)
Dental pain	Yes: 3 (2%) **No: 172 (90%)** I don't know: 17 (9%)	Yes: 49 (3%) **No: 264 (87%)** I don't know: 29 (10%)	Yes: 3 (1%) **No: 200 (87%)** I don't know: 26 (11%)	Yes: 8 (3%) **No: 280 (90%)** I don't know: 22 (7%)	Yes: 5 (2%) **No: 269 (87%)** I don't know: 36 (12%)	Yes: 4 (1%) **No: 283 (91%)** I don't know: 23 (7%)
Pain after surgery 12 month:	Yes: 40 (21%) **No: 120**	Yes: 52 (17%) **No: 207**	Yes: 44 (19%) **No: 161**	Yes: 65 (21%) **No: 210**	Yes: 69 (22%) **No: 199**	Yes: 63 (20%) **No: 212**

Acute or post-operative pain	**(68%)** I don't know: 22 (11%)	**(68.5%)** I don't know: 43 (14%)	**(70%)** I don't know: 24 (11%)	**(68%)** I don't know: 35 (11%)	**(64%)** I don't know: 42 (14%)	**(68%)** I don't know: 35 (11%)
Long-lasting painful conditions not caused by cancer 12 month: chronic non-cancer pain	Yes: 136 (71%) **No: 47 (24%)** I don't know: 9 (5%)	Yes: 210 (69%) **No: 66 (21%)** I don't know: 26 (9%)	Yes: 150 (65.5%) **No: 58 (25%)** I don't know: 21 (9%)	Yes: 135 (44%) **No: 136 (44%)** I don't know: 39 (13%)	Yes: 148 (48%) **No: 121 (39%)** I don't know: 41 (13%)	Yes: 120 (39%) **No: 149 (48%)** I don't know: 41 (13%)
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine	**True: 82 (43%)** False: 47 (24.5%) I don't know: 63 (33%)	**True: 103 (34%)** False: 87 (29%) I don't know: 112 (37%)	**True: 84 (37%)** False: 58 (25%) I don't know: 87 (38%)	**True: 122 (39%)** False: 93 (30%) I don't know: 95 (31%)	**True: 123 (40%)** False: 88 (28%) I don't know: 99 (32%)	**True: 134 (43%)** False: 88 (28%) I don't know: 88 (28%)
It is OK for patients to take TIRF medicines for headache pain.	True: 17 (9%) **False: 136 (71%)** I don't know: 39 (20%)	True: 21 (7%) **False: 206 (68%)** I don't know: 75 (25%)	True: 16 (7%) **False: 159 (69%)** I don't know: 54 (24%)	True: 20 (7%) **False: 232 (75%)** I don't know: 58 (19%)	True: 20 (7%) **False: 209 (67%)** I don't know: 81 (26%)	True: 17 (5.5%) **False: 225 (73%)** I don't know: 68 (22%)
TIRF medicines should be taken exactly as prescribed by the doctor.	**True: 192 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 301 (100%)** False: 0 (0%) I don't know: 1 (0.3%)	**True: 227 (99%)** False: 2 (1%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 309 (100%)** False: 1 (<1%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)
It is ok to take TIRF medicines for short-term pain that will go away in a few days.	True: 10 (5%) **False: 158 (82%)** I don't know: 24 (13%)	True: 15 (5%) **False: 252 (83%)** I don't know: 35 (12%)	True: 12 (5%) **False: 190 (83%)** I don't know: 27 (12%)	True: 13 (4%) **False: 267 (86%)** I don't know: 30 (10%)	True: 9 (3%) **False: 264 (85%)** I don't know: 37 (12%)	True: 12 (4%) **False: 257 (83%)** I don't know: 41 (13%)
Composite Score**	**39%**	**31%**	**32%**	**16%***	**11%***	**15.5%**

*Questions added to risk message in 48, 60, and 72-month surveys

**Composite score is 9/9 correct answers

Table D:Patients'/Caregivers' Understanding of Key Risk Message 4

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310	72 Month Survey N=310
It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	True: 1 (0.5%) **False: 186 (97%)** I don't know: 5 (3%)	True: 8 (3%) **False: 285 (94%)** I don't know: 9 (3%)	True: 2 (1%) **False: 222 (97%)** I don't know: 5 (2%)	True: 5 (2%) **False: 295 (95%)** I don't know: 10 (3%)	True: 6 (2%) **False: 297 (96%)** I don't know: 7 (2%)	True: 7 (2%) **False: 298 (96%)** I don't know: 5 (2%)
Composite Score*	**97%**	**94%**	**97%**	**95%**	**96%**	**96%**

*Composite score is 1/1 correct answer

Table E:Patients'/Caregivers' Understanding of Key Risk Message 5

Question	12 Month Survey N=192	24 Month Survey N=302	36 Month Survey N=229	48 Month Survey N=310	60 Month Survey N=310	72 Month Survey N=310
A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	True: 0 (0%) **False: 192 (100%)** I don't know: 0 (0%)	True: 5 (2%) **False: 296 (98%)** I don't know: 1 (0.3%)	True: 1 (0.4%) **False: 227 (99%)** I don't know: 1 (0.4%)	True: 0 (0%) **False: 308 (99%)** I don't know: 2 (1%)	True: 6 (2%) **False: 303 (98%)** I don't know: 1 (<1%)	True: 3 (1%) **False: 307 (99%)** I don't know: 0 (0%)
Selling or giving away TIRF medicines is against the law.	**True: 188 (98%)** False: 3 (2%) I don't know: 1 (0.5%)	**True: 297 (98%)** False: 2 (1%) I don't know: 3 (1%)	**True: 227 (99%)** False: 1 (0.4%) I don't know: 1 (0.4%)	**True: 306 (99%)** False: 2 (1%) I don't know: 2 (1%)	**True: 308 (99%)** False: 1 (<1%) I don't know: 1 (<1%)	**True: 306 (99%)** False: 2 (1%) I don't know: 2 (1%)
A side effect of TIRF medicines is the chance of abuse or addiction.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 287 (93%)** False: 5 (2%) I don't know: 18 (6%)	**True: 295 (95%)** False: 2 (1%) I don't know: 13 (4%)
TIRF medicines can be misused by people who	**N/A**	**N/A**	**N/A**	**N/A**	**True: 302 (97%)** False: 0 (0%)	**True: 302 (97%)** False: 1

abuse prescription medicines or street drugs.					I don't know: 8 (3%)	(<1%) I don't know: 7 (2%)
TIRF medicines should be kept in a safe place to prevent it from being stolen.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 308 (99%)** False: 1 (<1%) I don't know: 1 (<1%)	**True: 320 (100%)** False: 0 (0%) I don't know: 0 (0%)
Composite Score*	**98%**	**96%**	**98%**	**98%**	**88%**	**92%**

**Composite score is 5/5 correct answers

Table F:Patients'/Caregivers' Understanding of Key Risk Message 6

Question	**12 Month Survey** **N=192**	**24 Month Survey** **N=302**	**36 Month Survey** **N=229**	**48 Month Survey** **N=310**	**60 Month Survey** **N=310**	**72 Month Survey** **N=310**
TIRF medicines should be stored in a safe place out of reach of children.	**True: 192 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 302 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 227 (99%)** False: 1 (0.4%) I don't know: 1 (0.4%)	**True: 309 (100%)** False: 1 (<1%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 310 (100%)** False: 0 (0%) I don't know: 0 (0%)
TIRF medicines must be disposed of as described in the specific product's Medication Guide	**True: 184 (96%)** False: 2 (1%) I don't know: 6 (3%)	**True: 285 (94%)** False: 0 (0%) I don't know: 17 (6%)	**True: 215 (94%)** False: 1 (0.4%) I don't know: 19 (8%)	**True: 299 (97%)** False: 2 (1%) I don't know: 9 (3%)	**True: 303 (98%)** False: 2 (1%) I don't know: 5 (2%)	**True: 299 (96.5%)** False: 1 (<1%) I don't know: 10 (3%)
A TIRF medicine can cause an overdose and death in any child who takes it.	**True: 174 (91%)** False: 4 (2%) I don't know: 14 (7%)	**True: 275 (91%)** False: 2 (1%) I don't know: 25 (8%)	**True: 209 (91%)** False: 2 (1%) I don't know: 20 (9%)	**True: 289 (93%)** False: 2 (1%) I don't know: 19 (6%)	**True: 292 (94%)** False: 5 (2%) I don't know: 13 (4%)	**True: 296 (96.5%)** False: 0 (0%) I don't know: 14 (4.5%)
What should you do if an adult who has not been	**Get emergency help right away: 171**	**Get emergency help right away: 264**	**Get emergency help right away: 202**	**Get emergency help right away: 273**	**Get emergency help right away: 276**	**Get emergency help right away: 265**

prescribed a TIRF medicine takes a TIRF medicine?	**(89%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 6 (3%) I don't know: 15 (8%)	**(87%)** Do nothing: 17 (6%) Wait an hour and see if the person is OK: 2 (1%) I don't know: 19 (6%)	**(88%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 7 (3%) I don't know: 20 (9%)	**(88%)** Do nothing: 1 (0%) Wait an hour and see if the person is OK: 6 (2%) I don't know: 30 (10%)	**(89%)** Do nothing: 0 (0%) Wait an hour and see if the person is OK: 10 (3%) I don't know: 24 (8%)	**(85.5%)** Do nothing: 1 (<1%) Wait an hour and see if the person is OK: 14 (4.5%) I don't know: 24 (8%)
Composite Score*	**79%**	**78.5%**	**77%**	**81%**	**84%**	**80%**

**Composite score is 4/4 correct answers

Table G:Patients'/Caregivers' Understanding of Safe Use Questions

Question	**12 Month Survey** **N=192**	**24 Month Survey** **N=302**	**36 Month Survey** **N=229**	**48 Month Survey** **N=310**	**60 Month Survey** **N=310**	**72 Month Survey** **N=310**
Did the doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you?	**Yes: 165 (86%)** No: 23 (12%) I don't know: 4 (2%)	**Yes: 259 (86%)** No: 36 (12%) I don't know: 7 (2%)	**Yes: 200 (87%)** No: 23 (10%) I don't know: 6 (3%)	**Yes: 259 (84%)** No: 36 (12%) I don't know: 15 (5%)	**Yes: 265 (86%)** No: 37 (12%) I don't know: 3 (5%)	**Yes: 277 (89%)** No: 26 (8%) I don't know: 7 (2%)
Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for	Yes: 180 (94%) No: 12 (6%) I don't know: 0 (0%)	Yes: 281 (93%) No: 19 (6%) I don't know: 2 (1%)	Yes: 241 (93%) No: 13 (6%) I don't know: 21 (9%)	Yes: 296 (96%) No: 9 (3%) I don't know: 5 (2%)	Yes: 294 (95%) No: 15 (5%) I don't know: 1 (<1%)	Yes: 298 (96%) No: 11 (3.5%) I don't know: 1 (<1%)

you?						
Did the doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?	Yes: 155 (81%) No: 33 (17%) I don't know: 4 (2%)	Yes: 241 (80%) No: 52 (17%) I don't know: 9 (3%)	Yes: 185 (81%) No: 38 (17%) I don't know: 6 (3%)	Yes: 255 (82%) No: 49 (16%) I don't know: 6 (2%)	Yes: 270 (87%) No: 35 (11%) I don't know: 5 (2%)	Yes: 257 (83%) No: 47 (15%) I don't know: 6 (2%)
TIRF medicines are only available to patients through a special program (called the TIRF REMS Access Program).	**True: 97 (51%)** False: 23 (12%) I don't know: 72 (37%)	**True: 147 (49%)** False: 33 (11%) I don't know: 122 (40%)	**True: 162 (71%)** False: 9 (4%) I don't know: 58 (25%)	**True: 236 (76%)** False: 8 (3%) I don't know: 66 (21%)	**True: 238 (77%)** False: 10 (3%) I don't know: 62 (20%)	**True: 243 (78%)** False: 9 (3%) I don't know: 58 (19%)

E.2. PRESCRIBER SURVEY TABLES

Table H: Prescribers' Understanding of Key Risk Message 1

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=302**	**36 Month Survey** **N=300**	**48 Month Survey** **N=310**	**60 Month Survey** **N=294**	**72-Month Survey** **N=154**
TIRF medicines should only be taken by patients who are opioid tolerant.					**True: 284 (97%)** False: 8 (3%) I don't know: 2 (1%)	**True: 151 (98%)** False: 2 (1%) I don't know: 1 (1%)
24, 48, 60 month: According to labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: 12 month: According to the labeling, patients considered opioid-tolerant are those:						
Who are taking around-the-clock	**True: 24 (8%)**	**True: 273 (90%)**	**True: 270 (90%)**	**True: 295 (95%)**	**True: 279 (95%)**	**True: 143 (93%)**

opioid therapy for underlying persistent cancer pain for one week or longer (**T**/F/DK)	False: 271 (89%) I don't know: 7 (2%)	False: 24 (8%) I don't know: 5 (2%)	False: 22 (7%) I don't know: 8 (3%)	False: 14 (5%) I don't know: 1 (<1%)	False: 11 (4%) I don't know: 4 (1%)	False: 10 (6.5%) I don't know: 1 (1%)
Who are not currently taking opioid therapy, but have taken opioid therapy before.	True: 25 (8%) **False: 268 (89%)** I don't know: 9 (3%)	True: 28 (9%) **False: 266 (88%)** I don't know: 8 (3%)	True: 24 (8%) **False: 261 (87%)** I don't know: 15 (5%)	True: 15 (5%) **False: 291 (94%)** I don't know: 4 (1%)	True: 65 (5%) **False: 276 (94%)** I don't know: 2 (1%)	True: 6 (4%) **False: 145 (94%)** I don't know: 3 (2%)
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the clock opioid therapy 12 month: Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	True: 251 (83%) **False: 47 (16%)** I don't know: 4 (1%)	True: 39 (13%) **False: 248 (82%)** I don't know: 15 (5%)	True: 28 (9%) **False: 259 (86%)** I don't know: 13 (4%)	True: 33 (11%) **False: 269 (87%)** I don't know: 8 (3%)	True: 17 (6%) **False: 272 (93%)** I don't know: 5 (2%)	True: 15 (10%) **False: 137 (89%)** I don't know: 2 (1%)
TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**True: 264 (87%)** False: 35 (12%) I don't know: 3 (1%)	**True: 265 (88%)** False: 32 (11%) I don't know: 5 (2%)	**True: 260 (87%)** False: 32 (11%) I don't know: 8 (3%)	**True: 280 (90%)** False: 23 (7%) I don't know: 7 (2%)	**True: 270 (92%)** False: 21 (7%) I don't know: 3 (1%)	**True: 140 (91%)** False: 11 (7%) I don't know: 3 (2%)
Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**True: 289 (96%)** False: 4 (1%) I don't know: 9 (3%)	**True: 283 (94%)** False: 3 (1%) I don't know: 16 (5%)	**True: 287 (96%)** False: 2 (1%) I don't know: 11 (4%)	**True: 298 (96%)** False: 2 (1%) I don't know: 10 (3%)	**True: 281 (96%)** False: 3 (1%) I don't know: 10 (3%)	**True: 145 (94%)** False: 3 (2%) I don't know: 6 (4%)
TIRF medicines may be used in opioid non-tolerant patients.	True: 45 (15%) **False: 249 (82.5%)** I don't know: 8 (3%)	True: 43 (14%) **False: 242 (80%)** I don't know: 17 (6%)	True: 46 (15%) **False: 246 (82%)** I don't know: 8 (3%)	True: 38 (12%) **False: 263 (85%)** I don't know: 9 (3%)	True: 27 (9%) **False: 260 (88%)** I don't know: 7 (2%)	True: 12 (8%) **False: 138 (90%)** I don't know: 4 (3%)
Prescribers starting a patient on a TIRF medicine must	**True: 251 (83%)**	**True: 244 (81%)**	**True: 252 (84%)**	**True: 265 (86%)**	**True: 252 (86%)**	**True: 132 (86%)**

begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	False: 45 (15%) I don't know: 6 (2%)	False: 52 (17%) I don't know: 6 (2%)	False: 42 (14%) I don't know: 6 (2%)	False: 40 (13%) I don't know: 5 (2%)	False: 37 (13%) I don't know: 5 (2%)	False: 17 (11%) I don't know: 5 (3%)
According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:						
8 mg oral hydromorphone/day	**N/A**	**True: 207 (68.5%)** False: 64 (21%) I don't know: 31 (10%)	**True: 211 (70%)** False: 66 (22%) I don't know: 23 (8%)	**True: 226 (73%)** False: 57 (18%) I don't know: 27 (9%)	**True: 211 (72%)** False: 69 (24%) I don't know: 14 (5%)	**True: 119 (77%)** False: 25 (16%) I don't know: 10 (6.5%)
60 mg oral morphine/day	**N/A**	**True: 269 (89%)** False: 16 (5%) I don't know: 17 (6%)	**True: 277 (92%)** False: 42 (14%) I don't know: 12 (4%)	**True: 293 (95%)** False: 57 (18%) I don't know: 27 (9%)	**True: 281 (96%)** False: 6 (2%) I don't know: 7 (2%)	**True: 147 (95.5%)** False: 4 (3%) I don't know: 3 (2%)
30 mg oral oxycodone/day	**N/A**	**True: 230 (76%)** False: 47 (16%) I don't know: 25 (8%)	**True: 234 (78%)** False: 42 (14%) I don't know: 24 (8%)	**True: 244 (79%)** False: 46 (15%) I don't know: 20 (7%)	**True: 241 (82%)** False: 44 (15%) I don't know: 9 (3%)	**True: 128 (83%)** False: 19 (12%) I don't know: 7 (4.5%)
25 mcg transdermal fentanyl/hour	**N/A**	**True: 244 (81%)** False: 34 (11%) I don't know: 24 (8%)	**True: 251 (84%)** False: 31 (10%) I don't know: 18 (6%)	**True: 265 (86%)** False: 27 (9%) I don't know: 18 (6%)	**True: 262 (89%)** False: 21 (7%) I don't know: 11 (4%)	**True: 137 (89%)** False: 10 (6.5%) I don't know: 7 (4.5%)
25 mg oral oxymorphone/day	**N/A**	**True: 211 (70%)** False: 39 (13%) I don't know: 52 (17%)	**True: 224 (75%)** False: 41 (14%) I don't know: 34 (12%)	**True: 224 (72%)** False: 33 (11%) I don't know: 53 (17%)	**True: 234 (80%)** False: 33 (11%) I don't know: 27 (9%)	**True: 122 (79%)** False: 13 (8%) I don't know: 19 (12%)
An equianalgesic dose of another oral opioid	**N/A**	**True: 199 (66%)** False: 68 (22.5%) I don't know:	**True: 177 (59%)** False: 66 (22%) I don't know:	**True: 210 (68%)** False: 55 (18%) I don't know:	**True: 193 (66%)** False: 56 (19%) I don't know:	**True: 108 (70%)** False: 26 (17%) I don't know:

		35 (12%)	57 (19%)	45 (15%)	45 (15%)	20 (13%)
Composite Score**	**65%***	**45%**	**50%**	**30%**	**33%**	**40%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

** Composite score is 14/14/ correct responses

Table I: Prescribers' Understanding of Key Risk Message 2

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=302**	**36 Month Survey** **N=300**	**48 Month Survey** **N=310**	**60 Month Survey** **N=294**	**72-Month Survey** **N=154**
A cancer patient can be started on a TIRF medicine and an around-the-clock opioid at the same time.	**N/A**	True: 105 (35%) **False: 183 (61%)** I don't know: 14 (5%)	True: 101 (34%) **False: 180 (60%)** I don't know: 19 (6%)	True: 75 (24%) **False: 214 (69%)** I don't know: 21 (7%)	True: 52 (18%) **False: 227 (77%)** I don't know: 15 (5%)	True: 31 (20%) **False: 122 (79%)** I don't know: 1 (1%)
A cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	**N/A**	True: 86 (28.5%) **False: 196 (65%)** I don't know: 20 (7%)	True: 68 (23%) **False: 211 (70%)** I don't know: 21 (7%)	True: 62 (20%) **False: 226 (73%)** I don't know: 22 (7%)	True: 54 (18%) **False: 230 (78%)** I don't know: 10 (3%)	True: 20 (13%) **False: 126 (82%)** I don't know: 8 (5%)
Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?						
Acute or postoperative pain	Yes: 38 (13%) **No: 261 (86%)** I don't know: 3 (1%)	Yes: 17 (6%) **No: 281 (93%)** I don't know: 4 (1%)	Yes: 37 (12%) **No: 262 (87%)** I don't know: 1 (0.3%)	Yes: 28 (9%) **No: 280 (90%)** I don't know: 2 (1%)	Yes: 9 (3%) **No: 278 (95%)** I don't know: 7 (2%)	Yes: 12 (8%) **No: 140 (91%)** I don't know: 2 (1%)
Headache or migraine pain	Yes: 38 (13%) **No: 262 (87%)** I don't know: 2 (1%)	Yes: 20 (7%) **No: 279 (92%)** I don't know: 3 (1%)	Yes: 31 (10%) **No: 269 (90%)** I don't know: 0 (0%)	Yes: 16 (5%) **No: 294 (95%)** I don't know: 0 (0%)	Yes: 6 (2%) **No: 276 (94%)** I don't know: 12 (4%)	Yes: 1 (1%) **No: 148 (96%)** I don't know: 5 (3%)
Dental pain	Yes: 7 (2%) **No: 290 (96%)** I don't know: 5 (2%)	Yes: 5 (2%) **No: 292 (97%)** I don't know: 5 (2%)	Yes: 8 (3%) **No: 292 (97%)** I don't know: 0 (0%)	Yes: 5 (2%) **No: 305 (98%)** I don't know: 0 (0%)	Yes: 4 (1%) **No: 283 (96%)** I don't know: 7 (2%)	Yes: 1 (1%) **No: 150 (97%)** I don't know: 3 (2%)

Breakthrough pain from cancer	**Yes: 288 (95%)** No: 14 (5%) I don't know: 0 (0%)	**Yes: 279 (92%)** No: 22 (7%) I don't know: 1 (0.3%)	**Yes: 288 (96%)** No: 12 (4%) I don't know: 0 (0%)	**Yes: 288 (93%)** No: 22 (7%) I don't know: 0 (0%)	**Yes: 292 (99%)** No: 2 (1%) I don't know: 0 (0%)	**Yes: 152 (99%)** No: 2 (1%) I don't know: 0 (0%)
Chronic non-cancer pain	Yes: 134 (44%) **No: 164 (54%)** I don't know: 4 (1%)	Yes: 119 (39%) **No: 178 (59%)** I don't know: 5 (2%)	Yes: 112 (37%) **No: 186 (62%)** I don't know: 2 (1%)	Yes: 106 (34%) **No: 201 (65%)** I don't know: 3 (1%)	Yes: 54 (18%) **No: 230 (78%)** I don't know: 10 (3%)	Yes: 23 (15%) **No: 122 (79%)** I don't know: 9 (6%)
The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?						
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	**164 (54%)**	**199 (66%)**	**199 (66%)**	**227 (73%)**	**212 (72%)**	**127 (82.5%)**
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.	**True: 277 (92%)** False: 16 (5%) I don't know: 9 (3%)	**True: 278 (92%)** False: 16 (5%) I don't know: 8 (3%)	**True: 272 (91%)** False: 16 (5%) I don't know: 12 (4%)	**True: 291 (94%)** False: 12 (4%) I don't know: 7 (2%)	**True: 283 (96%)** False: 8 (3%) I don't know: 3 (1%)	**True: 145 (94%)** False: 7 (4.5%) I don't know: 2 (1%)
Instruct patients that, if they stop taking their around-the-clock opioid medicine, they can continue to take their TIRF medicine.	True: 63 (21%) **False: 207 (68.5%)** I don't know: 32 (11%)	True: 95 (31.5%) **False: 175 (58%)** I don't know: 32 (11%)	True: 89 (30%) **False: 183 (61%)** I don't know: 28 (9%)	True: 64 (21%) **False: 226 (73%)** I don't know: 20 (7%)	True: 58 (20%) **False: 225 (77%)** I don't know: 11 (4%)	True: 28 (18%) **False: 114 (74%)** I don't know: 12 (8%)
Composite Score**	**61%***	**39%**	**36%**	**33%**	**33%**	**36%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

** Composite score is 10/10 correct answers

Table J: Prescribers' Understanding of Key Risk Message 3

Question	12 Month Survey N=302	24 Month Survey N=302	36 Month Survey N=300	48 Month Survey N=310	60 Month Survey N=294	72-Month Survey N=154
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**True: 301 (100%)** False: 1 (0.3%) I don't know: 0 (0%)	**True: 299 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**True: 299 (100%)** False: 1 (0.3%) I don't know: 0 (0%)	**True: 306 (99%)** False: 2 (1%) I don't know: 2 (1%)	**True: 291 (99%)** False: 3 (1%) I don't know: 0 (0%)	**True: 152 (99%)** False: 0 (0%) I don't know: 2 (1%)
Which of the following are risk factors for opioid abuse?						
A personal history of psychiatric illness	**Yes: 249 (82.5%)** No: 37 (12%) I don't know: 16 (5%)	**Yes: 250 (83%)** No: 31 (10%) I don't know: 21(7%)	**Yes: 252 (84%)** No: 23 (8%) I don't know: 25 (8%)	**Yes: 262 (85%)** No: 28 (9%) I don't know: 20 (7%)	**Yes: 253 (86%)** No: 27 (9%) I don't know: 14 (5%)	**Yes: 139 (90%)** No: 9 (6%) I don't know: 6 (4%)
A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**Yes: 300 (99%)** No: 1 (0.3%) I don't know: 1 (0.3%)	**Yes: 299 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**Yes: 299 (100%)** No: 1 (0.3%) I don't know: 0 (0%)	**Yes: 306 (99%)** No: 4 (1%) I don't know: 0 (0%)	**Yes: 294 (100%)** No: 0 (0%) I don't know: 0 (0%)	**Yes: 151 (98%)** No: 2 (1%) I don't know: 1 (1%)
TIRF medicines can be abused in a manner similar to other opioid agonist.	**True: 295 (98%)** False: 6 (2%) I don't know: 1 (0.3%)	**True: 291 (96%)** False: 9 (3%) I don't know: 2 (1%)	**True: 292 (97%)** False: 7 (2%) I don't know: 1 (0.3%)	**True: 292 (94%)** False: 12 (4%) I don't know: 6 (2%)	**True: 282 (96%)** False: 10 (3%) I don't know: 2 (1%)	**True: 150 (97%)** False: 3 (2%) I don't know: 1 (1%)
Which of the following risks are associated with the use of TIRF medicines?						
Misuse	N/A	N/A	N/A	N/A	**True: 290 (99%)** False: 4 (1%) I don't know: 0 (0%)	**True: 152 (99%)** False: 2 (1%) I don't know: 0 (0%)
Abuse	N/A	N/A	N/A	N/A	**True: 291 (99%)** False: 2 (1%)	**True: 153 (99%)** False: 0 (0%)

					I don't know: 1 (<1%)	I don't know: 1 (1%)
Addiction	N/A	N/A	N/A	N/A	**True: 291 (99%)** False: 3 (1%) I don't know: 0 (0%)	**True: 153 (99%)** False: 1 (1%) I don't know: 0 (0%)
Overdose	N/A	N/A	N/A	N/A	**True: 292 (99%)** False: 2 (1%) I don't know: 0 (0%)	**True: 153 (99%)** False: 1 (1%) I don't know: 0 (0%)
Composite Score**	**80%**	**80%**	**82%**	**79%**	**61%***	**60%**

*Questions added for 60-month assessment

**Composite score is 10/10 correct answers

Table K: Prescribers' Understanding of Key Risk Message 4

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=302**	**36 Month Survey** **N=300**	**48 Month Survey** **N=310**	**60 Month Survey** **N=294**	**72-Month Survey** **N=154**
TIRF medicines are interchangeable with each other regardless of route of administration	True: 9 (3%) **False: 289 (96%)** I don't know: 4 (1%)	True: 16 (5%) **False: 279 (92%)** I don't know: 7 (2%)	True: 15 (5%) **False: 279 (93%)** I don't know: 6 (2%)	True: 13 (4%) **False: 287 (93%)** I don't know: 10 (3%)	True: 15 (5%) **False: 271 (92%)** I don't know: 8 (3%)	True: 5 (3%) **False: 147 (95.5%)** I don't know: 2 (1%)
The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of the differences in the pharmacokinetics of fentanyl absorption.	**True: 286 (95%)** False: 5 (2%) I don't know: 11 (4%)	**True: 286 (95%)** False: 7 (2%) I don't know: 9 (3%)	**True: 290 (97%)** False: 6 (2%) I don't know: 4 (1%)	**True: 296 (96%)** False: 6 (2%) I don't know: 8 (3%)	**True: 283 (96%)** False: 5 (2%) I don't know: 6 (2%)	**True: 148 (96%)** False: 2 (1%) I don't know: 4 (3%)
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True: 273 (90%)** False: 12 (4%) I don't know:	**True: 274 (91%)** False: 16 (5%) I don't know:	**True: 272 (91%)** False: 18 (6%) I don't know:	**True: 279 (90%)** False: 21 (7%) I don't know:	**True: 269 (92%)** False: 11 (4%) I don't know:	**True: 145 (94%)** False: 7 (4.5%) I don't know:

	17 (6%)	12 (4%)	10 (3%)	10 (3%)	14 (5%)	2 (1%)
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. His/her doctor decides to prescribe a different TIRF medicine in its place. According to the labeling, how should the prescriber proceed?						
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.	**228 (75.5%)**	**225 (74.5%)**	**223 (74%)**	**240 (77%)**	**231 (79%)**	**125 (81%)**
Composite Score	**85%***	**65%**	**67%**	**67%**	**70%**	**75%**

* Questions added to the 24 and 36-month assessment Key Risk Message that were not included for the 12-month

** Composite score is 4/4 correct answers

Table L: Prescribers' Understanding of Safe Use Questions

Question	**12 Month Survey N=302**	**24 Month Survey N=302**	**36 Month Survey N=300**	**48 Month Survey N=310**	**60 Month Survey N=294**	**72-Month Survey N=154**
A patient is starting titration with TIRF medicine. What dose must they start with? The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.	**276 (91%)**	**252 (84%)**	**267 (89%)**	**267 (86%)**	**266 (91%)**	**143 (93%)**
A prescriber has started titrating a patient with the lowest dose of a	**273 (90%)**	**205 (68%)**	**199 (66%)**	**213 (69%)**	**208 (71%)**	**101 (66%)**

TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Provide guidance based on the product-specific MG because the instructions are not the same for all TIRF medicines.						
A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described. Use of a TIRF medicine with a CYP2A4 inhibitor may require dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.	**262 (87%)**	**225 (74.5%)**	**232 (77%)**	**235 (76%)**	**235 (80%)**	**114 (74%)**
TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in	**True: 299 (99%)** False: 1 (0.3%) I don't know:	**True: 298 (99%)** False: 1 (0.3%) I don't know:	**True: 298 (99%)** False: 0 (0%) I don't know: 2 (1%)	**True: 308 (99%)** False: 1 (<1%) I don't know:	**True: 293 (99.7%)** False: 0 (0%) I don't know: 1 (<1%)	**True: 152 (99%)** False: 0 (0%) I don't know: 2 (1%)

individuals for whom they were not prescribed, and in those who are not opioid tolerant.	2 (1%)	3 (1%)		1 (<1%)		
Instruct patients never to share their TIRF medicines with anyone else, even if that person has the same symptoms.	**True: 300 (99%)** False: 1 (0.3%) I don't know: 1 (0.3%)	**True: 299 (99%)** False: 3 (1%) I don't know: 0 (0%)	**True: 297 (99%)** False: 2 (1%) I don't know: 1 (0.3%)	**True: 309 (99.7%)** False: 0 (0%) I don't know: 1 (<1%)	**True: 294 (100%)** False: 0 (0%) I don't know: 0 (0%)	**True: 151 (98%)** False: 2 (1%) I don't know: 1 (1%)

Table M: Prescribers' Reported Activities When Dispensing TIRF Medicines

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=302**	**36 Month Survey** **N=300**	**48 Month Survey** **N=310**	**60 Month Survey** **N=294**	**72-Month Survey** **N=154**
How frequently do you perform the following activities when dispensing TIRF medicines?						
Ask patients about the presence of children in the home.	Always: 175 (58%) Only with the first prescription: 76 (25%) Sometimes: 44 (15%) Never: 5 (2%) I don't know: 2 (1%)	Always: 170 (56%) Only with the first prescription: 70 (23%) Sometimes: 48 (16%) Never: 11 (4%) I don't know: 3 (1%)	Always: 169 (56%) Only with the first prescription: 81 (27%) Sometimes: 42 (14%) Never: 7 (2%) I don't know: 1 (0.3%)	Always: 178 (57%) Only with the first prescription: 75 (24%) Sometimes: 42 (14%) Never: 11 (4%) I don't know: 4 (1%)	Always: 182 (62%) Only with the first prescription: 66 (22%) Sometimes: 35 (12%) Never: 10 (3%) I don't know: 1 (<1%)	Always: 182 (62%) Only with the first prescription: 66 (22%) Sometimes: 35 (12%) Never: 10 (3%) I don't know: 1 (<1%)
Instruct patients not to share the TIRF medicines with anyone else.	Always: 239 (79%) Only with the first prescription: 36 (12%) Sometimes: 24 (8%) Never: 1 (0.3%) I don't know: 2 (1%)	Always: 239 (79%) Only with the first prescription: 37 (12%) Sometimes: 19 (6%) Never: 5 (2%) I don't know: 2 (1%)	Always: 235 (78%) Only with the first prescription: 41 (14%) Sometimes: 17 (6%) Never: 6 (2%) I don't know: 1 (0.3%)	Always: 249 (80%) Only with the first prescription: 43 (14%) Sometimes: 13 (4%) Never: 3 (1%) I don't know: 2 (1%)	Always: 236 (80%) Only with the first prescription: 43 (15%) Sometimes: 14 (5%) Never: 1 (<1%) I don't know: 0 (0%)	Always: 133 (86%) Only with the first prescription: 15 (10%) Sometimes: 5 (3%) Never: 1 (<%) I don't know: 0 (0%)

Counsel patients that accidental exposure to TIRF medicines by a child may be fatal	Always: 199 (66%) Only with the first prescription: 59 (19.5%) Sometimes: 24 (8%) Never: 1 (0.3%) I don't know: 2 (1%)	Always: 197 (65%) Only with the first prescription: 63 (21%) Sometimes: 31 (10%) Never: 8 (3%) I don't know: 3 (1%)	Always: 204 (68%) Only with the first prescription: 66 (22%) Sometimes: 26 (9%) Never: 3 (1%) I don't know: 1 (0.3%)	Always: 203 (66%) Only with the first prescription: 66 (21%) Sometimes: 27 (9%) Never: 11 (4%) I don't know: 3 (1%)	Always: 208 (71%) Only with the first prescription: 55 (19%) Sometimes: 23 (8%) Never: 8 (3%) I don't know: 0 (0%)	Always: 103 (67%) Only with the first prescription: 33 (21%) Sometimes: 17 (11%) Never: 1 (1%) I don't know: 0 (0%)
Instruct patients to keep TIRF medicines out of reach of children to prevent accidental exposure.	Always: 220 (73%) Only with the first prescription: 51 (17%) Sometimes: 25 (8%) Never: 4 (1%) I don't know: 2 (1%)	Always: 220 (73%) Only with the first prescription: 46 (15%) Sometimes: 28 (9%) Never: 5 (2%) I don't know: 3 (1%)	Always: 223 (74%) Only with the first prescription: 52 (17%) Sometimes: 22 (7%) Never: 2 (1%) I don't know: 1 (0.3%)	Always: 220 (71%) Only with the first prescription: 61 (20%) Sometimes: 19 (6%) Never: 7 (2%) I don't know: 3 (1%)	Always: 232 (79%) Only with the first prescription: 44 (15%) Sometimes: 13 (4%) Never: 5 (2%) I don't know: 0 (0%)	Always: 121 (79%) Only with the first prescription: 24 (16%) Sometimes: 8 (5%) Never: 1 (1%) I don't know: 0 (0%)
Instruct patients about proper disposal of any unused or partially used TIRF medicines.	Always: 184 (61%) Only with the first prescription: 75 (25%) Sometimes: 37 (12%) Never: 4 (1%) I don't know: 2 (1%)	Always: 187 (62%) Only with the first prescription: 62 (20.5%) Sometimes: 37 (12%) Never: 12 (4%) I don't know: 4 (1%)	Always: 186 (62%) Only with the first prescription: 68 (23%) Sometimes: 38 (13%) Never: 7 (2%) I don't know: 1 (0.3%)	Always: 190 (61%) Only with the first prescription: 74 (24%) Sometimes: 37 (12%) Never: 6 (2%) I don't know: 3 (1%)	Always: 197 (67%) Only with the first prescription: 56 (19%) Sometimes: 34 (12%) Never: 7 (2%) I don't know: 0 (0%)	Always: 98 (64%) Only with the first prescription: 34 (22%) Sometimes: 19 (12%) Never: 3 (2%) I don't know: 0 (0%)
Give patients the Medication Guide for their TIRF medicine.	Always: 122 (40%) Only with the first prescription: 128 (42%) Sometimes: 28 (9%) Never: 20 (7%)	Always: 142 (47%) Only with the first prescription: 108 (36%) Sometimes: 26 (9%) Never: 20 (7%)	Always: 127 (42%) Only with the first prescription: 124 (41%) Sometimes: 35 (12%) Never: 11 (4%)	Always: 140 (45%) Only with the first prescription: 123 (40%) Sometimes: 23 (7%) Never: 21 (7%)	Always: 130 (44%) Only with the first prescription: 131 (45%) Sometimes: 17 (6%) Never: 15 (5%)	Always: 67 (43.5%) Only with the first prescription: 64 (42%) Sometimes: 12 (8%) Never: 11 (7%)

	I don't know: 4 (1%)	I don't know: 6 (2%)	I don't know: 3 (1%)	I don't know: 3 (1%)	I don't know: 1 (<1%)	I don't know: 0 (0%)
Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 223 (76%) Only with the first prescription: 53 (18%) Sometimes: 16 (5%) Never: 0 (0%) I don't know: 2 (1%)	Always: 118 (77%) Only with the first prescription: 23 (15%) Sometimes: 13 (8%) Never: 0 (0%) I don't know: 0 (0%)
Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 204 (69%) Only with the first prescription: 67 (23%) Sometimes: 21 (7%) Never: 0 (0%) I don't know: 2 (1%)	Always: 116 (75%) Only with the first prescription: 27 (17.5%) Sometimes: 11 (7%) Never: 0 (0%) I don't know: 0 (0%)
Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	N/A	N/A	N/A	N/A	Always: 156 (53%) Only with the first prescription: 102 (35%) Sometimes: 22 (8%) Never: 12 (4%) I don't know: 2 (1%)	Always: 85 (55%) Only with the first prescription: 49 (32%) Sometimes: 20 (13%) Never: 0 (0%) I don't know: 0 (0%)

E.3. PHARMACIST SURVEY TABLES

Table N: Pharmacists' Understanding of Key Risk Message 1

Question	12 Month Survey N=302	24 Month Survey N=300	36 Month Survey N=300	48 Month Survey N=301	60 Month Survey N=318	72 Month Survey N=308
According to the labeling, patients considered opioid-tolerant are those: (12-month and 60-month) According to labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: (24, 36, and 48 month)						
Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	**True: 38 (13%)** False: 255 (84%) I don't know: 9 (3%)	**True: 271 (90%)** False: 23 (8%) I don't know: 6 (2%)	**True: 281 (94%)** False: 11 (4%) I don't know: 8 (3%)	**True: 279 (93%)** False: 22 (7%) I don't know: 0 (0%)	**True: 304 (96%)** False: 10 (3%) I don't know: 4 (1%)	**True: 281 (91%)** False: 21 (7%) I don't know: 6 (2%)
Who are not currently taking opioid therapy, but have taken opioid therapy before.	True: 46 (15%) **False: 242 (80%)** I don't know: 14 (5%)	True: 41 (14%) **False: 242 (81%)** I don't know: 17 (6%)	True: 29 (10%) **False: 261 (87%)** I don't know: 10 (3%)	True: 9 (27%) **False: 263 (87%)** I don't know: 11 (4%)	True: 30 (9%) **False: 278 (87%)** I don't know: 10 (3%)	True: 38 (12%) **False: 254 (82.5%)** I don't know: 16 (5%)
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the clock opioid therapy **12 month**: Who are not currently taking opioid therapy, but with no known intolerance or hypersensitivity to the drug fentanyl	True: 242 (80%) **False: 47 (16%)** I don't know: 13 (4%)	True: 52 (17%) **False: 228 (76%)** I don't know: 20 (7%)	True: 44 (15%) **False: 236 (79%)** I don't know: 20 (7%)	True: 44 (15%) **False: 248 (82%)** I don't know: 9 (3%)	True: 46 (15%) **False: 261 (82%)** I don't know: 11 (4%)	True: 57 (18.5%) **False: 241 (78%)** I don't know: 10 (3%)
TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**True: 260 (86%)** False: 24 (8%) I don't know: 18 (6%)	**True: 258 (86%)** False: 27 (9%) I don't know: 15 (5%)	**True: 271 (91%)** False: 19 (6%) I don't know: 9 (3%)	**True: 274 (91%)** False: 19 (6%) I don't know: 8 (3%)	**True: 281 (88%)** False: 23 (7%) I don't know: 14 (4%)	**True: 285 (92.5%)** False: 18 (6%) I don't know: 5 (2%)
Death has occurred	**True: 278**	**True: 281**	**True: 281**	**True: 287**	**True: 303**	**True: 298**

in opioid non-tolerant patients treated with some fentanyl products.	**(92%)** False: 5 (2%) I don't know: 19 (6%)	**(94%)** False: 2 (1%) I don't know: 17 (6%)	**(94%)** False: 4 (1%) I don't know: 15 (5%)	**(95%)** False: 4 (1%) I don't know: 10 (3%)	**(95%)** False: 3 (1%) I don't know: 12 (4%)	**(97%)** False: 2 (1%) I don't know: 8 (3%)
TIRF medicines may be used in opioid non-tolerant patients.	True: 48 (16%) **False: 237 (78.5%)** I don't know: 17 (6%)	True: 40 (13%) **False: 246 (82%)** I don't know: 14 (5%)	True: 39 (13%) **False: 251 (84%)** I don't know: 10 (3%)	True: 35 (12%) **False: 257 (85%)** I don't know: 9 (3%)	True: 28 (9%) **False: 278 (87%)** I don't know: 12 (4%)	True: 28 (9%) **False: 270 (88%)** I don't know: 10 (3%)
Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**True: 237 (78.5%)** False: 46 (15%) I don't know: 19 (6%)	**True: 248 (83%)** False: 38 (13%) I don't know: 14 (5%)	**True: 237 (79%)** False: 50 (17%) I don't know: 13 (4%)	**True: 243 (81%)** False: 45 (15%) I don't know: 13 (4%)	**True: 267 (84%)** False: 34 (11%) I don't know: 17 (5%)	**True: 265 (86%)** False: 29 (9%) I don't know: 14 (4.5%)
According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:						
8 mg oral hydromorphone/day	**N/A**	**True: 237 (79%)** False: 29 (10%) I don't know: 34 (11%)	**True: 229 (76%)** False: 31 (10%) I don't know: 40 (13%)	**True: 237 (79%)** False: 30 (10%) I don't know: 13 (4%)	**True: 237 (75%)** False: 38 (12%) I don't know: 43 (14%)	**True: 230 (75%)** False: 34 (11%) I don't know: 44 (14%)
60 mg oral morphine/day	**N/A**	**True: 255 (85%)** False: 14 (5%) I don't know: 31 (10%)	**True: 253 (85%)** False: 15 (5%) I don't know: 31 (10%)	**True: 270 (90%)** False: 11 (4%) I don't know: 20 (7%)	**True: 280 (88%)** False: 13 (4%) I don't know: 25 (8%)	**True: 265 (86%)** False: 13 (4%) I don't know: 30 (10%)
30 mg oral oxycodone/day	**N/A**	**True: 214 (71%)** False: 44 (15%) I don't know: 42	**True: 220 (73%)** False: 38 (13%) I don't know: 42	**True: 232 (77%)** False: 41 (14%) I don't know: 28	**True: 247 (78%)** False: 37 (12%) I don't know: 34 (11%)	**True: 235 (76%)** False: 39 (13%) I don't know: 34 (11%)

		(14%)	(14%)	(9%)		
25 mcg transdermal fentanyl/hour	**N/A**	**True: 216 (72%)** False: 45 (15%) I don't know: 39 (13%)	**True: 223 (74%)** False: 31 (10%) I don't know: 46 (15%)	**True: 232 (77%)** False: 42 (14%) I don't know: 27 (9%)	**True: 253 (80%)** False: 39 (12%) I don't know: 26 (8%)	**True: 239 (78%)** False: 28 (9%) I don't know: 41 (13%)
25 mg oral oxymorphone/day	**N/A**	**True: 213 (71%)** False: 29 (10%) I don't know: 58 (19%)	**True: 213 (71%)** False: 26 (9%) I don't know: 61 (20%)	**True: 221 (73%)** False: 36 (12%) I don't know: 44 (15%)	**True: 229 (72%)** False: 30 (9%) I don't know: 59 (19%)	**True: 218 (71%)** False: 32 (10%) I don't know: 58 (19%)
An equianalgesic dose of another oral opioid	**N/A**	**True: 177 (59%)** False: 61 (20%) I don't know: 62 (21%)	**True: 177 (59%)** False: 57 (19%) I don't know: 66 (22%)	**True: 196 (65%)** False: 49 (16%) I don't know: 56 (19%)	**True: 207 (65%)** False: 51 (16%) I don't know: 60 (19%)	**True: 197 (64%)** False: 53 (17%) I don't know: 58 (19%)
TIRF medicines should only be taken by patients who are opioid tolerant.	**N/A**	**N/A**	**N/A**	**N/A**	**True: 284 (97%)** False: 8 (3%) I don't know: 2 (1%)	**True: 292 (95%)** False: 12 (4%) I don't know: 4 (1%)
Composite Score**	**57%***	**43%**	**50%**	**30%**	**31%**	**27%**

* Questions added to the 24 and 36 month assessment Key Risk Message that were not included for the 12-month

**Composite score is 14/14 correct answers

Table O: Pharmacists' Understanding of Key Risk Message 2

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=300**	**36 Month Survey** **N=300**	**48 Month Survey** **N=301**	**60 Month Survey** **N=318**	**72-Month Survey** **N=308**
According to the product labeling, a cancer patient may start a TIRF medicine and	N/A	True: 80 (27%) **False: 196 (65%)** I don't know: 24 (8%)	True: 85 (28%) **False: 190 (63%)** I don't know: 25 (8%)	True: 70 (23%) **False: 208 (69%)** I don't know: 23 (8%)	True: 82 (26%) **False: 197 (62%)** I don't know: 39 (12%)	True: 75 (24%) **False: 206 (67%)** I don't know: 27 (9%)

an around-the-clock opioid at the same time.						
According to the product labeling, a cancer patient who has been on an around the clock opioid for 1 day can start taking a TIRF medicine for breakthrough pain.	N/A	True: 50 (17%) **False: 224 (75%)** I don't know: 26 (9%)	True: 57 (19%) **False: 222 (74%)** I don't know: 21 (7%)	True: 37 (12%) **False: 247 (82%)** I don't know: 17 (6%)	True: 34 (11%) **False: 256 (81%)** I don't know: 28 (9%)	True: 38 (12%) **False: 244 (79%)** I don't know: 26 (8%)
A patient must stop taking their TIRF medicine if they stop taking their around the clock opioid pain medicine	N/A	N/A	N/A	**True: 126 (42%)** False: 136 (45%) I don't know: 39 (13%)	**True: 131 (41%)** False: 151 (48%) I don't know: 36 (11%)	**True: 148 (41%)** False: 128 (42%) I don't know: 32 (10%)
Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients?						
Acute or postoperative pain	Yes: 52 (17%) **No: 236 (78%)** I don't know: 14 (5%)	Yes: 31 (10%) **No: 254 (85%)** I don't know: 15 (5%)	Yes: 33 (11%) **No: 260 (87%)** I don't know: 7 (2%)	Yes: 22 (7%) **No: 271 (90%)** I don't know: 8 (3%)	Yes: 35 (11%) **No: 273 (86%)** I don't know: 10 (3%)	Yes: 38 (12%) **No: 263 (85%)** I don't know: 7 (2%)
Headache or migraine pain	Yes: 12 (4%) **No: 269 (89%)** I don't know: 21 (7%)	Yes: 8 (3%) **No: 277 (92%)** I don't know: 15 (5%)	Yes: 9 (3%) **No: 272 (91%)** I don't know: 19 (6%)	Yes: 12 (4%) **No: 280 (93%)** I don't know: 9 (3%)	Yes: 7 (2%) **No: 300 (94%)** I don't know: 11 (4%)	Yes: 11 (4%) **No: 286 (93%)** I don't know: 11 (4%)
Dental pain	Yes: 6 (89%) **No: 286 (95%)** I don't know: 10 (3%)	Yes: 3 (1%) **No: 290 (97%)** I don't know: 7 (2%)	Yes: 5 (2%) **No: 291 (97%)** I don't know: 4 (1%)	Yes: 2 (1%) **No: 296 (98%)** I don't know: 3 (1%)	Yes: 2 (1%) **No: 306 (96%)** I don't know: 10 (3%)	Yes: 8 (3%) **No: 296 (96%)** I don't know: 4 (1%)
Breakthrough pain from cancer	**Yes: 252 (83%)** No: 46 (15%)	**Yes: 268 (89%)** No: 27 (9%)	**Yes: 275 (92%)** No: 23 (8%)	**Yes: 277 (92%)** No: 24 (8%)	**Yes: 292 (92%)** No: 22 (7%)	**Yes: 280 (91%)** No: 24 (8%)

	I don't know: 4 (1%)	I don't know: 5 (2%)	I don't know: 2 (1%)	I don't know: 0 (0%)	I don't know: 4 (1%)	I don't know: 4 (1%)
Chronic non-cancer pain	Yes: 194 (64%) **No: 90 (30%)** I don't know: 18 (6%)	Yes: 126 (42%) **No: 141 (47%)** I don't know: 33 (11%)	Yes: 146 (49%) **No: 131 (44%)** I don't know: 23 (8%)	Yes: 131 (44%) **No: 153 (51%)** I don't know: 17 (6%)	Yes: 138 (43%) **No: 162 (51%)** I don't know: 18 (6%)	Yes: 128 (42%) **No: 165 (54%)** I don't know: 15 (5%)
Composite Score**	**61%***	**40%**	**37%**	**22%**	**22%**	**25%**

* Questions added to the 24 and 36-month assessment Key Risk Message that were not included for the 12-month

**Composite score includes 8/8 correct answers

Table P: Pharmacists' Understanding of Key Risk Message 3

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=300**	**36 Month Survey** **N=300**	**48 Month Survey** **N=301**	**60 Month Survey** **N=318**	**72 Month Survey** **N=308**
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**True: 295 (98%)** False: 5 (2%) I don't know: 2 (1%)	**True: 290 (97%)** False: 5 (2%) I don't know: 5 (2%)	**True: 288 (96%)** False: 7 (2%) I don't know: 5 (2%)	**True: 293 (97%)** False: 7 (2%) I don't know: 1 (<1%)	**True: 312 (98%)** False: 4 (1%) I don't know: 2 (1%)	**True: 300 (97%)** False: 4 (1%) I don't know: 4 (1%)
Which of the following are risk factors for opioid abuse?						
A personal history of psychiatric illness	**Yes: 201 (67%)** No: 62 (20.5%) I don't know: 39 (13%)	**Yes: 216 (72%)** No: 48 (16%) I don't know: 36 (12%)	**Yes: 213 (71%)** No: 46 (15%) I don't know: 41 (14%)	**Yes: 227 (75%)** No: 43 (14%) I don't know: 31 (10%)	**Yes: 247 (78%)** No: 42 (13%) I don't know: 29 (9%)	**Yes: 244 (79%)** No: 44 (14%) I don't know: 20 (6.5%)
A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**Yes: 301 (100%)** No: 0 (15%) I don't know: 1 (0.3%)	**Yes: 297 (99%)** No: 0 (0%) I don't know: 3 (1%)	**Yes: 298 (99%)** No: 0 (0%) I don't know: 2 (1%)	**Yes: 297 (99%)** No: 2 (1%) I don't know: 2 (1%)	**Yes: 314 (99%)** No: 1 (<1%) I don't know: 3 (1%)	**Yes: 303 (98%)** No: 2 (1%) I don't know: 3 (1%)
TIRF medicines can	**True: 273 (90%)**	**True: 282 (94%)**	**True: 283 (94%)**	**True: 288 (96%)**	**True: 298 (94%)**	**True: 287 (93%)**

be abused in a manner similar to other opioid agonist.	False: 19 (6%) I don't know: 10 (3%)	False: 10 (3%) I don't know: 8 (3%)	False: 12 (4%) I don't know: 5 (2%)	False: 8 (3%) I don't know: 5 (2%)	False: 12 (4%) I don't know: 8 (3%)	False: 15 (5%) I don't know: 6 (2%)
Which of the following risks are associated with the use of TIRF medicines?						
Misuse	N/A	N/A	N/A	N/A	**True: 314 (99%)** False: 3 (1%) I don't know: 1 (<1%)	**True: 303 (98%)** False: 2 (1%) I don't know: 3 (1%)
Abuse	N/A	N/A	N/A	N/A	**True: 315 (99%)** False: 2 (1%) I don't know: 1 (<1%)	**True: 304 (99%)** False: 3 (1%) I don't know: 1 (<1%)
Addiction	N/A	N/A	N/A	N/A	**True: 314 (99%)** False: 3 (1%) I don't know: 1 (<1%)	**True: 304 (99%)** False: 3 (1%) I don't know: 1 (<1%)
Overdose	N/A	N/A	N/A	N/A	**True: 316 (99%)** False: 1 (<1%) I don't know: 1 (<1%)	**True: 305 (99%)** False: 1 (<1%) I don't know: 2 (1%)
Composite Score	**60%**	**66%**	**66%**	**69%**	**59%***	**52%***

* Questions added to the 60-month assessment Key Risk Message that were not included for the previous months

**Composite score includes 10/10 correct answers

Table Q: Pharmacists' Understanding of Key Risk Message 4

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=300**	**36 Month Survey** **N=300**	**48 Month Survey** **N=301**	**60 Month Survey** **N=318**	**72-Month Survey** **N=308**
TIRF medicines are interchangeable with each other regardless of route of administration	True: 9 (3%) **False: 287 (95%)** I don't know: 6 (2%)	True: 6 (2%) **False: 284 (95%)** I don't know: 10 (3%)	True: 13 (4%) **False: 280 (93%)** I don't know: 7 (2%)	True: 14 (5%) **False: 281 (93%)** I don't know: 6 (2%)	True: 6 (2%) **False: 305 (96%)** I don't know: 7 (2%)	True: 13 (4%) **False: 286 (93%)** I don't know: 9 (3%)

The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of the differences in the pharmacokinetics of fentanyl absorption.	**True: 280 (93%)** False: 10 (3%) I don't know: 12 (4%)	**True: 276 (92%)** False: 5 (2%) I don't know: 19 (6%)	**True: 279 (93%)** False: 13 (4%) I don't know: 8 (3%)	**True: 279 (93%)** False: 11 (4%) I don't know: 11 (4%)	**True: 296 (93%)** False: 10 (3%) I don't know: 12 (4%)	**True: 288 (93.5%)** False: 12 (4%) I don't know: 8 (3%)
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**True: 279 (92%)** False: 10 (3%) I don't know: 13 (4%)	**True: 274 (91%)** False: 10 (3%) I don't know: 16 (5%)	**True: 270 (90%)** False: 20 (7%) I don't know: 10 (3%)	**True: 279 (93%)** False: 14 (5%) I don't know: 8 (3%)	**True: 283 (89%)** False: 16 (5%) I don't know: 19 (6%)	**True: 277 (90%)** False: 19 (6%) I don't know: 12 (4%)
TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product	True: 5 (2%) **False: 289 (96%)** I don't know: 8 (3%)	True: 6 (2%) **False: 289 (96%)** I don't know: 5 (2%)	True: 2 (1%) **False: 293 (98%)** I don't know: 5 (2%)	True: 3 (1%) **False: 296 (98%)** I don't know: 2 (1%)	True: 10 (3%) **False: 304 (96%)** I don't know: 4 (1%)	True: 11 (4%) **False: 294 (96%)** I don't know: 3 (1%)
Composite Score*	**84%**	**85%**	**81%**	**81%**	**80%**	**80%**

*Composite score includes 4/4 correct answers

Table R: Pharmacists' Understanding of Safe Use Questions

Question	**12 Month Survey** **N=302**	**24 Month Survey** **N=300**	**36 Month Survey** **N=300**	**48 Month Survey** **N=301**	**60 Month Survey** **N=318**	**72 Month Survey** **N=308**
Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially	**N/A**	N/A	N/A	**True: 275 (91%)** False: 8 (3%) I don't know: 18 (6%)	**True: 293 (92%)** False: 3 (1%) I don't know: 22 (7%)	**True: 282 (92%)** False: 7 (2%) I don't know: 19 (6%)

fatal respiratory depression could occur.						
TIRF medicines may be sold, loaned, or transferred to another pharmacy.	True: 14 (5%) **False: 262 (87%)** I don't know: 26 (9%)	True: 8 (3%) **False: 274 (91%)** I don't know: 18 (6%)	True: 11 (4%) **False: 276 (92%)** I don't know: 13 (4%)	True: 7 (2%) **False: 279 (93%)** I don't know: 15 (5%)	True: 16 (5%) **False: 288 (91%)** I don't know: 14 (4%)	True: 18 (6%) **False: 273 (89%)** I don't know: 17 (5.5%)
All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access Program.	**True: 280 (93%)** False: 12 (4%) I don't know: 10 (3%)	**True: 282 (94%)** False: 6 (2%) I don't know: 12 (4%)	**True: 284 (95%)** False: 10 (3%) I don't know: 6 (2%)	**True: 273 (91%)** False: 23 (8%) I don't know: 5 (2%)	**True: 286 (90%)** False: 18 (6%) I don't know: 14 (4%)	**True: 290 (94%)** False: 12 (4%) I don't know: 6 (2%)
It is ok to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home. *Inpatient pharmacists only (12 month: n=16; 24 month: n=15; 36 month: n=15; 48 month: n=15); 60 month: n=65	True: 2 (12.5%) **False: 14 (87.5%)** I don't know: 0 (0%)	True: 0 (0%) **False: 13 (87%)** I don't know: 2 (13%)	True: 2 (13%) **False: 13 (87%)** I don't know: 0 (0%)	True: 0 (0%) **False: 13 (87%)** I don't know: 2 (13%)	True: 3 (5%) **False: 54 (83%)** I don't know: 8 (12%)	True: 0 (0%) **False: 15 (83%)** I don't know: 3 (17%)

Table S: Pharmacists' Reported Activities When Dispensing TIRF Medicines

Question	**12 Month Survey**	**24 Month Survey**	**36 Month Survey**	**48 Month Survey**	**60 Month Survey**	**72-Month Survey**

	N=302	N=300	N=300	N=301	N=318	N=308
How frequently do you perform the following activities when dispensing TIRF medicines?						
Ask patients about the presence of children in the home.	Always: 146 (48%) Only with the first prescription: 68 (22.5%) Sometimes: 54 (18%) Never: 28 (9%) I don't know: 6 (2%)	Always: 167 (56%) Only with the first prescription: 54 (18%) Sometimes: 54 (18%) Never: 13 (4%) I don't know: 12 (4%)	Always: 174 (58%) Only with the first prescription: 68 (23%) Sometimes: 33 (11%) Never: 14 (5%) I don't know: 11 (4%)	Always: 180 (60%) Only with the first prescription: 67 (22%) Sometimes: 36 (12%) Never: 9 (3%) I don't know: 9 (3%)	Always: 180 (60%) Only with the first prescription: 67 (22%) Sometimes: 36 (12%) Never: 9 (3%) I don't know: 9 (3%)	Always: 180 (58%) Only with the first prescription: 77 (25%) Sometimes: 33 (11%) Never: 11 (4%) I don't know: 7 (2%)
Instruct patients not to share the TIRF medicines with anyone else.	Always: 202 (67%) Only with the first prescription: 54 (18%) Sometimes: 26 (9%) Never: 15 (5%) I don't know: 5 (2%)	Always: 208 (69%) Only with the first prescription: 52 (17%) Sometimes: 26 (9%) Never: 8 (3%) I don't know: 6 (2%)	Always: 224 (75%) Only with the first prescription: 45 (15%) Sometimes: 17 (6%) Never: 6 (2%) I don't know: 8 (3%)	Always: 235 (78%) Only with the first prescription: 42 (14%) Sometimes: 14 (5%) Never: 6 (2%) I don't know: 4 (1%)	Always: 235 (78%) Only with the first prescription: 42 (14%) Sometimes: 14 (5%) Never: 6 (2%) I don't know: 4 (1%)	Always: 223 (72%) Only with the first prescription: 55 (18%) Sometimes: 21 (7%) Never: 6 (2%) I don't know: 3 (1%)
Counsel patients that accidental exposure to TIRF medicines by a child may be fatal	Always: 190 (63%) Only with the first prescription: 63 (21%) Sometimes: 29 (10%) Never: 13 (4%) I don't know: 7 (2%)	Always: 198 (66%) Only with the first prescription: 57 (19%) Sometimes: 29 (10%) Never: 8 (3%) I don't know: 8 (3%)	Always: 216 (72%) Only with the first prescription: 53 (18%) Sometimes: 16 (5%) Never: 6 (2%) I don't know: 9 (3%)	Always: 216 (72%) Only with the first prescription: 48 (16%) Sometimes: 27 (9%) Never: 4 (1%) I don't know: 6 (2%)	Always: 216 (72%) Only with the first prescription: 48 (16%) Sometimes: 27 (9%) Never: 4 (1%) I don't know: 6 (2%)	Always: 212 (69%) Only with the first prescription: 64 (21%) Sometimes: 22 (7%) Never: 4 (1%) I don't know: 6 (2%)
Instruct patients to keep TIRF medicines out of reach of children to prevent accidental	Always: 208 (69%) Only with the first prescription: 56 (18.5%) Sometimes:	Always: 223 (74%) Only with the first prescription: 44 (15%) Sometimes:	Always: 224 (75%) Only with the first prescription: 48 (16%) Sometimes:	Always: 238 (79%) Only with the first prescription: 39 (13%) Sometimes:	Always: 238 (79%) Only with the first prescription: 39 (13%) Sometimes:	Always: 218 (71%) Only with the first prescription: 58 (19%) Sometimes:

exposure.	21 (7%) Never: 12 (4%) I don't know: 5 (2%)	23 (8%) Never: 4 (1%) I don't know: 5 (2%)	17 (6%) Never: 3 (1%) I don't know: 8 (3%)	16 (5%) Never: 4 (1%) I don't know: 4 (1%)	16 (5%) Never: 4 (1%) I don't know: 4 (1%)	23 (7.5%) Never: 6 (2%) I don't know: 3 (1%)
Instruct patients about proper disposal of any unused or partially used TIRF medicines.	Always: 172 (57%) Only with the first prescription: 76 (25%) Sometimes: 34 (11%) Never: 13 (4%) I don't know: 7 (2%)	Always: 198 (66%) Only with the first prescription: 67 (22%) Sometimes: 26 (9%) Never: 4 (1%) I don't know: 5 (2%)	Always: 203 (68%) Only with the first prescription: 63 (21%) Sometimes: 23 (8%) Never: 2 (1%) I don't know: 8 (3%)	Always: 209 (69%) Only with the first prescription: 66 (22%) Sometimes: 20 (7%) Never: 3 (1%) I don't know: 3 (1%)	Always: 209 (69%) Only with the first prescription: 66 (22%) Sometimes: 20 (7%) Never: 3 (1%) I don't know: 3 (1%)	Always: 211 (68.5%) Only with the first prescription: 66 (21%) Sometimes: 20 (6.5%) Never: 8 (3%) I don't know: 3 (1%)
Give patients the Medication Guide for their TIRF medicine.	Always: 272 (90%) Only with the first prescription: 17 (6%) Sometimes: 5 (2%) Never: 3 (1%) I don't know: 5 (2%)	Always: 274 (91%) Only with the first prescription: 11 (4%) Sometimes: 10 (3%) Never: 0 (0%) I don't know: 5 (2%)	Always: 268 (89%) Only with the first prescription: 20 (7%) Sometimes: 3 (1%) Never: 1 (0.3%) I don't know: 8 (3%)	Always: 278 (92%) Only with the first prescription: 14 (5%) Sometimes: 4 (1%) Never: 2 (1%) I don't know: 3 (1%)	Always: 278 (92%) Only with the first prescription: 14 (5%) Sometimes: 4 (1%) Never: 2 (1%) I don't know: 3 (1%)	Always: 277 (90%) Only with the first prescription: 22 (7%) Sometimes: 5 (2%) Never: 2 (1%) I don't know: 2 (1%)
Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access	Yes: 8 (50%) No: 6 (37.5%) I don't know: 2 (12.5%)	Yes: 8 (53%) No: 4 (27%) I don't know: 3 (20%)	Yes: 7 (48%) No: 5 (33%) I don't know: 3 (20%)	Yes: 8 (53%) No: 7 (47%) I don't know: 0 (0%)	Yes: 8 (53%) No: 7 (47%) I don't know: 0 (0%)	Yes: 13 (72%) No: 1 (6%) I don't know: 4 (22%)

Program? *Inpatient pharmacists only (12 month: n=16; 24 month: n=15; 36 month: n=15; 48 month: n=15)						
Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? *Outpatient pharmacist only (12 month: n=280; 24 month: 281; 36 month: n=284; 48 month: n=289)	Yes: 235 (84%) No: 7 (2.5%) I don't know: 38 (14%)	Yes: 231 (82%) No: 5 (2%) I don't know: 45 (16%)	Yes: 254 (89%) No: 6 (2%) I don't know: 24 (8.5%)	Yes: 262 (92%) No: 10 (4%) I don't know: 14 (5%)	Yes: 262 (92%) No: 10 (4%) I don't know: 14 (5%)	Yes: 235 (82.5%) No: 10 (3.5%) I don't know: 40 (14%)
Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? *CSP Outpatient pharmacists	Yes: 5 (83%) No: 0 (0%) I don't know: 1 (17%)	Yes: 2 (50%) No: 0 (0%) I don't know: 2 (50%)	Yes: 1 (100%) No: 0 (0%) I don't know: 0 (0%)	N/A	N/A	Yes: 4 (80%) No: 1 (20%) I don't know: 0 (0%)

only (12 month: n=6; 24 month: n=2; 36 month: n=1)						

APPENDIX F: 60-MONTH ASSESSMENT REPORT FINDINGS

The 60-month REMS assessment report for the TIRFs was reviewed December 4, 2017, and determined to be complete; however, it was not meeting its stated goal nor most of the objectives. Key findings included:

- The submitted surveillance data (spontaneously reported adverse events as well as RADARS data) contained a small number of events associated with TIRF products, especially in the RADARS Poison Center data, resulting in great variability in the data. However, the data appeared to indicate that for most outcomes assessed, TIRF event rates had increased over time. In contrast, event rates for the composite comparators in most cases either decreased over time or had much smaller increases than those noted for TIRF products. A number of recommendations were provided for the TRIG such as the submittal of product-specific reports to facilitate FDA's evaluation of any individual TIRF products that are driving the increases in adverse events over time.
- In the Supplemental Report, the TRIG used the IMS Health Longitudinal Prescription Database (LRx) to capture opioid dispensations prior to a TIRF product dispensation to estimate opioid tolerance. Findings from individual NDA/ANDA submissions of opioid tolerance data generated via claims data indicated that regardless of the type of analysis, the proportion of opioid-non-tolerant patients receiving a TIRF product ranged from 34.6% to 55.4%. Because the proportion of patients receiving TIRFs as calculated by these analyses remained concerning, the first objective (prescribing only to appropriate/opioid-tolerant patients) was not being achieved. The TRIG was investigating the use of an alternative algorithm for the determination of opioid tolerance, and the FDA asked them to move forward with validating opioid tolerance algorithms, without delay. The validation studies may identify evidence of opioid tolerance that was not apparent in claims data, or will confirm the poor adherence by prescribers to opioid-tolerance requirements.
- The TRIG's pharmacy switch database was the data source for the persistency analysis and uses outpatient TIRF prescription data. The persistency analysis examining TIRF product switches that were submitted in the 48-month REMS Assessment Addendum were difficult to interpret due to numerous methodologic concerns and thus resulted in the conclusion that it was not possible to tell if the second objective (prevention of inappropriate TIRF product interchanges) was being met. The TRIG was asked to re-submit these data using non-overlapping definitions and with numerators and denominators clarified.
- The data provided by the TRIG regarding the third objective (prevention of accidental exposure) were sparse and had many missing data elements. Therefore, it was not possible to determine whether this objective was being met. In multiple communications between FDA and the TRIG after the 60-month REMS Assessment Report, FDA provided suggestions including the use of additional data sources for identification of unintentional pediatric exposures such as (e.g.) death certificate data as well as emergency department administrative claims data.

- Regarding the fourth objective, overall, patients, prescribers, and pharmacists had an adequate understanding of most of the key risk messages related to accidental exposure and the potential for misuse, abuse, addiction, and overdose of TIRF medicines; however all groups were less aware of the need to only prescribe and dispense TIRF medicines to appropriate patients (opioid-tolerant) than they were of other components of the TIRF REMS program. Although the respondents had adequate understanding of most of the key risk messages, the surveys were not based on probability random samples and had high non-response rate. Some results indicated that those who volunteered to respond to the surveys had different characteristics than those who were targeted to answer the surveys (e.g. education level). Therefore, the survey results may have been biased and may not have been generalizable to the general population of: patients who received a TIRF prescription; TIRF prescribers; and pharmacists who dispensed a TIRF prescription. Given the survey results, the FDA concluded that this objective was being partially met, and requested the TRIG to continue to provide comparisons of the baseline characteristics between survey respondents and general population
- Concerns with the REMS's compliance program were noted to the TRIG, such as: the number of patients (five) enrolled by a prescriber without a complete PPAF on file needed to be considered a non-compliance event; the TRIG's corrective action processes; and the passive nature of detecting non-compliance events
- Concerns with some of the TRIG's administrative processes were noted to the TRIG such as the increasing median prescription processing time after at least one initial REMS-related rejection; lack of sufficient REMS process reminders in the closed governmental systems; the fact that the reason prescribers/pharmacies choose to leave the REMS was unknown; and low numbers of inpatient pharmacies audited.

The TRIG was sent a REMS Assessment Acknowledgment letter (RAAL) on December 11, 2017.

APPENDIX G: SUMMARY OF THE MOST RECENT REMS MODIFICATION

On December 16, 2016, Safety Labeling Changes (SLC) were made to the labeling of TIRF products to include information pertaining to the risks of misuse, abuse, addiction, overdose, death, and neonatal opioid withdrawal syndrome; serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; and androgen deficiency. Thus on April 10, 2017, REMS Modification Notification letters were submitted to the TRIG Sponsors requesting modifications to the TIRF REMS to align the REMS document and materials with the labeling approved in December 16, 2016 SLC. The TIRF Sponsors submitted sNDAs dated June 12, 2017, with the proposed modifications, and these were approved September 7, 2017.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Risk Evaluation and Mitigation Strategy (REMS) Assessment Report

Date:	July 12, 2018
Reviewer(s):	Rose Radin, PhD, MPH, Epidemiologist Division of Epidemiology II Sara Karami, PhD, MPH, Epidemiologist Data Management and Analysis Team Division of Epidemiology I
Team Leader:	Tamra Meyer, PhD, MPH Division of Epidemiology II
Tertiary Reviewer:	Judy Staffa, PhD, RPh, Associate Director, Public Health Initiatives Office of Surveillance and Epidemiology
Subject:	Review of Surveillance Data from the 72-month REMS Assessment Report for the Transmucosal Immediate-Release Fentanyl Shared REMS
Application Type/Number:	DMF: (b) (4) NDAs: 022510 (Abstral), 020747 (Actiq), 021947 (Fentora), 022569 (Lazanda), 022266 (Onsolis), 202788 (Subsys) ANDAs: 78907, 077312, 079075
Applicant/sponsor:	Sentynl Therapeutics, Inc. (Abstral), Cephalon, Inc. (Actiq and Fentora), DepoMed, Inc. (Lazanda), BioDelivery Sciences International, Inc. (Onsolis), Insys Therapeutics, Inc. (Subsys), Mallinckrodt Inc. (fentanyl citrate), Par Pharmaceutical, Inc. (fentanyl citrate), Watson Laboratories, Inc. (fentanyl citrate)
OSE RCM #:	2018-452

This document contains proprietary data from the American Association of Poison Control Centers obtained by FDA under contract. The poison control center data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

TABLE OF CONTENTS

TABLE OF ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
AC	Advisory Committee
AE	Adverse Event
ASI-MV®	Addiction Severity Index-Multimedia Version
CI	Confidence Interval
DEPI	Division of Epidemiology
DRISK	Division of Risk Management
ED	Emergency Department
ER	Extended-release
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
IR	Immediate-release
NAVIPPRO™	National Addictions Vigilance Intervention and Prevention Program
NPDS	National Poison Data System
OPE	Office of Pharmacovigilance and Epidemiology
OSE	Office of Surveillance and Epidemiology
PCCs	Poison Control Centers
PCP	Poison Control Program
PPAF	Patient-Prescriber Agreement Form
OTC	Over-the-counter
QA	Quality Assurance
QC	Quality Control
RADARS®	Researched Abuse, Diversion, and Addiction-related Surveillance
REMS	Risk Evaluation Mitigation Strategy
TCPC	Treatment Center Programs Combined
TIRF	Transmucosal immediate release fentanyl
U.S.	United States

EXECUTIVE SUMMARY

Transmucosal immediate release fentanyl (TIRF) medicines became subject to a shared system Risk Evaluation and Mitigation Strategy (REMS) as of December 2011, with implementation starting in March 2012. The goals of the REMS 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; and
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

Sponsors submit a joint annual report to assess whether the REMS is effective at mitigating the serious risks associated with TIRF medicines. Surveillance data in the report compare the pre- to post-REMS changes in rates of adverse events (AEs) attributed to TIRF medicines versus other opioid comparator groups. The Division of Risk Management (DRISK) asked the Division of Epidemiology II (DEPI) to review the surveillance data results contained in the 72-month assessment.

In reviewing the prior, i.e., 60-month, TIRF REMS assessment, DEPI had recommended that the 72-month assessment report present TIRF product-specific data. The rationale for requesting product-specific data was: (1) not all TIRF medicines were marketed in the pre-REMS period, and (2) from pre- to post-REMS, the TIRF aggregate data suggested there were increases in the prescription-adjusted rates of certain AEs attributed to TIRF medicines, while the opioid comparator data showed these AE rates either increased to a lesser extent, or decreased. Specifically, these AEs were abuse, unintentional therapeutic errors, emergency department visits/hospitalizations, and major medical outcomes. The TRIG declined to provide product-specific data, citing small numbers of events per product. FDA therefore conducted its own analyses of TIRF product-specific data, which are evaluated in this review alongside the TIRF aggregate data from the TIRF REMS Assessment report. Also, so that results from TIRF aggregate and product-specific data could be presented in a consistent manner throughout the review, it was necessary for FDA to conduct some analyses of TIRF aggregate data, and to present these results in some parts of the review.

The purpose of the product-specific analysis was to (1) verify that there was no one product implicated in the increasing prescription-adjusted AE rates that had been observed in the 60-month REMS Assessment report and (2) make pre- versus post-REMS comparisons in AE rates among TIRF medicines that were marketed in both periods. The available TIRF product-specific data enabled us to make general conclusions for selected outcomes. As expected, product-specific case numbers were low. In the RADARS® Treatment Center Programs Combined, the average number of abuse cases per quarter ranged from 7 – 31, depending on the product; in other data sources, quarterly averages were even lower.

TIRF aggregate data from several data streams suggested that the prescription-adjusted rate of TIRF medicines abuse increased from the pre- to post-REMS period, or, that there was a positive trend in the prescription-adjusted abuse rate post-REMS through 2016, although the abuse rate

appeared to decline starting in Q1 2017. These patterns in abuse are concerning giving that prescription-adjusted abuse rates of comparators showed either contemporaneous declines or no change. The TIRF product-specific data showed that individual product trends tracked with the TIRF aggregate trend, except for Lazanda, which exhibited an apparent decrease in the prescription-adjusted abuse rate pre- to post-REMS. Of note, Lazanda's trend appears to be influenced by extremely high prescription-adjusted abuse rates when it first appeared on the survey, which may have been produced by respondent errors and the low utilization during this period.

Unintentional general TIRF-related exposures calls to poison control centers, overall and among children age <6 years, decreased on both the population-adjusted and prescription-adjusted scales, and to as great an extent or greater than decreases in rates of comparator unintentional general exposure calls. All told, there were nine TIRF-related exposure calls for children age <6 years in the pre-REMS period and nine in the post-REMS period. Due to the small number of unintentional general TIRF medicines exposure calls, the product-specific data were uninformative. FDA has requested that the TRIG examine additional data sources to generate a more robust evidence base, and the process of obtaining these data is ongoing.

Other indicators from the poison center data exhibited pre- to post-REMS increases. TIRF-involved calls to poison control centers resulting in major medical outcomes/ deaths increased pre- to post-REMS on both the population-adjusted and prescription-adjusted scales. The increase in the prescription adjusted rate was significant and of larger magnitude relative to that of comparators. TIRF medicine exposure calls for reasons of intentional misuse and unintentional therapeutic errors decreased from pre- to post-REMS, but there were suggestive increases in the prescription-adjusted rates while the rates of comparators remained constant or decreased. Also, the prescription-adjusted rates of emergency department (ED) visits/ hospitalizations increased while the rates of comparators remained constant or decreased. In the product-specific data, it was feasible to estimate increases for Actiq/generic lozenge and Fentora, pre- to post-REMS, in the prescription-adjusted rate of ED visits/hospitalizations. Otherwise, the event numbers were too low to produce informative results.

General estimates from a persistency analysis of utilization suggested that approximately 20% of patients with two or more TIRF prescriptions changed their index TIRF regimen. To assess whether the REMS is preventing inappropriate product conversions, data are still needed on details of the doses and products involved in the index and second regimens, and patient outcomes associated with switching regimens.

In summary, observed increases in the prescription-adjusted rates of abuse and calls to poison control centers resulting in major medical outcomes/deaths raise concerns.. Also, there were suggestive increases in the prescription-adjusted rates of intentional misuse, unintentional therapeutic errors, and ED visits/hospitalizations, although estimates were imprecise. Based on small numbers pre- and post-REMS, rates of poison center calls for unintentional general TIRF medicines exposures decreased among adults and children. For all outcomes, making conclusions based on the evaluated data sources was difficult due to the limited number of events and the relatively low utilization of TIRF medicines. Indeed, in the review of the 60-month REMS Assessment Surveillance Data, DEPI had noted these concerning patterns in the results, and since then, communications with the TRIG about obtaining additional safety data have been ongoing. That process will be further explained in a forthcoming addendum to this review.

1 INTRODUCTION

1.1 BACKGROUND

Transmucosal immediate release fentanyl (TIRF) medicines are opioid agonists indicated for management of breakthrough pain in adult (all TIRF medicines) or adolescent cancer patients ages 16 or older (Actiq only) who are opioid-tolerant and are receiving around-the-clock opioid therapy for persistent cancer pain. There are labeled limitations of use including:

1. not for use in opioid non-tolerant patients,
2. not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency department (ED), and
3. can only be dispensed in an outpatient setting to patients enrolled in the Risk Evaluation and Mitigation Strategy (REMS) Access program.

TIRF medicines carry boxed warnings that include life-threatening respiratory depression; accidental exposure/ingestion; cytochrome P450 3A4 interaction; risks from concomitant use with benzodiazepines or other CNS depressants; risk of medication errors; addiction, abuse, and misuse; and neonatal opioid withdrawal syndrome. Because of the serious, life-threatening, adverse effects of TIRF medicines, an adequate risk-benefit balance could only be maintained through a REMS program. To minimize the burden on the healthcare system, a single, shared REMS for all TIRF brand and generic products was approved on 12/28/2011 and implemented on 3/12/2012. Prior to the single shared REMS, other individual REMS were approved for the brand products, but some products had several years on the market prior to REMS approval (Table 1). Generic products were not subject to a REMS until the shared system REMS was approved at the end of 2011.

Table 1. Transmucosal immediate release fentanyl medicines and approval dates

Drug Name	Dosage and Route	NDA/ANDA	Applicant	Approval Date	First REMS approved [a]
Abstral	Sublingual Tablet	NDA 022510	Sentynl Therapeutics, Inc.	1/7/2011	1/7/2011
Actiq	Oral Transmucosal Lozenge	NDA 020747	Cephalon, Inc.	11/4/1998	7/20/2011
Fentora	Buccal Tablet	NDA 021947	Cephalon, Inc.	9/25/2006	7/20/2011
Lazanda	Nasal Spray	NDA 022569	DepoMed, Inc.	6/30/2011	6/30/2011
Onsolis	Buccal Soluble Film	NDA 022266	BioDelivery Sciences International, Inc.	7/16/2009	7/16/2009
Subsys	Sublingual Spray	NDA 202788	Insys Therapeutics, Inc.	1/4/2012	1/4/2012
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 78907	Mallinckrodt, Inc.	10/30/2009	12/28/2011
fentanyl citrate	Oral Transmucosal Lozenge	ANDA 077312	Par Pharmaceuitcal, Inc.	10/30/2009	12/28/2011
fentanyl citrate	Oral buccal tablet	ANDA 079075	Watson Laboratories, Inc.	1/7/2011	12/28/2011

[a] Shared system REMS was approved 12/28/2011 and implemented 3/12/2012.

1.2 GOALS OF THE REMS

The goals of the TIRF REMS 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; and
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

1.3 REMS ASSESSMENT PLAN

This review focuses on REMS Assessment Plan element 8c.

8.c. Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report:

i. Non-medical use of prescription drugs

ii. Surveys conducted at substance abuse treatment programs

iii. College surveys

iv. Poison center data

*v. Impaired health care workers**

vi. Drug-related hospital emergency department visits

vii. Drug-related deaths

viii. Other databases as relevant

* Data from impaired health care workers are no longer included in the surveillance data submission, per FDA recommendation in the 60-month REMS Assessment Acknowledgment Letter. DEPI concluded in its review of the 60-month REMS Assessment report that data from impaired health care workers no longer aided understanding of the trends in AEs related to TIRF medicines.

1.4 TIRF REMS

The REMS includes a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timeline for submission of assessments (annually by December 28). ETASU include:

- (ETASU A) training and certifying outpatient TIRF prescribers;
- (ETASU B) training and certifying pharmacies who dispense TIRFs;
- (ETASU C) assurances that TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions;
    i. patients are enrolled when their first prescription is processed at a pharmacy;
    ii. a completed Patient-Prescriber Agreement Form (PPAF) must be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription;
    iii. a maximum of three prescriptions are allowed within 10 working days from when the patient had their first prescription filled with no additional TIRF dispensing allowed until a completed PPAF is received;
    iv. upon receipt of a prescription for a TIRF medicine at an enrolled outpatient pharmacy, the pharmacist enters the prescription details into the pharmacy management system (PMS) which sends the transaction to the TIRF REMS Access program via a "switch" provider to ensure that all elements meet the safe use requirements of the TIRF REMS Access program
    v. Since closed-system pharmacies do not electronically transmit the validation and claim information required by the REMS (and thus do not use a switch provider), these pharmacies must instead call or FAX the TIRF REMS to ensure that safe use conditions have been met prior to dispensing.

A Medication Guide is dispensed with each TIRF medicine.

Patients, providers, and pharmacies are enrolled in the REMS program in different ways. Providers and pharmacies must actively pursue the training and certification to prescribe and dispense TIRF medicines. However, only one authorized pharmacist or one chain representative needs to be trained per pharmacy who then certifies that pharmacy staff are educated on the risks associated with TIRF medicines and the requirements of the REMS. All

patients are passively enrolled in REMS program when their first TIRF medicine prescription is processed at the pharmacy and must have a PPAF submitted to the TIRF REMS within 10 days this prescription. The PPAF expires after two years or when there are no fills for six months. After the first prescription per patient, outpatient pharmacies verify that both prescriber and patient are enrolled in the TIRF REMS Access program and that the REMS requirements are met prior to dispensing.

1.5 REVIEW PURPOSE

This review aimed to determine the extent to which the REMS was effective at mitigating the pre-specified adverse outcomes—misuse, abuse, addiction, overdose, and serious complications due to medication errors.

1.6 PRIOR FDA REVIEW OF SURVEILLANCE DATA

The 48-month REMS Assessment surveillance data assessed opioid dispensing patterns preceding a TIRF medicines dispensing, and an analysis of TIRF regimen switching and time on treatment. These analyses intended to inform an evaluation of the TIRF REMS effectiveness at (1) prescribing and dispensing TIRF medicines only to appropriate patients, including only in opioid-tolerant patients, and (2) preventing inappropriate conversion between TIRF medicines. DEPI concluded that the 48-month REMS Assessment surveillance data were insufficient to inform the impact of the TIRF REMS on achieving its goals and made recommendations to the TRIG to revise the analysis. Main revisions included distinguishing the three outcomes of regimen persistence, discontinuation, and change by using mutually exclusive categories, and clarifying the denominators used in various sub-analyses.

The surveillance data in the 60-month TIRF REMS Assessment report displayed increasing trends over time in certain, prescription-adjusted adverse event (AE) rates:

- Treatment center data: past 30-day abuse of TIRF medicines;
- Poison center data: TIRF medicines abuse; intentional misuse; unintentional therapeutic errors; ED visits/ hospitalizations; and major medical outcomes.

FDA expressed concern to the TRIG about these trends and requested that future REMS Assessments report pre- to post-REMS changes in adverse events by TIRF medicine. This request served two purposes: 1) to see if individual products appeared to be driving the increasing trend in prescription-adjusted AE rates and 2) to target further assessment of the REMS effectiveness to the products that had both a pre- and post-REMS period. FDA made this request in December 2017.

The TRIG responded in February 2018 that it would provide analyses of AEs for all TIRF medicines, in aggregate, but not by product, because small event counts in the product-specific data would produce highly unstable results. However, FDA noted that the REMS Assessment Report indicated there were 1,367 cases of TIRF medicines abuse in the Researched Abuse, Diversion, and Addiction-related Surveillance (RADARS®) Treatment Center Programs Combined (TCPC) data, Q3 2010 – Q2 2016, and expected that this quantity could provide stable estimates of change for at least some TIRF medicines. So, FDA proceeded to obtain product-specific data independently of the TRIG through existing FDA contracts. These efforts included:

- Contracting with RADARS® for analyses of Treatment Center Program data, the same contractor used by the TRIG to perform analyses of time trends and pre- to post-REMS changes in abuse rates of each TIRF medicine as reported by individuals entering treatment for opioid use disorder.
- Contracting with Inflexxion® to perform these same analyses in their data collected from individuals entering treatment for substance use disorder.
- Contracting with the American Association of Poison Control Centers (AAPCC) to obtain data on exposure calls related to specific TIRF medicines. FDA reviewers then analyzed these data to produce prescription-adjusted trends in call rates.

Sections of the review that address individual data sources note whether it was FDA or the TRIG that conducted the work on that data source. Where we had access to the data sources through contracts, FDA replicated the TIRF medicines aggregate data analyses that the TRIG submitted as it allowed us to analyze and report results in a consistent manner for aggregate TIRF medicines and product-specific results. Therefore, this review frequently refers to the FDA-conducted analyses, instead of the TRIG-conducted analyses, since the FDA-conducted analyses replicated the TIRF medicines aggregate data and added TIRF-specific trends and results for unknown TIRF medicines or unknown fentanyl.

Of note, in the prior review of the 60-month REMS Assessment report, DEPI also requested that the TRIG pursue additional analyses of safety data. Review of the TRIG's progress on these requests will be provided in a separate addendum to the DEPI review because of ongoing discussions with the TRIG and expected submission of additional data. Briefly, the requested analyses aimed to estimate AEs including the occurrence of opioid overdose among patients who are opioid-tolerant when they initiate TIRF medicines, versus patients who are non-opioid-tolerant, and occurrence of TIRF-involved poisonings among children.

2 REVIEW METHODS AND MATERIALS

2.1 DOCUMENTS TO BE REVIEWED

- TIRF REMS Access Program 72-Month Assessment Report:
  - Persistency Analysis
  - Surveillance Monitoring Report: RADARS® Poison Center Program (PCP), TCPC, Survey of Non-Medical Use of Prescription Drugs Program (NMURx)
- RADARS® TCPC report obtained by the FDA through a contract with RADARS®
- National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) report obtained by the FDA through a contract with Inflexxion®
- National Poison Data System (NPDS) report obtained by the FDA through a contract with the American Association of Poison Control Centers (AAPCC)
  - FDA reviewers conducted statistical analyses of these NPDS data. The methods and results of these analyses are summarized in sections 3.1.4 and 3.2.4, respectively.

2.2 CRITERIA APPLIED TO REVIEW

In reviewing the documents summarized above, DEPI assessed whether the REMS appeared to be mitigating the risk of misuse, abuse, addiction, overdose, and serious complications due to

medication errors, and whether there were any concerning trends of pre-specified AEs that might warrant regulatory action. Mainly, REMS effectiveness was determined by the extent to which rates of the pre-specified AEs were declining or constant over time, relative to comparator opioid analgesics. For some TIRF medicines, it was also possible to compare outcomes pre- versus post-REMS. The reviewers reviewed the data with the expectation that the REMS Assessment followed sound epidemiologic principles in its design, data collection, and analysis. Strengths and limitations in the methods were noted and incorporated in the evaluation regarding REMS effectiveness. Also, because prior DEPI reviews had recommended changes and additions to the TIRF REMS Assessment, the current review makes note of particular results that conform to or deviate from these recommendations.

3 REVIEW RESULTS

3.1 SURVEILLANCE DATA METHODS

In this section, we provide a summary of the methods and results of several data streams from the TRIG, from FDA-conducted work through contracts with RADARS® System and Inflexxion®, and from FDA analyses in NPDS.

3.1.1 RADARS® Treatment Center Program Combined (TCPC)

These analyses were submitted by the TRIG, except for TIRF product-specific analyses, which were obtained by the FDA through a contract with RADARS®. The FDA-conducted analyses also generated estimates for aggregated TIRFs to allow consistent presentation format for aggregate and product-specific results.

3.1.1.1 Design and Population

The RADARS® System TCPC uses an ecological study design to compare changes over time in past 30-day abuse of TIRF medicines with changes over time in abuse of comparator opioid analgesics. The study population consists of adults age ≥18 years who are entering treatment for substance addiction/dependence and who report abusing heroin or prescription opioids in the last 30 days. Research participants voluntarily complete a one-time, self-administered, anonymous questionnaire within one week of entering the treatment program. They endorse the use of heroin or prescription opioid medicine or medicines they have used to get high in the past 30 days from a checklist of product names with descriptions of the dosage form (e.g., tablets, oral film, lollipop, nose spray, sublingual spray), grouped by active ingredient. The survey instrument provides options to indicate an unknown type of the active ingredient (e.g., oxycodone, type unknown; fentanyl, type unknown) as well as an option to select unknown product name of specific dosage forms (e.g., fentanyl tablet/lollipop/film/spray, not sure of name). TCPC comprises two complementary data sources that use the same data collection and management methods:

- The **Opioid Treatment Program** includes a convenience sample of primarily publicly-funded, medication-assisted maintenance treatment programs in urban and rural areas throughout the US. In 2016, 65 treatment centers from 35 states provided information.
- The **Survey of Key Informants' Patients Program** includes a convenience sample of primarily privately-funded treatment centers, most of which do not use medication-assisted treatment. In 2016, 129 treatment centers from 45 states provided information.

Surveillance data were collected for the entire surveillance period, pre-REMS (Q3 2010 – Q2 2012) and post-REMS (Q3 2012 – Q2 2017).

3.1.1.2 Outcome

The TIRF items that were included on the survey for the entire surveillance period were: *Actiq® (lollipop)*; *Fentora® (fentanyl tablet)*; *Onsolis™ (oral film); Fentanyl, tablet/lollipop/film/spray, not sure of name; fentanyl "lollipop" manufactured by Mallinckrodt;* and *Fentanyl "lollipop," not mentioned above.*

TIRF items that were included on the survey for part of the surveillance period were:

- *Abstral® (fentanyl tablet):* Q3 2011 – Q2 2012; Q3 2014 – end of surveillance period;
- *Lazanda® (nose spray):* Q4 2011 – end of surveillance period;
- *Subsys® (sublingual spray):* Q3 2014 – end of surveillance period;

For the TIRF medicines aggregated data analysis, if a respondent indicated they had used any of the TIRF medicines "to get high," in the past 30 days, he or she counted as one case of TIRF medicine abuse**.**

Cases of abuse of each comparator were defined analogously to the definition of abuse of any TIRF medicine. Each respondent could be counted as no more than one case of TIRF medicine abuse and no more than one case of abuse of each comparator opioid.

For the TIRF product-specific data analysis, endorsement of a specific TIRF medicine name counted as a case of abuse of that medicine. Each respondent could be counted as a case of abuse of each TIRF medicine they endorsed, except that endorsement of any of the three, fentanyl oral transmucosal lozenge items counted as one case of abuse of Actiq/generic lozenge: *Actiq (lollipop)*; *fentanyl "lollipop" manufactured by Mallinckrodt; fentanyl "lollipop," not mentioned above.*

3.1.1.3 Comparators

There were four comparators defined by active ingredient and formulation type, per DEPI's recommendation from the review of the 60-month TIRF REMS Assessment:

1. **Oxycodone immediate-release (IR):** Branded and generic IR tablets, capsules, and solutions that contain oxycodone.
2. **Oxycodone extended-release (ER):** Branded and generic ER tablets and capsules that contain oxycodone.
3. **Oxymorphone IR:** Branded and generic IR tablets, capsules, and solutions that contain oxymorphone.
4. **Hydromorphone IR:** Branded and generic IR tablets, capsules, suppositories, and solutions that contain hydromorphone.

3.1.1.4 Statistical Analysis

To obtain quarterly abuse rates per 100,000 population, per 10,000 prescriptions dispensed, and per 100,000 dosage units dispensed, respectively, the sum of abuse cases per quarter was divided by the sum of the population, prescriptions dispensed, or dosage units dispensed in the geographic area covered by the TCPC in that quarter. The geographic area covered was defined by the three-digit ZIP codes in which at least one survey respondent reported residing.

Respective means in quarterly rate of abuse were calculated in the pre-REMS and post-REMS period, and the percentage change and 95% confidence interval (CI) were estimated by using a log-Poisson regression model. Further details of the regression model are provided in Appendix 7.1.

To compare the pre- to post-REMS change in TIRF abuse rates with those of comparators, a ratio of rate ratios and 95% CI were estimated. This conformed to DEPI's prior recommendation against using *P*-values for comparison.

A sensitivity analysis restricted the data to centers that contributed at least one valid survey in each quarter of the surveillance period, per DEPI's prior recommendation.

The TIRF-product specific analysis used the same methods as the TIRF medicines aggregated data analysis, and additionally presented quarterly numbers of cases and quarterly population- and prescription-adjusted abuse rate estimates. The DEPI reviewer plotted these numbers for inspection of patterns and trends.

3.1.2 National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)

These analyses were conducted by Inflexxion® under contract with FDA to obtain additional analyses of TIRF medicines aggregated data and product-specific data from other types of treatment centers.

3.1.2.1 Design and Population

These surveillance data come from one component of NAVIPPRO™, the data derived from administration of a computerized survey instrument, the Addiction Severity Index-Multimedia Version® (ASI-MV®), which includes questions relating to use or abuse of specific medicines. ASI-MV® is administered to a convenience sample of adults seeking treatment at a participating facility, with variable adoption by state and locality— during the year 2016, NAVIPPRO™ included a total of 445 treatment sites in 38 states.[1]
Surveillance data were collected for the entire surveillance period, pre-REMS (Q3 2010 – Q2 2012) and post-REMS (Q3 2012 – Q2 2017).

3.1.2.2 Outcome

ASI-MV® collected self-reported data on abuse in the past 30 days of Actiq, Fentora, and Onsolis. Each respondent could count as up to one case of abuse of each TIRF medicine, one case of TIRF medicine abuse for the TIRF medicines aggregated data analysis, and one case of abuse of each comparator.

3.1.2.3 Comparators

The four comparators comprised the same active ingredients as the comparators for RADARS® TCPC but were restricted to oral solid dosage forms.

1. **Oxycodone IR:** Branded and generic IR tablets and capsules that contain oxycodone.
2. **Oxycodone ER:** Branded and generic ER tablets and capsules that contain oxycodone.
3. **Oxymorphone IR:** Branded and generic IR tablets and capsules that contain oxymorphone.

4. **Hydromorphone IR:** Branded and generic IR tablets and capsules that contain hydromorphone.

3.1.2.4 Statistical Analysis

Log-binomial regression models were employed to estimate population-adjusted drug-specific proportions of past-month abuse within each calendar quarter. The population consisted of all survey respondents in that quarter. A log-binomial model was also utilized to estimate prescription volume-adjusted rates of abuse where total prescriptions dispensed were treated as denominators and incorporated in the regression models as offsets.

Generalized Linear Mixed models were used to estimate the slopes and intercepts for the trends for both population-adjusted and prescription volume-adjusted abuse rates. Slopes and intercepts were calculated for the full study period (Q3 2010 - Q2 2017), pre-period (Q3 2010 - Q2 2012) and post-period (Q3 2012 - Q2 2017). The percent changes in slopes between the post- and pre-periods were calculated as single point estimates. No standard errors or CI were provided around the estimates of percent change.

Quarterly numbers of cases and quarterly population- and prescription-adjusted abuse rate estimates were also presented, and the DEPI reviewer plotted them for inspection of patterns and trends.

3.1.3 RADARS® Poison Center Program

These analyses were submitted by the TRIG. FDA conducted analyses of a different source of poison control call data to add TIRF product-specific results (see section 3.1.4).

3.1.3.1 Design and Population

In 2016, the PCP included data on poison center calls involving exposure to a prescription opioid from 50 (of 55) poison centers in 48 states across the US, covering over 93% of the US population. RADARS® staff review the records of calls for prescription opioid exposure to identify inconsistent information. The PCP data thus comprise a subset of the NPDS with additional review of prescription opioid exposure information. The NPDS, maintained by the AAPCC, captures data on calls to U.S. Poison Control Centers (PCCs) on a near real-time basis. Currently, AAPCC's 55 PCCs serves the entire U.S. population, individuals across the 50 states as well as U.S. territories. These PCCs receive calls for exposures to a variety of substances through the Poison Help Line 24 hours per day, offer medical advice, and document reported events in the database. Quality control (QC) measures are used to ensure the accuracy and completeness of the data collected.

Case records in the database reflect information provided when the public or healthcare professionals call about an actual or potential exposure to a substance or request information or educational materials. Each year the database is locked to prevent inadvertent changes and ensure consistent, reproducible reports. Exposures do not necessarily represent a poisoning or overdose, as the AAPCC does not completely verify the accuracy of every call made to member centers.[2]

Surveillance data were collected for the entire surveillance period, pre-REMS (Q3 2010 – Q2 2012) and post-REMS (Q3 2012 – Q2 2017).

3.1.3.2 Outcomes

The PCP uses the NPDS outcome definitions. The outcomes are as follows, quoting excerpts from the TIRF REMS 72-month Assessment Surveillance Monitoring Report.

Intentional Abuse: "an exposure resulting from the intentional improper or incorrect use where the patient was likely attempting to gain a high, euphoric effect, or some other psychotropic effect, including recreational use of a substance for any effect."

Intentional Misuse: "an exposure resulting from the intentional improper or incorrect use for reasons other than the pursuit of a psychotropic effect."

Unintentional General Exposure: "all unintended exposures that are not specifically defined as: environmental, occupational, therapeutic error, unintentional misuse, bite/sting, food poisoning or intentional unknown."

Unintentional Therapeutic Error Exposure: "unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance."

Level of Health Care Facility Care (to assess Emergency Department (ED) Visits and Hospitalizations): Cases seen at a healthcare facility and coded as treated, evaluated and released; admitted to critical care unit; admitted to noncritical care unit; admitted to psychiatric care facility. This category excludes cases that are coded as refused referral/did not arrive at health care facility, or patient lost to follow-up/left against medical advice.

Medical Outcomes:

> **Deaths:** described as "direct death."
>
> **Major Effects:** "The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement."

3.1.3.3 Comparators

Comparators were identical to the ones used for the RADARS® TCPC.

1. **Oxycodone IR:** Branded and generic IR tablets, capsules, and solutions that contain oxycodone.
2. **Oxycodone ER:** Branded and generic ER tablets and capsules that contain oxycodone.
3. **Oxymorphone IR:** Branded and generic IR tablets, capsules, and solutions that contain oxymorphone.
4. **Hydromorphone IR:** Branded and generic IR tablets, capsules, suppositories, and solutions that contain hydromorphone.

3.1.3.4 Statistical Analysis

Two outcomes, *major medical effect* and *death* were combined for analysis due to the small number of deaths. Pre- and post-REMS means in the quarterly rates of each AE were calculated using the same analysis methods as described for the RADARS® TCPC.

Also, the TRIG provided a list of all pediatric exposures with the following variables: year and quarter, age (0-5 years, 6-19 years), exposure reason, medical outcome. DEPI tabulated these variables.

3.1.4 American Association of Poison Control Centers (AAPCC), National Poison Data System (NPDS)

These analyses were conducted by FDA to generate both TIRF medicines aggregate and product-specific results for PCC exposure calls.

3.1.4.1 Design and Population

As the RADARS® PCP comprise a subset of the NPDS, see Section 3.1.3.1 for a description of the NPDS design and population.

3.1.4.2 Search Strategy

In our review of NPDS, we assessed calls for TIRF medicines and comparators of interest (i.e., oxycodone ER, oxycodone IR, hydromorphone IR, oxymorphone IR, and *fentanyl, unknown*). We limited our search to "closed" exposure cases (i.e., no unverified or "open" cases) reported for humans (i.e., exposures and outcomes validated by NPDS). Drug codes (i.e., "generic" and/or "product" codes) used to search NPDS for exposures involving TIRF medicines and comparators, including both single-ingredient and combination products, were obtained from Micromedex™ as well as the online lookup tool available through NPDS. We searched calls dated July 2010 – June 2017. Search parameters used for TIRF medicines and the comparator drugs of interest are summarized below (Table 2).

Table 2. National Poison Data System search parameters- TIRF medicines and comparators.

Report name	Case Log (Generic Code/Product Code)
Drug names	Abstral, Actiq, Fentora, Lazanda, Onsolis, Subsys, generic fentanyl citrate lozenge *unknown fentanyl, illicit fentanyl, patch fentanyl* Oxycodone ER tablets and capsules IR tablets and capsules containing oxycodone, hydromorphone, or oxymorphone
Month/year of query	4/2018
Date range for query	7/1/2010- 6/30/2017
Call type	Exposure
Case status	Closed
Species	Human
Exposure Reasons queried	Abuse, Intentional Misuse, Unintentional Therapeutic Error, Unintentional General
Additional variables	Level of Heath Care Facility Care (resulted in an admittance to a critical care unit, a noncritical care unit, a psychiatric care facility, or resulting in treatment/evaluation and release); Related Medical Outcomes (major effects and death)
Minimum Age	none

ER, extended-release; IR, immediate-release; NPDS, National Poison Data System; TIRF, transmucosal immediate-release fentanyl

3.1.4.3 Statistical Analysis

Because each TIRF medicine was involved in a limited number of calls, it was feasible to estimate product-specific AE rates only for ED visits/hospitalizations. For calls involving exposure to *fentanyl, unknown,* the analysis estimated rates of the various exposure reasons (Table 2) as well as ED visits/hospitalizations and major medical outcomes/deaths. A log-Poisson regression model estimated the mean of quarterly rates in the post-REMS period and, where applicable, estimating the mean of quarterly rates in the pre-REMS period and the pre- to post-REMS percentage change and 95% CI. The rates of calls related to prescription opioid analgesic exposures were expressed per 10,000 prescriptions dispensed, and the rates of calls related to *fentanyl, unknown* were expressed per 1,000,000 U.S. Census population.

To calculate the prescription-adjusted rates, we used national projections of prescriptions dispensed in the outpatient retail setting per quarter per TIRF medicine. The DEPI Drug Utilization analyst obtained the prescription data as part of her review. [3]

Analyses were performed independently by two analysts to optimize accuracy of results, and all results were consistent.

3.1.5 Persistency Analysis

This work was submitted by the TRIG.

The persistency analysis addresses a risk management objective that FDA identified in the Acknowledgment Letter for the 36-month TIRF REMS Assessment Report: "in order to better understand how many people are at risk for inappropriate conversion between TIRF medicines, we need a better idea of how long patients stay on one TIRF and whether they shift between TIRF medicines or just stop them completely."

Thus, the persistency analysis addressed a safety issue not addressed in other components of the REMS Assessment Surveillance Data. The objectives were:

1. To demonstrate the number of patients starting on a TIRF medicine and follow them over weeks and months to summarize their treatment course and change in therapy.
2. To depict what treatment option the patient uses next following the discontinuation of one TIRF medicine, as applicable.
3. To propose what duration of gap will be considered to mean that the patient has remained on treatment with a TIRF medicine and provide a rationale for selection of that gap length.

Appendix 7.5 contains a detailed description of the study setting, the TIRF REMS pharmacy switch database. Briefly, the main persistency analysis included outpatient pharmacy claims data from 18,160 patients who received two or more TIRF dispensings between March 12, 2012 and October 28, 2014. The dispensings could be for the same medicine, or for different medicines. The brand and generic equivalents were treated as the same medicine/regimen in the analysis. The analysis included Abstral, Actiq (and generic fentanyl citrate lozenge), Fentora, Lazanda, and Subsys; it excluded Onsolis. In product-level analyses, products were blinded by random-letter assignment.

Additionally, 8,113 patients who received only one TIRF dispensing, and who met the other eligibility criteria, were included in a descriptive analysis (Appendix 7.5, Table A6).

There were three, mutually exclusive outcomes:

1. **Change regimen:** "having a prescription filled for a TIRF medicine other than what composes the patient's current TIRF regimen." A change regimen could be either of the two:
    a. **switch in regimen** – having a prescription filled for a TIRF medicine other than the current TIRF, and having no refill for the current TIRF regimen, by the end of the grace period.
    b. adding a **concurrent therapy –** prior to the end of the grace period for the index TIRF regimen, a prescription is filled for a different TIRF medicine, and a prescription is filled for the index TIRF to confirm its continued use.
2. **Discontinue index TIRF regimen:** if there was no dispensing of the index TIRF regimen by the end of the grace period. Following discontinuation, the patient could fill a prescription for the index TIRF regimen again, thereby **re-initiating the index TIRF regimen**
3. **Persistent with index TIRF regimen:** "a patient is considered persistent with their TIRF regimen as long as the grace period for the regimen is not exceeded." Patients who were persistent on October 28, 2015 were censored in the analysis.

Among patients who changed regimens, another analysis described the numbers who changed, discontinued, and persisted with their second regimen.

From the date of the index dispensing until the data cut-off date of October 28, 2015, patients were at risk of the three mutually exclusive outcomes. Thus, depending on the year of the index dispensing, there were 12-44 months of data in the pharmacy switch database, during which a subsequent dispensing could be identified. To account for the variation in the maximum possible observation time, and the change in prescribing practices from 2012 to 2015, the TRIG presented the results of analyzing the overall data and analyzing within strata defined by maximum observation time (i.e., month of index TIRF dispensing): March – October 2012 (36-44 months maximum observation time, "early stratum"), November 2012-October 2013 (24-35 months maximum observation time, "middle stratum"), November 2013-October 2014 (12-23 months maximum observation time, "late stratum).

This review addresses the results estimating the prevalence of the three, mutually-exclusive outcomes; median time-to-event; and percent of patients persisting at six months, twelve months, etc. However, the reported mean and standard deviation in the time-to-event were not reviewed since these statistics are influenced by the maximum values, i.e., from individuals who reach the end of observation time without experiencing the event.

3.1.6 Survey of Non-Medical Use of Prescription Drugs (NMURx)

This work was submitted by the TRIG.

3.1.6.1 Design and Population

The NMURx Program was initiated in the U.S. in 2016. It employs an online survey of the general adult population to understand non-medical use of prescription drugs. Respondents are recruited through a survey panel company in which respondents voluntarily register to complete surveys for modest compensation. This program collects demographic information and whether the respondent is a student, healthcare professional, or current/former member of the armed forces.

Non-probability quota sampling is used to provide a distribution of survey respondents that is proportional to census populations within U.S. geographic regions and has an even gender distribution in each region. Surveys of 30,000 respondents are conducted biannually. Survey results are weighted to provide a national prevalence estimate of non-medical use of specific medications among the general U.S. adult population.

Respondents are excluded from the sample if they:

- complete the survey too quickly (<2/5 of the median survey time), or
- if they endorse use of all illicit drugs in the last week and if they endorse use of all the opioids, all the benzodiazepines, or all the stimulants in the last week.

3.1.6.2 Outcome

A case of non-medical use was defined as a survey response endorsing use of a medication without a prescription or for any other reason than what was recommended by one's doctor, in the time-frame of last 7 days, last 30 days, last 90 days, or last 12 months.

Prescription opioid medicine names are grouped by active ingredient. In 2016 and Q1 2017, fentanyl medicines appeared first. In Q3 2017, the order of appearance was randomized.

3.1.6.3 Comparators

Comparators were identical to the comparators in RADARS® TCPC and PCP:

1. **Oxycodone IR:** Branded and generic IR tablets, capsules, and solutions that contain oxycodone.
2. **Oxycodone ER:** Branded and generic ER tablets and capsules that contain oxycodone.
3. **Oxymorphone IR:** Branded and generic IR tablets, capsules, and solutions that contain oxymorphone.
4. **Hydromorphone IR:** Branded and generic IR tablets, capsules, suppositories, and solutions that contain hydromorphone.

3.1.6.4 Statistical Analysis

Data were analyzed by bi-annual survey period (Q3 2016, Q1 2017, and Q3 2017). First, data were weighted to represent the demographic distribution of the general adult U.S. population, age 18 – 110 years. Details of the weighting methods are provided in Appendix 7.6. For aggregated TIRF medicines and for each comparator, a cumulative weighted population rate was estimated for college students and for non-college students by using 2015 U.S. Census Bureau residential population estimates. Also, a cumulative weighted rate per 100,000 dosage units dispensed was estimated for college students and non-college students.

3.2 SURVEILLANCE DATA RESULTS

Results are grouped by data stream. Some parts of the review present results from FDA-conducted analyses of TIRF medicines aggregate data, unknown TIRF medicines, and unknown fentanyl. This was done to ensure that TIRF medicines aggregate and product-specific results that come from the same data source also come from the same analysis methods. Every table and figure has its source noted. Where FDA-conducted analyses and TRIG-conducted analyses used similar methods and data, they produced consistent results.

This review excludes analyses of abuse cases per 100,000 dosage units that were reported in the TRIG-conducted work due to the concern over uncertainty about the quality of the dosage unit data for some TIRF medicines, e.g., multi-dose sprays. The rate per 10,000 prescriptions is preferred for utilization-adjusted rates for consistency between the various TIRF dosage forms and the comparators. In any case, the analyses of rates per 100,000 dosage units yielded similar results to the analyses of rates per 10,000 prescriptions.

3.2.1 RADARS® Treatment Center Programs Combined

3.2.1.1 TIRF Medicines Aggregated Data

The analyses of TIRF medicines aggregated data conducted by FDA were consistent with the analyses submitted by the TRIG. To describe trends in abuse rates of TIRF medicines pre- and post-REMS, and compare these trends with those of comparators, the review preferentially used plots instead of model-estimated slope and intercept. The conclusions from both approaches are similar, and the results of the regression model analysis submitted by the TRIG are included in Appendix 7.1, Tables A1-A2.

Overall, reports of abuse of TIRF medicines were less numerous than reports of abuse of the IR oxymorphone comparator, and they were less numerous by two orders of magnitude compared to reports of abuse for products containing IR oxycodone, ER oxycodone, and IR hydromorphone. TIRF medicines had lower utilization than all comparators. [3] When examining abuse rates per 10,000 dispensed prescriptions, the TIRF medicine abuse rates were higher than those of the comparators IR oxycodone, ER oxycodone, IR hydromorphone, and TIRF medicine abuse rates were lower than abuse rates of the IR oxymorphone comparator (Figure 3).

Pre-REMS to Post-REMS Change in Mean Quarterly Abuse Rate

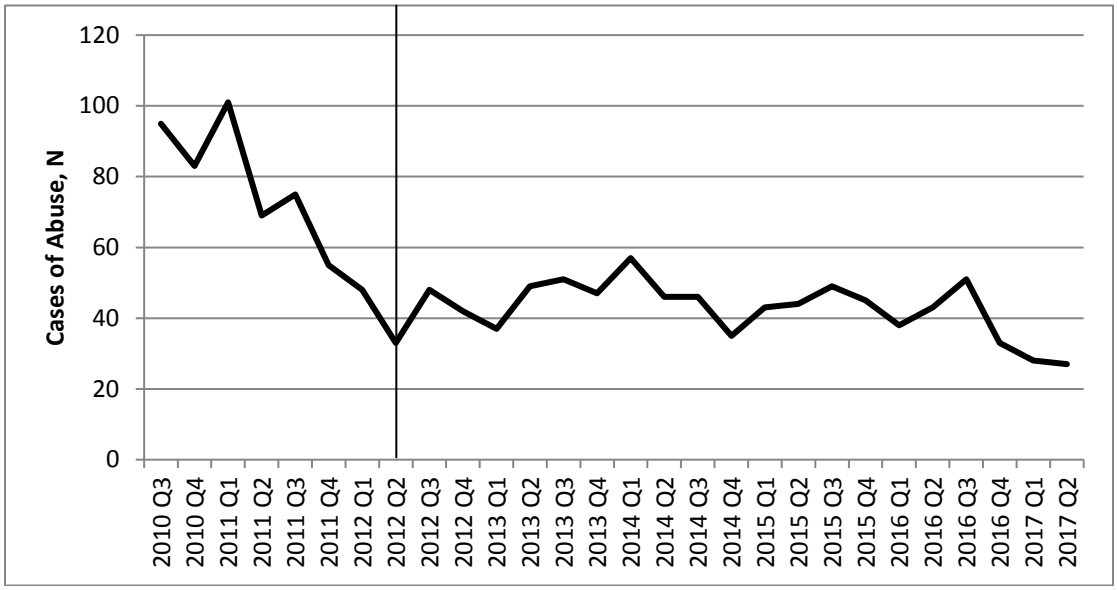
- Comparing the pre-REMS period to the post-REMS period, TIRF mean quarterly abuse cases declined, as did the quarterly means of ER oxycodone, IR hydromorphone, and IR oxymorphone abuse. IR oxycodone mean abuse cases did not decline meaningfully from the pre- to post-REMS period.
- This decline in abuse cases for TIRF medicines and most comparators resulted in a relative decline in the mean abuse rate per 100,000 population for TIRF medicines (-44%, CI: -54%, -31%), ER oxycodone (-56%, CI: -64%, -47%), IR hydromorphone (-24%, CI: -32%, -15%), and IR oxymorphone (-39%, CI: -47%, -29%). For IR oxycodone, the percent change in the mean abuse rate was negligible (-4%, CI: -26%, 25%).
- The TIRF mean abuse rate per 10,000 prescriptions dispensed did not decline from pre-REMS to post-REMS (2%, CI: -17%, 25%). In contrast, ER oxycodone (-38%, CI: -45%, -29%), IR hydromorphone (-20%, CI: -28%, -12%) and IR oxymorphone (-29%, CI: -45%, -9%) all exhibited declines in the mean abuse rate per 10,000 prescriptions dispensed. Again, the percent change in the IR oxycodone mean abuse rate was negligible (5%, 95% CI: -19%, 37%).

  Trends

  Cases of Abuse: In the pre-REMS period, cases of abuse of any TIRF medicines peaked in the first quarter of 2011 (n=101 cases) and then declined substantially (Figure 1). However, the decline ceased after REMS implementation, and cases of abuse increased

through the first quarter of 2014. Since then, abuse cases have declined; there were 27 cases in the second quarter of 2017.

Figure 1. Quarterly cases of abuse of any TIRF medicines in the past 30 days: RADARS® Treatment Center Programs Combined, pre-REMS (2010 Q3-2012 Q2), post-REMS (2012 Q3-2017 Q2).



Source: DEPI reviewer plot of analysis conducted by RADARS® through FDA-conducted contract

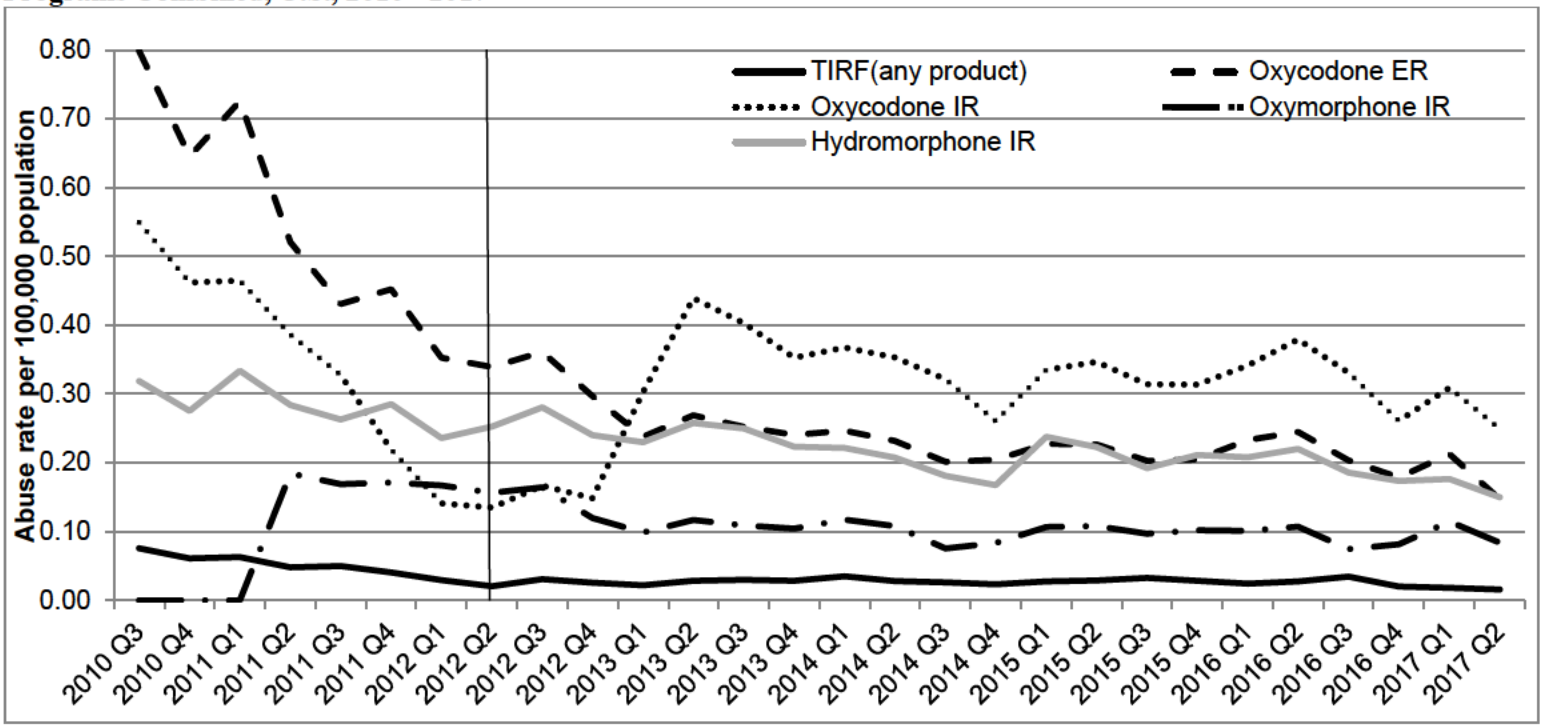
The TIRF medicines population-adjusted abuse rate exhibited a downward trend in the Pre-REMS period; so did all comparators (Figure 2). (IR oxymorphone was added to the survey in the second quarter of 2011). Post-REMS, the TIRF medicines trend flattened and made small increases through the first quarter of 2014, after which it declined gradually. Visually, the Post-REMS TIRF medicines trend was generally similar to the trends in ER oxycodone, IR hydromorphone, and IR oxymorphone. In contrast, the IR oxycodone abuse rate increased sharply early in the Post-REMS period, peaking in the second quarter of 2013 before slowly dropping.

The TIRF medicines prescription-adjusted abuse rate also exhibited a downward trend in the pre-REMS period, but in the post-REMS period, the TIRF medicines abuse rate trended steadily upward to the second quarter of 2016, shot up in the third quarter of 2016, and has since fallen back to the rate in early 2016 (Figure 3). Among the comparators, ER oxycodone, IR oxycodone, and IR hydromorphone trended downward gradually in the pre-REMS period, while IR oxymorphone trended sharply upward. In the post-REMS period, ER oxycodone and IR hydromorphone trended flat to subtly downward, IR oxycodone increased slightly before going back down, and IR oxymorphone declined dramatically.

The regression-model analyses of the population-adjusted rate and of the prescription-adjusted rate both found that the regression line in the pre-REMS period had a significantly different slope from the regression line in the post-REMS period (Appendix 7.1, Tables A1-A2). The pre- to post-REMS change was significantly different from what was observed among the comparators oxycodone ER (only the prescription-adjusted rate), hydromorphone IR, and oxymorphone IR (Appendix 7.1, Tables A1-A2). **Sensitivity analyses of the trends confirmed**

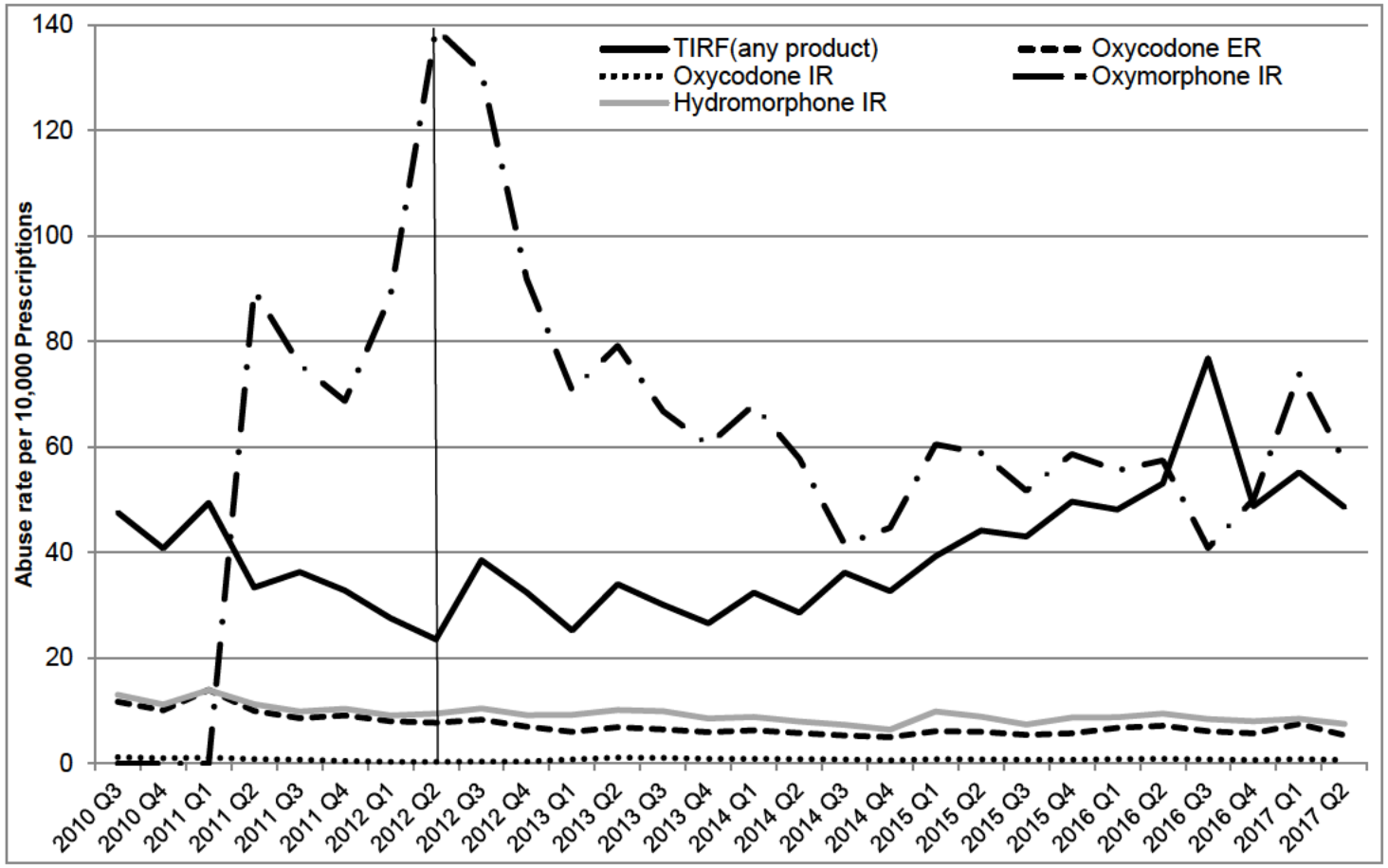
the main regression model results when the data were restricted to treatment centers that had contributed at least one valid survey in (1) 100%, or in (2) 80% of the calendar quarters.

Figure 2. Quarterly population-adjusted abuse rate of any TIRF medicines and opioid analgesic comparators, RADARS® Treatment Center Programs Combined, U.S., 2010 - 2017



Source: DEPI review plot of quarterly, population-adjusted abuse rates estimated by RADARS® through FDA-conducted contract.

Figure 3. Quarterly prescription-adjusted abuse rates, RADARS® Treatment Center Programs Combined, U.S., 2010 - 2017



Source: DEPI review plot of quarterly, prescription-adjusted abuse rates estimated by RADARS® through FDA-conducted contract.

3.2.1.2 TIRF Product-specific Data

Cases of Abuse

- Per quarter, Actiq averaged the highest number of endorsements (31), followed by Fentora (15), Lazanda (10), Onsolis (10), Subsys (8), and Abstral (7). The *unknown/other TIRF products* category averaged 21 endorsements per quarter. **Table 3** depicts the variation in product-specific abuse reports by quarter (it was difficult to distinguish the product-specific data on a line-plot).
- Although the Sponsor voluntarily withdrew Onsolis from the market in 2011 with plans to re-launch it, Onsolis remained on the survey through the end of the surveillance period, receiving as many as 20 endorsements per quarter. Since 2016, it has received fewer than 12 endorsements per quarter. See the Discussion section for potential explanations for these endorsements.

Abuse Rates

- Actiq/generic lozenge and Fentora were marketed throughout the pre-REMS and post-REMS periods. From pre-REMS to post-REMS, the mean abuse rate per 100,000 population declined, although mean abuse rate per 10,000 prescriptions increased (Table 4, Figures 4A, 4B).
- Lazanda had data available for three calendar quarters during the pre-REMS period plus the entire post-REMS period. In contrast to what was observed for Actiq/generic lozenge and Fentora, Lazanda's mean population-adjusted abuse rate increased pre- to post-REMS, while its mean prescription-adjusted abuse rate declined (Table 4). High prescription-adjusted abuse rates during the first five quarters of survey data influenced this pre- to post-REMS comparison (Figure 4C).
- Onsolis's mean population-adjusted abuse rate declined pre- to post-REMS (Table 4); it was marketed only pre-REMS. Prescription-adjusted abuse rates could not be estimated.
- Abstral first appeared on the survey in Q3 2011, was subsequently removed beginning Q2 2012, and was re-added beginning Q3 2014. Abstral's mean population-adjusted abuse rate increased pre- to post-REMS, while its mean prescription-adjusted abuse rate remained the same (Table 4). Quarterly prescription-adjusted abuse rates increased sharply following Abstral's re-introduction to the survey in Q3 2014 (Figure 4D).
- Subsys first appeared on the survey in Q3 2014. Quarterly prescription-adjusted abuse rates increased from Q3 2014 through Q1 2016 and subsequently decreased (Figure 4E).

Table 3. Quarterly counts of reported abuse in the past 30 days: RADARS® Treatment Center Programs Combined Program, U.S. pre-REMS (2010 Q3 – 2012 Q2), post-REMS (2012 Q3 – 2017 Q2).

Year-Qtr	Actiq	Fentora	Onsolis	Abstral	Lazanda	Subsys	TIRF:unk /other
2010 Q3	36	25	11				52
2010 Q4	39	23	10				30
2011 Q1	54	35	16				39
2011 Q2	47	27	21				30
2011 Q3	45	27	18	8			39
2011 Q4	34	11	9	7	6		31
2012 Q1	33	14	6	4	9		14
2012 Q2	22	11	6	1	9		7
2012 Q3	29	22	14		19		22
2012 Q4	29	11	14		9		17
2013 Q1	26	9	10		10		11
2013 Q2	35	13	9		9		12
2013 Q3	35	16	20		14		19
2013 Q4	32	14	10		12		22
2014 Q1	39	20	18		19		21
2014 Q2	25	14	12		9		21
2014 Q3	30	7	6	3	8	6	18
2014 Q4	17	7	2	3	7	4	9
2015 Q1	23	12	5	6	7	6	16
2015 Q2	24	10	9	6	7	7	23
2015 Q3	33	18	16	16	18	18	27
2015 Q4	29	8	9	7	9	9	15
2016 Q1	29	15	11	14	12	13	24
2016 Q2	28	11	7	9	11	8	23
2016 Q3	34	17	9	6	10	9	21
2016 Q4	22	11	5	10	7	6	13
2017 Q1	18	8	2	5	3	1	8
2017 Q2	20	7	3	4	4	4	12

REMS, Risk Evaluation and Mitigation Strategy; TIRF, transmucosal immediate-release fentanyl; unk, unknown

Source: Table and analysis by RADARS® through FDA-conducted contract. Cell shading added by DEPI reviewer.

Table 4. Percent change in mean quarterly abuse rate of specific TIRF medicines and comparators from pre-REMS (2010 Q3 – 2012 Q2) to post-REMS (2012 Q3 – 2017 Q2): RADARS® Treatment Center Programs Combined.

	Abuse cases, n		% Change in means (95% CI)	
Drug group	**Pre-period**	**Post-period**	**Per 100,000 population**	**Per 10,000 prescriptions**
Actiq and generic lozenge	310	557	-34.31% (-44.97%, -21.60%)	85.42% (44.64%, 137.70%)
Fentora	173	250	-47.17% (-60.52%, -29.30%)	25.16% (-8.65%, 71.47%)
Onsolis	97	191	-28.11% (-51.78%, 7.19%)	
Abstral	20	89	20.54% (-40.12%, 142.66%)	3.24% (-54.93%, 136.49%)
Lazanda	24	204	18.58% (-33.52%, 111.51%)	-79.09% (-95.43%, -4.25%)
Subsys		91		
TIRF: unknown/other	242	354	-46.52% (-61.06%, -26.55%)	
Oxycodone ER	6,176	7,428	-56.03% (-63.70%, -46.73%)	-37.71% (-45.10%, -29.33%)
Oxycodone IR	3,855	10,141	-3.83% (-25.76%, 24.57%)	4.97% (-19.29%, 36.53%)
Oxymorphone IR	1,270	3,329	-38.78% (-47.14%, -29.09%)	-28.98% (-44.78%, -8.66%)
Hydromorphone IR	3,291	6,818	-24.26% (-32.56%, -14.94%)	-20.37% (-28.29%, -11.57%)
Transdermal Fentanyl/Patch	1,730	2,136	-54.86% (-63.91%, -43.54%)	-49.49% (-59.38%, -37.19%)

CI, confidence interval; ER, extended-release; IR, immediate-release; REMS, Risk Evaluation and Mitigation Strategy; TIRF, transmucosal immediate-release fentanyl

Source: Table and analysis by RADARS® through FDA-conducted contract.

Figure 4A-E. Prescription-adjusted abuse rates of TIRF medicines in the RADARS® Treatment Center Programs Combined, Q3 2010 – Q2 2017.
Vertical line demarcates pre-REMS period (Q3 2010 – Q2 2012) from post-REMS period (Q3 2012 – Q2 2017).
Source: DEPI reviewer plots, Analysis performed by RADARS® through FDA-conducted contract.

Figure 4A

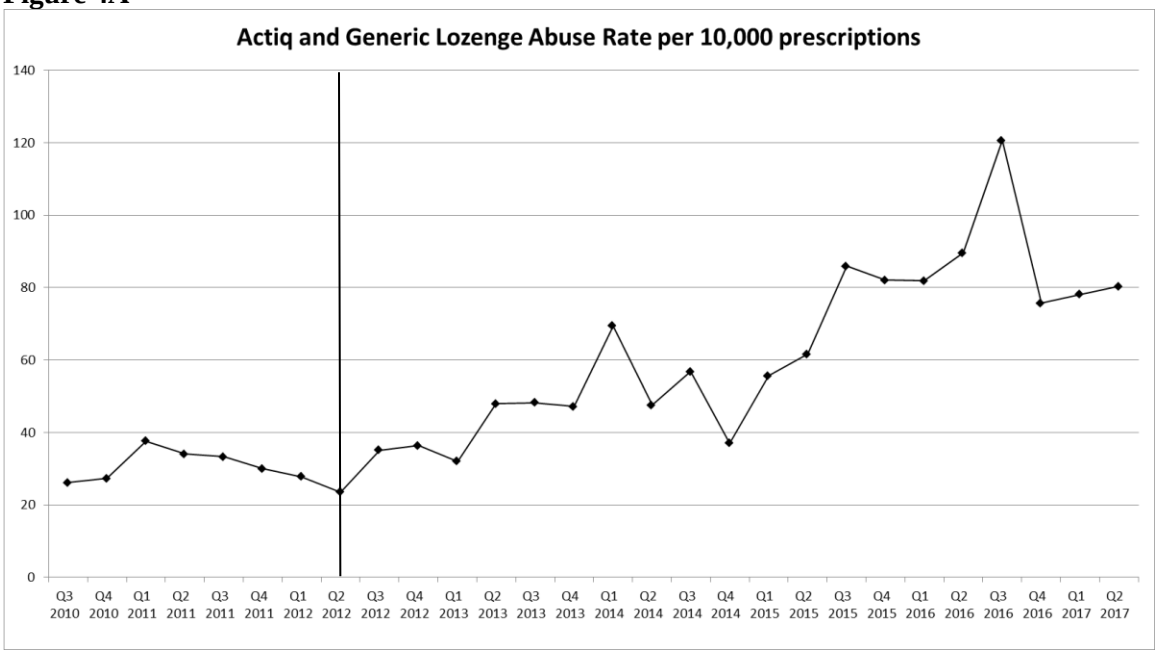


Figure 4B

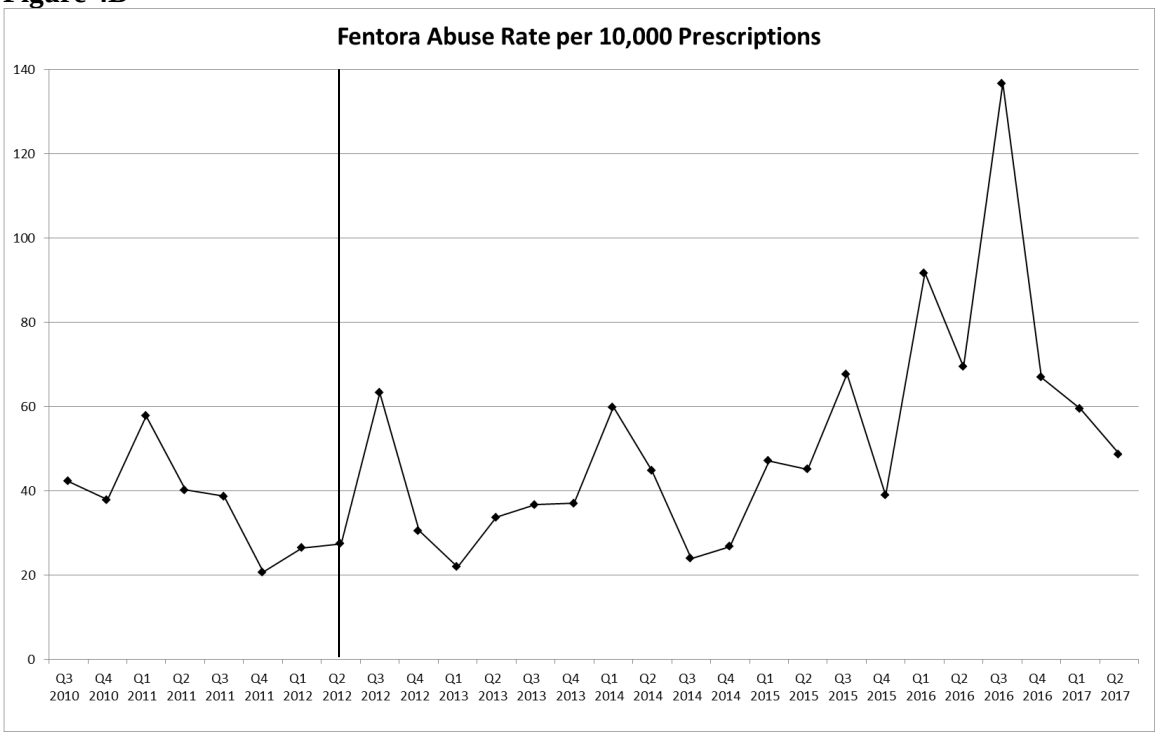


Figure 4C

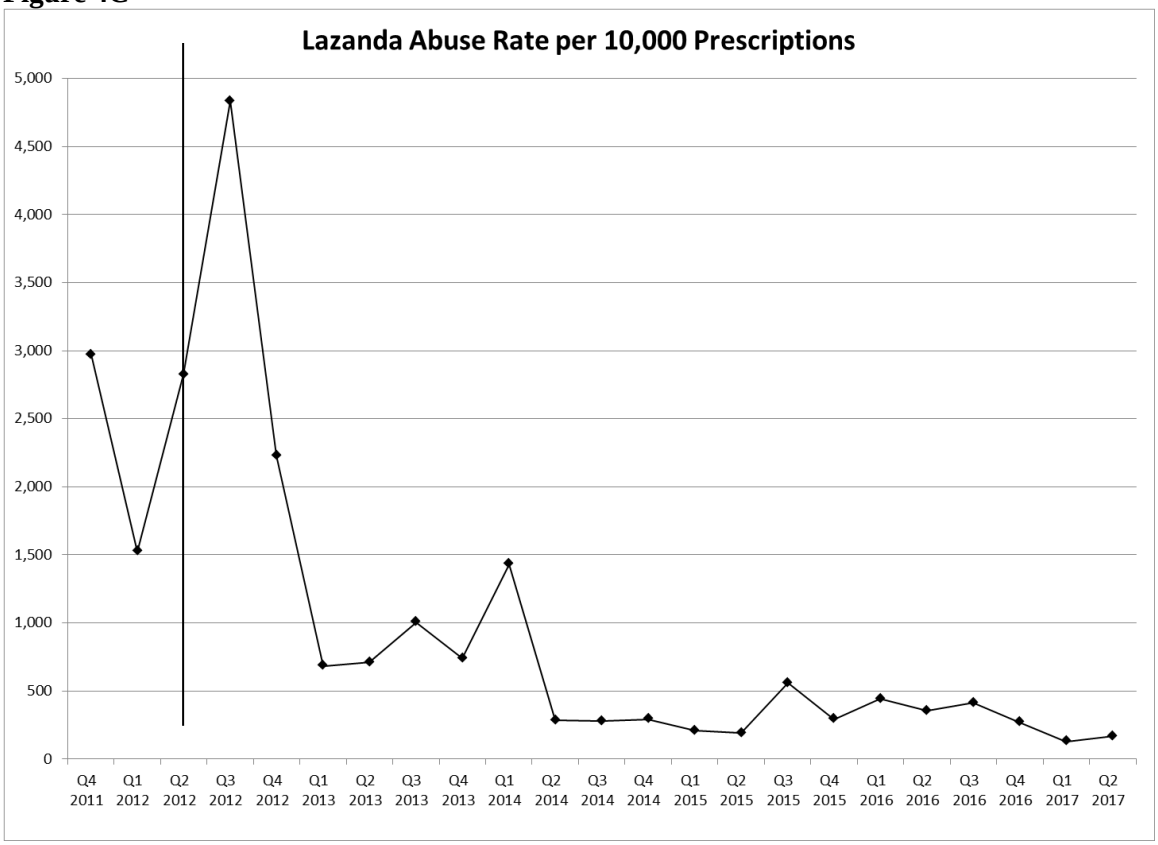
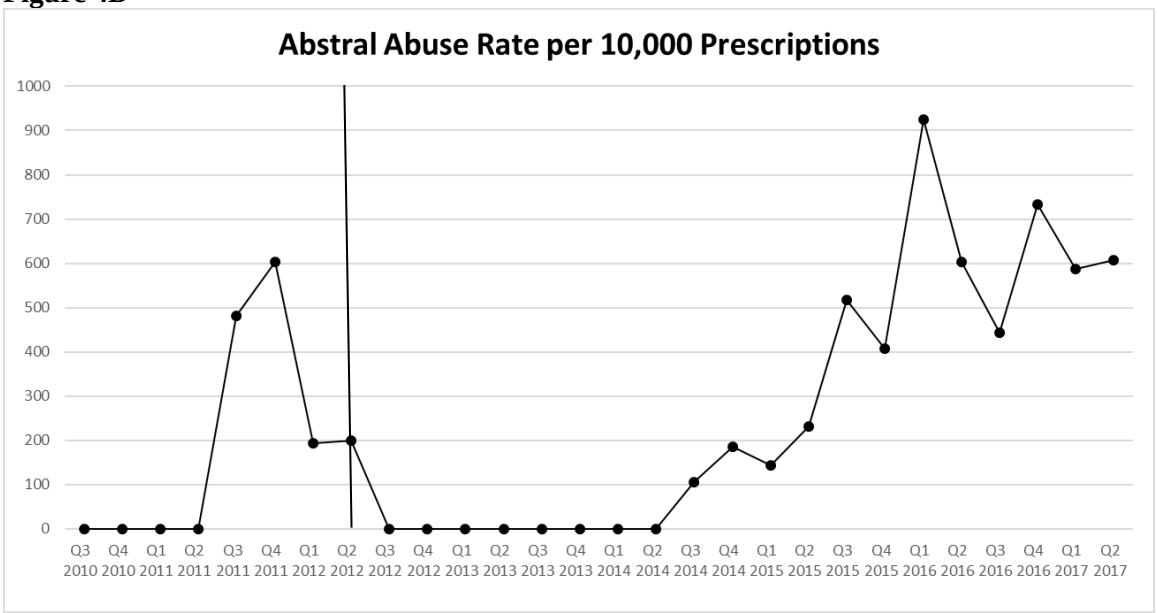
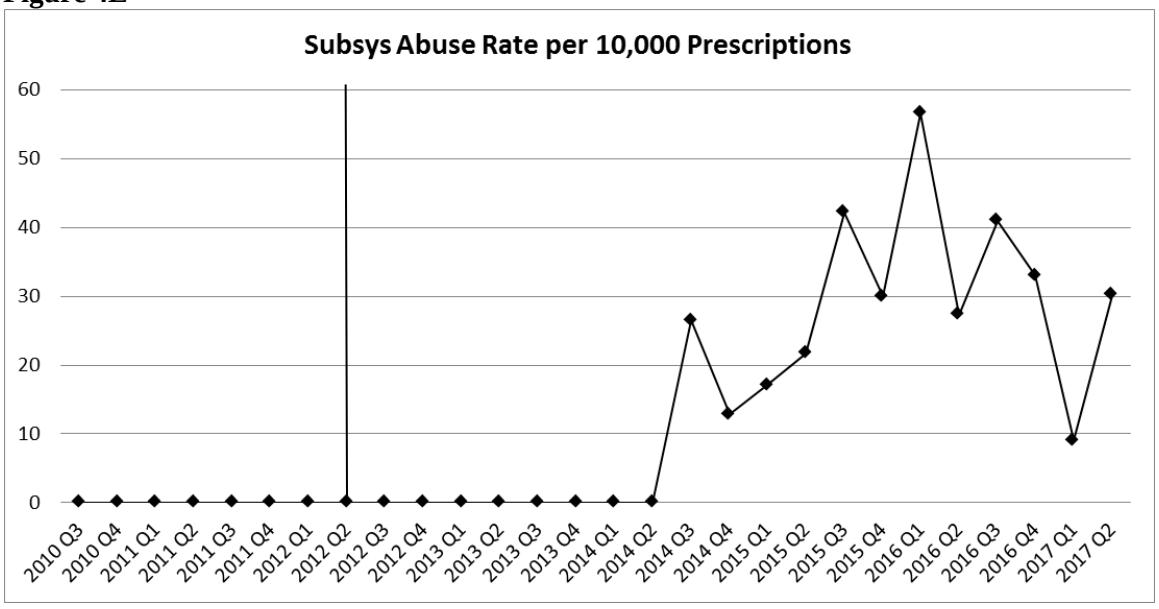


Figure 4D



Note: Abstral first appeared on the survey in Q3 2011, was subsequently removed beginning Q2 2012, and was re-added beginning Q3 2014.

Figure 4E



Note: Subsys was marketed only in the post-REMS period, beginning Q3 2012. Subsys first appeared on the survey beginning Q3 2014.

3.2.2 National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)

The NAVIPPRO™ analyses were conducted by Inflexxion® under contract with FDA.

3.2.2.1 TIRF Medicines Aggregated Data

Pre-REMS to Post-REMS Change in Mean Quarterly Abuse Rate

Note that no standard errors or CIs were provided.

- TIRF medicines and most comparators exhibited pre- to post-REMS increases in the mean quarterly abuse rate per 100,000 assessments: TIRF medicines 17%, oxycodone IR 14%, hydromorphone IR 34%, oxymorphone IR 59%, *fentanyl, unknown* 59%. The exception was oxycodone ER, which declined by 28%.
- TIRF medicines and most comparators exhibited pre- to post-REMS increases in the mean quarterly abuse rate per 1,000,000 prescriptions dispensed: TIRF medicines 178%, oxycodone IR 13%, hydromorphone IR 32%, oxymorphone IR 70%. Oxycodone ER was again the exception, with a 4% decline.

3.2.2.2 TIRF Product-specific Data

Pre-REMS to Post-REMS Change in Mean Quarterly Abuse Rate

Note that no standard errors or CIs were provided.

Cases of Abuse were very rare in NAVIPPRO™; Actiq and Fentora averaged six cases each per quarter, and Onsolis averaged three cases per quarter.

Population-adjusted abuse rates increased by 7% for Actiq, by 36% for Fentora, and by 3% for Onsolis, while changes in the comparators were as follows: oxycodone ER -28%, oxycodone IR 14%, hydromorphone IR 34%, oxymorphone IR 59%, *fentanyl, unknown* 59%.

Prescription-adjusted abuse rates increased from pre-REMS to post-REMS for Actiq (310%) and Fentora (205%); among comparators, the estimated change in mean quarterly abuse rate ranged from -4% to 70%. the prescription-adjusted abuse rate for Onsolis could not be calculated because of its low utilization.

Trends

Population-adjusted abuse rates

No trend was observed in the population-adjusted abuse rates of Actiq, Fentora, or Onsolis in the pre-period or post-period (*See following pages:* Figure 5A-C; Tables 5 and 6). The oxycodone ER abuse rate exhibited downward trends in the pre-period and the post-period, respectively. The oxycodone IR abuse rate increased in the pre-period; in the post-period, there was a suggestive, minimal downward trend. The oxymorphone IR abuse rate exhibited positive trends in the pre-period and the post-period, respectively. The hydromorphone IR abuse rate increased in the pre-period and decreased in the post-period. The *fentanyl, unknown* abuse rate decreased in the pre-period and increased in the post-period.

Prescription-adjusted abuse rates

Actiq's and Fentora's respective prescription-adjusted abuse rates increased in both the Pre-REMS and Post-REMS periods (*See following pages:* Figure 6; Tables 5 and 6). The Onsolis

prescription-adjusted abuse rate could not be calculated reliably. The oxycodone ER abuse rate showed no trend in the Pre-REMs period, and a downward trend in the post-REMS period. The oxycodone IR abuse rate showed a positive trend in the pre-REMS period, and a downward trend in the post-REMS period. The oxymorphone IR abuse rate exhibited positive trends in the pre-Period and the post-Period, respectively. The hydromorphone IR abuse rate increased in the pre-period and decreased in the post-period.

Table 5. Trend analysis of abuse rates in the <u>pre-REMS period</u>, Q3 2010 – Q2 2012: National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™).

	Past 30-day abuse	Trend in abuse rate per 100,000 population			Trend in prescription-adjusted abuse rate		
	n	Intercept (mean)	Slope	P-value of slope	Intercept (mean)	Slope	P-value of slope
Actiq	54	-8.04	0.03	0.6193	3.03	0.15	0.0149
Fentora	41	-8.24	0.01	0.8509	1.20	0.08	0.2389
Onsolis	25	-8.43	-0.02	0.7974	NA	NA	NA
Oxycodone ER	8,457	-2.57	-0.06	<.0001	1.93	0.00	0.3841
Oxycodone IR	12,454	-2.55	0.02	<.0001	0.12	0.02	<.0001
Oxymorphone IR	384	-6.25	0.07	0.004	1.75	0.10	0.0001
Hydromorphone IR	2,537	-4.28	0.05	<.0001	1.29	0.04	<.0001
Unknown Fentanyl	196	-6.45	-0.04	0.2385	2.25	0.04	0.2299
Transdermal Fentanyl/Patch	1,082	-4.81	-0.02	0.1354	0.12	-0.01	0.5869

NA, not applicable

Note: Trend in Onsolis prescription-adjusted abuse rate not presented due to low prescription volume.

<u>Source:</u> Table and analysis by Inflexxion® through an FDA-conducted contract.

Table 6. Trend analysis of abuse rates in the post-REMS period, Q3 2012 – Q2 2017: National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)

	Past 30-day abuse	Trend in abuse rate per 100,000 population			Trend in prescription-adjusted abuse rate		
	n	Intercept (mean)	Slope	P-value of slope	Intercept (mean)	Slope	P-value of slope
Actiq	123	-7.64	-0.01	0.459	3.84	0.07	<.0001
Fentora	119	-8.20	0.02	0.2972	1.42	0.06	0.0002
Onsolis	55	-8.77	0.01	0.618	NA	NA	NA
Oxycodone ER	13,272	-2.31	-0.05	<.0001	2.44	-0.04	<.0001
Oxycodone IR	30,936	-2.30	-0.002	0.0889	0.38	-0.01	<.0001
Oxymorphone IR	1,301	-6.32	0.04	<.0001	2.03	0.03	<.0001
Hydromorphone IR	7,296	-3.23	-0.03	<.0001	2.10	-0.03	<.0001
Unknown Fentanyl	665	-6.89	0.04	<.0001	1.84	0.07	<.0001
Transdermal Fentanyl/Patch	2,627	-4.74	-0.003	0.3765	0.09	0.001	0.6824

NA, not applicable

Note: Trend in Onsolis prescription-adjusted abuse rate not presented due to low prescription volume.

Source: Table and analysis by Inflexxion® through an FDA-conducted contract.

Figure 5A-C. ACTIQ (solid black), FENTORA (dotted black), and ONSOLIS (solid gray) Abuse Rate per 100,000 Surveys, Q3 2010 – Q2 2017: National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™). Rectangle around Q2 2012 denotes the end of the pre-REMS period. Source: DEPI reviewer plot; analysis performed by Inflexxion® through FDA-conducted contract.

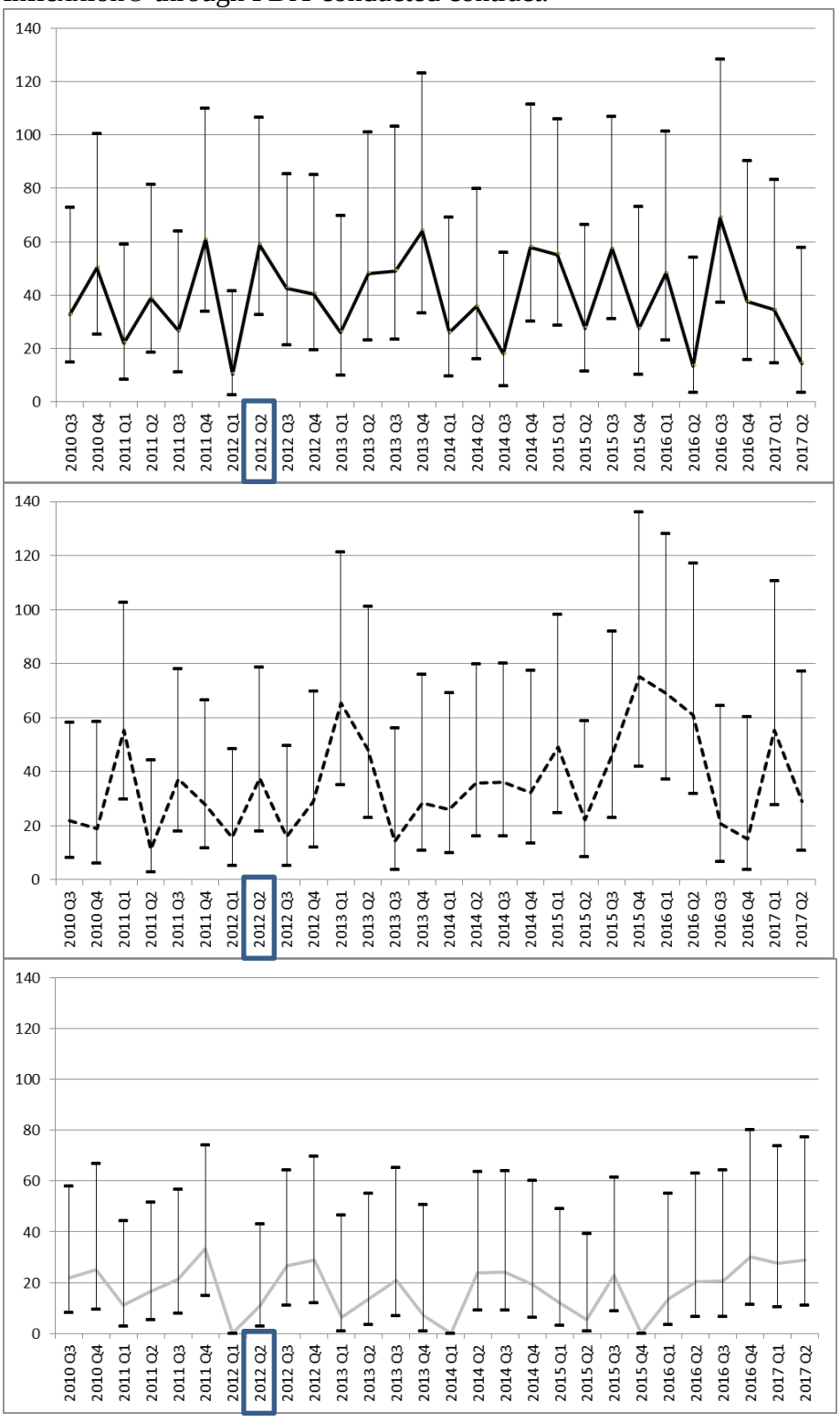
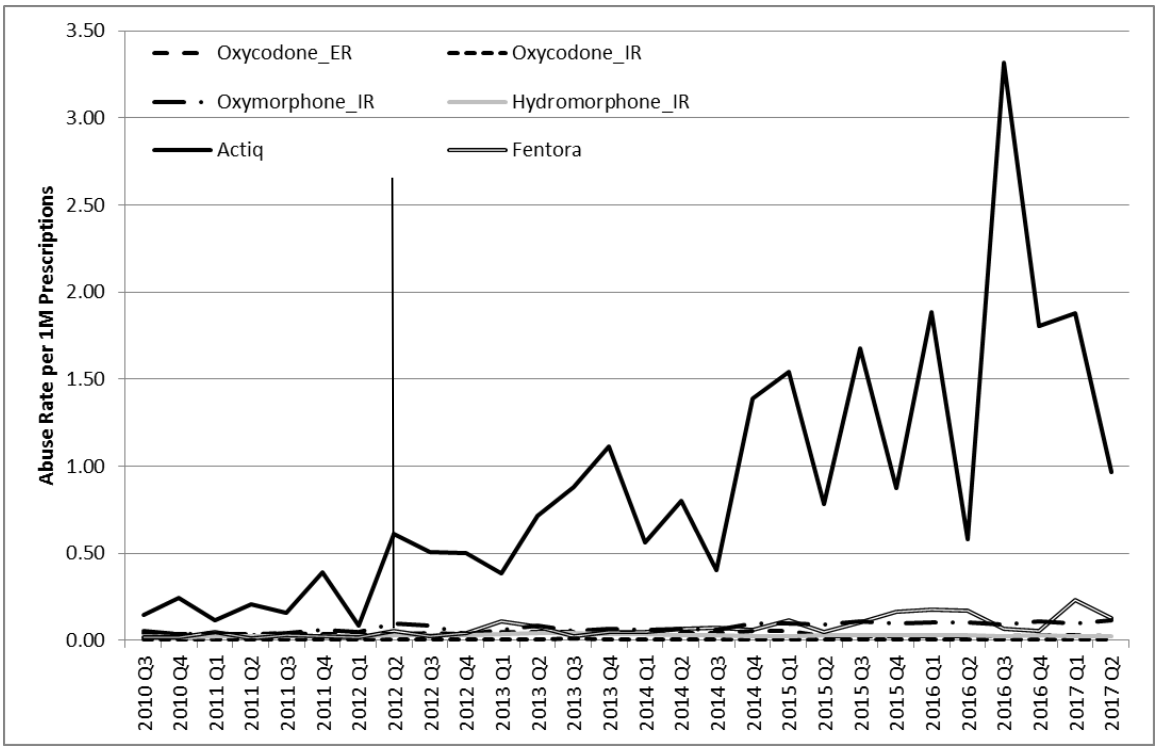


Figure 6. Abuse rates for Actiq, Fentora, and comparators, per 1,000,000 prescriptions, Q3 2010 – Q2 2017: National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™)

Source: DEPI reviewer plot; analysis performed by Inflexxion® through FDA-conducted contract.



3.2.3 RADARS® Poison Center Program

The results from the RADARS® Poison Center Program were submitted by the TRIG. The results by outcome are summarized below. See Appendix 7.3, Table A4 for detailed results: mean rate, percent change, and ratio of rate ratios.

Abuse

TIRF medicine abuse cases increased from the pre- to post-REMS period, per 100,000 population (38%, CI: -45%, 249%) and per 10,000 prescriptions dispensed (169%, CI: -1%, 630%). In contrast, comparators' abuse rates declined (population-adjusted estimated rates: -65% to -5%; prescription-adjusted estimated rates: -60% to -2%).

Intentional Misuse

The relative decrease in the mean TIRF medicine population-adjusted misuse rate from the pre- to post-REMS period was similar in magnitude to the comparators' respective relative decreases. However, the mean TIRF medicine prescription adjusted misuse rate increased, although the estimate was imprecise due to low numbers of calls (41%, 95% CI: -48%, 283%). In contrast, for every comparator, the mean prescription-adjusted misuse rate decreased (range: -29% to -20%).

Unintentional Therapeutic Error

TIRF medicine unintentional therapeutic error population-adjusted rate decreased from the pre- to post-REMS period (-21%, 95% CI: -57%, 47%), and the comparators also exhibited decreases of similar magnitude. However, the TIRF medicine unintentional therapeutic error prescription-adjusted rate increased (54%, 95% CI: -25%, 217%), although the estimate was imprecise due to the low number of calls, while estimated relative changes among the comparators ranged from -15% to 2%.

Unintentional General Exposures

The TIRF medicine unintentional general exposure rate decreased from the pre- to post-REMS period, regardless of denominator used. The decrease in the population adjusted rate was larger than that of comparators (-64%, compared to -39% to -16%), and the decrease in the prescription-adjusted rate was similar to comparators (-29%, compared to -31% to -13%).

Unintentional General **Pediatric** Exposures

The change in unintentional general pediatric exposures was almost identical to the change in unintentional general overall exposures. The TIRF medicine unintentional general **pediatric** exposure rate decreased from the pre- to post-REMS period, regardless of denominator used. The percent change in the population-adjusted rate was -64% (CI: -87%, -0.3%), and comparators changed by -39% to -14%. The percent change in the prescription-adjusted rate was -29% (CI: -74%, 93%), and comparators changed by -31% to -12%).

Calls for pediatric exposures were extremely rare in the pre-REMS and post-REMS periods (Table 7).

Table 7. Pediatric exposure calls, stratified by age, pre-REMS (Q3 2010 – Q2 2012) and post-REMS (Q3 2012 – Q2 2017): RADARS® Poison Center Program

Count, n	Pre-REMS	Post-REMS
Age group: <6 years		
Total exposure calls, n	**9**	**9**
Exposure Reason		
Unintentional general	9	8
Unintentional therapeutic error	0	1
Clinical Effect		
No effect	1	2
Minor effect	5	4
Moderate effect	2	0
Major effect	0	0
Unable to follow, potential toxic	1	
Not followed, minimal clinical effects possible	0	2
Not followed, nontoxic	0	1
Age group:6-19 years		
Total exposure calls, n	**0**	**5**
Exposure Reason		
Abuse	0	3
Intentional Misuse	0	1
Suspected Suicide[1]	0	1
Clinical Effect		
Minor effect	0	1
Moderate effect	0	2
Major effect	0	1
Not followed, minimal clinical effects possible	0	1

[1] Minor clinical effect

Source: DEPI reviewer tabulation of data from list provided by TIRF REMS Assessment Surveillance Monitoring Report, Table C.1.1.

ED Visits and Hospitalization Cases

TIRF medicine exposure cases resulting in ED visits and hospitalizations decreased per 100,000 population from the pre- to post-REMS period (-20%, 95% CI: -45%, 15%), while the comparators' estimated relative changes ranged from -45% to 1%. However, TIRF exposure cases resulting in ED visits and hospitalizations increased per 10,000 prescriptions dispensed (55%, 95% CI: -1%, 141%), while the rate among comparators decreased or remained constant (estimates ranged from -37% to 5%).

Major Medical Outcomes and Deaths

TIRF medicine exposure cases resulting in major medical outcomes and deaths increased from the pre- to post-REMS period, per 100,000 population (54%; CI: -31%, 246%), and per 10,000 prescriptions dispensed (200%; CI: 25%, 621%). In contrast, comparators exhibited no change or a decrease from the pre- to post-REMS period, per 100,000 population (estimates: -35% to 3%) and per 10,000 prescriptions dispensed (estimates: -25% to 5%).

3.2.4 American Association of Poison Control Centers (AAPCC), National Poison Data System (NPDS)

For the pre-specified exposure reasons, NPDS had 88 cases while RADARS® PCP had 95 (Table 8), although PCP receives the NPDS data from some 90% of AAPCC-member centers. Both analyses used closed cases from the same period. The discrepancy may be due to the RADARS® staff reviewing the case notes in every exposure case they receive, and using this information to verify key categorical variables, such as exposure reason, product codes, and generic codes. [4] In contrast, the NPDS variables are not updated with information from the case notes. [4] As the case notes contain information from follow-up calls, reading them can uncover information to classify an exposure call that the NPDS had marked as unknown reason, or to reclassify an exposure reason.

Table 8. Call numbers for pre-specified exposure reasons, National Poison Data System (NPDS) and RADARS® Poison Center Program (PCP).

Exposure Reason:	**NPDS**	**PCP**
Abuse	27	24
Intentional Misuse	18	18
Unintentional general	19	18
Unintentional therapeutic error	24	35
Sum of exposure reasons	**88**	**95**
Outcome severity:		
Major medical/death	25	21
Emergency department visits/hospitalizations	101	102

Sources: PCP data: Surveillance Monitoring Report in the 72-month TIRF REMS Assessment Report; NPDS data: search conducted by AAPCC through an FDA-conducted contract.

The number of any type of poison center exposure calls per product was generally low, which limited our ability to calculate statistical estimates and trends. The number of calls per product per quarter ranged from 0 to 11 (Appendix 7.4, Table A5). No calls were reported for Onsolis exposure; there was never more than one call per quarter for Abstral exposure and Lazanda exposure, respectively, and Subsys exposure calls ranged from zero to three per quarter.

For both Actiq and Fentora, there were increases pre- to post-REMS in the prescription-adjusted rate of exposure calls resulting in ED visits and hospitalizations (Actiq: 68%, CI: 4%, 170%; Fentora: 59%, CI: -53%, 444%).

Calls for exposure to *fentanyl, unknown* per quarter ranged from 75 to 211. This category includes mentions of fentanyl that cannot be classified as pharmaceutical or illicit with certainty. Thus, it may contain exposures to TIRF medicines, other pharmaceutical fentanyl products, and

illicit fentanyl. The population-adjusted rate of ED visits and hospitalizations increased 14% (CI: 4%, 24%) from pre- to post-REMS. Major medical outcomes and deaths increased 4% (CI: -10%, 21%); abuse exposure calls increased 22% (CI: 8%, 39%); unintentional general exposure calls increased 21% (CI: -18%, 78%); and unintentional general exposure calls for children age <6 years increased 38% (CI: -27%, 163%).

3.2.5 Persistency Analysis

The results for the persistency analysis were submitted by the TRIG. This analysis was revised satisfactorily per DEPI's recommendations from the review of the 48-month TIRF REMS Assessment report. Product names were blinded in this analysis.

Definition of the Grace Period. In an exploratory analysis of episodes consisting of one TIRF dispensing followed by another dispensing for the same product (or its generic equivalent), the subsequent dispensing occurred within 2.5 times the days' supply of the first dispensing in 95% of episodes. **Therefore, the TRIG defined a grace period, i.e., a permissible gap indicating the patient stayed on treatment, as 2.5 times the days' supply**. When this analysis was stratified by product, the resulting 95th percentile varied by product, from 2.2 to 4 times the days' supply. Sensitivity analyses used these other values to define the permissible gap.

Description of persistency: patient-level results. Among all patients who received two or more TIRF prescriptions, 10.4% persisted with their index regimen, 20.5% changed their TIRF regimen, and 69.1% discontinued their index regimen (Table 9). Among the patients who discontinued their index regimen, 44.3% reinitiated their index regimen at a time after the grace period had ended, so that 30.6% of all patients reinitiated.

When the analysis was stratified by the index TIRF dispensing date, the early cohort of patients who received their index TIRF prescription in March 2012-October 2012 were the most likely to persist with their index regimen (12.4%, versus 5.4% in the middle cohort and 10.8% in the late cohort); they were also the most likely to change (25.2% versus 19.0% and 13.9%), and the least likely to discontinue their index regimen (62.4% versus 75.6% and 75.3%). Therefore, the median time to either changing or discontinuing index regimen was:

- 9.4 months (95% CI: 9.0, 10.0) among the early stratum;
- 3.4 months (95% CI: *not estimable*) among the middle stratum;
- 3.5 months (95% CI: 3.4, 3.6) among the late stratum.

The analysis of persistency of a second TIRF regimen found a similar relative distribution among the three, mutually exclusive outcomes: 10.5% persisted with their second regimen, 25.6% changed to a different regimen, and 63.9% discontinued their second regimen (Table 10).

The results were essentially unchanged in sensitivity analyses that varied the length of the grace period, from 2 – 4 times the days' supply, and when the analysis excluded the 1% of patients who were dispensed more than 24 units per day.

Characteristics of the study population are reported in Appendix 7.5, Table A6.

Table 9. Persistence with index TIRF regimen, by month of index TIRF regimen prescription: TIRF REMS Pharmacy Switch Database, March 2012 – October 2014.

	"Late" November 2013 – October 2014 (N=5,378)	" Middle" November 2012 – October 2013 (N=4,001)	"Early" March 2012 – October 2012 (N=8,781)	Total (N=18,160)
Persistent with index TIRF regimen (N,%)[1]	**582 (10.8%)[4]**	**218 (5.4%)[5]**	**1,092 (12.4%)[6]**	**1,892 (10.4%)[7]**
- N (%) persistent at least 6 months	1,677 (31.2%)	1,255 (31.4%)	5,278 (60.1%)	8,210 (45.2%)
- N (%) persistent at least 12 months	876 (16.3%)	713 (17.8%)	3,897 (44.4%)	5,486
- N (%) persistent at least 24 months	N/A*	280 (7.0%)	2,341 (26.7%)	2,621 (14.4%)
- N (%) persistent at least 36 months	N/A**	N/A**	1,439 (16.4%)	1,439 (7.9%)
Changed index TIRF regimen (N, %)[1,2]	**747 (13.9%)[4]**	**759 (19.0%)[5]**	**2,212 (25.2%)[6]**	**3,718 (20.5%)[7]**
Added another TIRF (concurrent therapy) (N)	45	50	269	364
Switched to a different TIRF (N)	679	673	1,735	3,087
Discontinued part of TIRF regimen (N)	23	36	208	267
Discontinuation of index TIRF regimen (N, %)[1,3]	**4,049 (75.3%)[4]**	**3,024 (75.6%)[5]**	**5,477 (62.4%)[6]**	**12,550 (69.1%)[7]**
Re-initiated index TIRF regimen (N)	1,706	1,532	2,327	5,565
Discontinued index TIRF regimen completely (N)	2,343	1,492	3,150	6,985

REMS, Risk Evaluation and Mitigation Strategy; TIRF, transmucosal immediate-release fentanyl

*Not applicable, patients followed up to less than 24 months.

**Not applicable, Patients followed up to less than 36 months.

1 Persistence, change and discontinuation are mutually exclusive categories.

2 Sub-categories under "Change in index TIRF regimen" are mutually exclusive.

3 Sub-categories under "Discontinuation of index TIRF regimen" are mutually exclusive.

4 Denominator, n=5,378. Patients who had less than 24 months of prescription fill data.

5 Denominator, n=4,001. Patients who had less than 36 months of prescription fill data.

6 Denominator, n=8,781. Patients who had more than 36 months of prescription fill data.

7 Denominator, n=18,160. Overall analysis set for the persistency analysis.

Source: 72-month TIRF REMS Assessment Report, Appendix 12.9, Table 3a

Table 10. Persistence with second TIRF regimen, by month of second TIRF regimen prescription: TIRF REMS Pharmacy Switch Database, March 2012 – October 2014.

	"Late" November 2013 – October 2014 (N=2,453)	"Middle" November 2012 – October 2013 (N=2,291)	"Early" March 2012 – October 2012 (N=4,539)	Total (N=9,283)
Persistent with second TIRF regimen (N,%)[1]	**359 (14.6%)[3]**	**195 (8.5%)[4]**	**420 (9.3%)[5]**	**974 (10.5%)[6]**
Changed second TIRF regimen (N, %)[1,2]	**382 (15.6%)[3]**	**458 (20.0%)[4]**	**1,538 (33.9%)[5]**	**2,378 (25.6%)[6]**
Added another TIRF (concurrent therapy) (N)	21	37	136	194
Switched to a different TIRF (N)	330	392	1,181	1,903
Discontinued part of TIRF regimen (N)	31	29	221	281
Discontinuation of second TIRF regimen (N, %)[1,3]	**1,712 (69.8%)[3]**	**1,638 (71.5%)[4]**	**2,581 (56.9%)[5]**	**5,931 (63.9%)[6]**
Re-initiated second TIRF regimen (N)	567	621	1,339	2,527
Discontinued second TIRF regimen completely (N)	1,145	1,017	1,242	3,404

REMS, Risk Evaluation and Mitigation Strategy; TIRF, transmucosal immediate-release fentanyl

[1] Includes only patients with a second regimen.

[2] Since the initiation of second TIRF regimen until end of the patient's observation period. Patients who initiated a second regimen did so at different time points during their respective observation period.

[3] Denominator, n=2,453. Patients who had a second TIRF regimen with less than 24 months of prescription fill data.

[4] Denominator, n=2,291. Patients who had a second TIRF regimen with less than 36 months of prescription fill data.

[5] Denominator, n=4,539. Patients who had a second TIRF regimen with more than 36 months of prescription fill data.

[6] Denominator, n=9,283. Total number of patients who had initiated a second TIRF regimen.

Source: 72-month TIRF REMS Assessment Report, Appendix 12.9, Table 3a

Description of persistency: Product-level results.

Persistency by type of index TIRF regimen ranged from 0-13.7%. When the index regimen consisted of only one TIRF medicine, persistency ranged from 1.4-13.7%. When the second regimen consisted of only one TIRF medicine, persistency ranged from 5.1-13.7%. Appendix 7.5, Figure A1 depicts the percent persistent with regimen over time, by index TIRF regimen.

3.2.6 Survey of Non-Medical Use of Prescription Drugs

NMURx data analyses were submitted by the TRIG.

The estimated prevalence of TIRF medicine non-medical use in the last 90 days among U.S. adults excluding college students showed substantial variability between survey periods for TIRF medicines, and for comparators to a lesser extent (Table 11). These patterns were consistent with results among U.S. college students and with results for non-medical use in other timeframes, from 7 days to 12 months (Appendix 7.6, Table A7).

Table 11. Estimated national prevalence of non-medical use of TIRF medicines and of comparator opioid analgesics in the Past 90 days among U.S. adults, excluding college students: RADARS® Survey of Non-Medical Use of Prescription Drugs.

	3rd Quarter 2016	1st Quarter 2017	3rd Quarter 2017
TIRF medicines	2.5 (2.28, 2.68)	1.3 (1.13, 1.42)	0.1 (0.10, 0.20)
IR oxycodone	0.9 (0.81, 1.05)	0.5 (0.38, 0.56)	0.6 (0.50, 0.68)
ER oxycodone	0.7 (0.57, 0.77)	0.4 (0.31, 0.48)	0.4 (0.34, 0.50)
IR hydromorphone	0.3 (0.23, 0.37)	0.1 (0.05, 0.13)	0.2 (0.14, 0.24)
IR oxymorphone	0.3 (0.27, 0.41)	0.1 (0.07, 0.16)	0.2 (0.11, 0.21)

Source: Table 13.2.9.1, Surveillance Monitoring Data Report, 72-month TIRF REMS Assessment.

The DEPI reviewer did not include the results for non-medical use per 100,000 dosage units dispensed due to the concern over uncertainty about the accuracy of dosage units recorded for prescription fills for some TIRF medicines, e.g., multi-dose sprays. However, these rate estimates were also highly variable between survey periods.

The DEPI reviewer agrees with the TRIG's findings that the data show that more non-college students than college students reported non-medical use of TIRF medicines in every survey period. In the Q1 2017 and Q3 2017 survey periods, the odds of non-medical use of TIRF medicines in the past 90 days was higher among college students than among non-college students (Appendix 7.6, Table A8).

4 DISCUSSION

4.1 RADARS® TREATMENT CENTER PROGRAMS COMBINED

In the post-REMS period, aggregated cases of recent TIRF medicine abuse persisted at around 40 – 50 each quarter, with some fluctuation, until a decline in the most recent 12 months of reporting. As TIRF prescriptions in aggregate also fell during the post-REMS period, the prescription-adjusted abuse rate increased, although the population-adjusted abuse rate remained constant. Nearly every TIRF medicine exhibited this increasing trend in the prescription-adjusted abuse rate post-REMS, except Lazanda. Lazanda's trend appears to be influenced by extremely high prescription-adjusted abuse rates when it first appeared on the survey, which may have been produced by respondent errors and the low utilization during this period. In contrast, the prescription-adjusted abuse rates of comparators oxycodone ER, oxycodone IR, and hydromorphone IR were lower than the TIRF prescription-adjusted abuse rate, and exhibited flat trends during the post-REMS period. The oxymorphone IR prescription adjusted abuse rate was higher than the TIRF medicine abuse rate early in the post-REMS period, and it decreased over time.

It is difficult to know whether the apparent increases in prescription-adjusted abuse rates during the post-REMS period are real or driven by other explanations such as false positive identification of TIRF medicines on the survey instrument. Reasoning that some degree of clustering by geography and time would increase the confidence that the increase in reports reflects actual abuse, rather than false-positive reporting, FDA asked RADARS® to conduct a post-hoc, descriptive evaluation of any such clustering of abuse reports for Lazanda, Abstral, and Onsolis, the TIRF medicines with low abuse numbers and high inter-quarter variability. No geographic-temporal clustering was observed. [5] Another factor that may have contributed to the variability in quarterly case counts was that individual treatment centers may drop in and out of the sample over time. Still, the post-REMS, positive trend in the prescription-adjusted abuse rate of aggregate TIRF medicines appears to be robust to participation by individual centers, as the trend was observed when the data were restricted to treatment centers with data in every quarter.

Limitations:

- Product-specific abuse cases per quarter were so limited in number and variable over quarters that we acknowledge the plausibility of a minor increase in false-positive reports contributing to some of the apparent increasing trend in prescription-adjusted abuse rates.
- For example, Onsolis continued to receive endorsements years after U.S. marketing ceased. These endorsements may represent abuse of products smuggled from other countries, confusion of Onsolis with transmucosal abuse of fentanyl transdermal patches, or other respondent errors.
- Two hypothetical mechanisms for false-positive reporting that may have increased in prevalence over time are: respondents indicating ever-abuse, rather than recent abuse, and, misreporting recent abuse of a product if they unwittingly abused a counterfeit, illicit fentanyl, or other non-TIRF fentanyl product.

Strengths:

- The surveys have clear instructions to report products abused in the past 30 days.
- Rigorous processes for data checks and data entry uphold accuracy of the data entry from the paper survey instrument.

4.2 NATIONAL ADDICTIONS VIGILANCE INTERVENTION AND PREVENTION PROGRAM (NAVIPPRO™)

NAVIPPRO™ data suggest that cases of abuse of Actiq, Fentora, and Onsolis were rare and exhibited almost no change from the pre- to post-REMS period. Prescription-adjusted abuse rates of Actiq and Fentora increased from the pre-REMS to post-REMS period, and to a greater extent than changes in comparators. The quantitative estimates should be interpreted with caution due to the low number of abuse cases. Also, NAVIPPRO™ data showed different trends in the opioid comparators hydromorphone IR and oxycodone IR when compared with RADARS® TCPC. Differences in study populations likely produced the different trends, as NAVIPPRO™ collects data from a more heterogeneous population of individuals presenting for evaluation of substance use disorder rather than opioid use disorder, specifically.

Limitations:

- NAVIPPRO collected data only on recent abuse of Actiq, Fentora, and Onsolis throughout the pre- and post-REMS periods. Some of the reports may have been misreported by respondents who had abused other TIRF medicines, as there were no options for reporting recent abuse of Abstral, Lazanda, Subsys, or "other/unknown."
- The small number of cases are vulnerable to influence from false-positive reports. Indeed, Onsolis's quarterly endorsement numbers frequently exceeded the number of U.S. prescriptions.
- There was no measure of variability around the estimated change in mean quarterly abuse rate.

Strengths:

- Data collection was by a standard instrument that has been validated among adults presenting for substance abuse treatment.
- NAVIPPRO™ replicated the findings from RADARS® TCPC with regards to certain contemporaneous trends in prescription-drug abuse among adults presenting for substance abuse treatment, i.e., prescription-adjusted rate of oxymorphone IR abuse increased, while the prescription-adjusted rate of oxycodone ER abuse decreased.

4.3 RADARS® POISON CENTER PROGRAM

TIRF medicine exposure calls resulting in major medical outcomes and deaths, and TIRF medicine abuse exposure calls increased in terms of number of calls per quarter, population-adjusted rate, and prescription-adjusted rate. The wide confidence intervals for the changes in the population-adjusted rates mean the data are not inconsistent with no change in calls from pre- to post-REMS. However, the respective increases in the prescription adjusted rates were significant and of larger magnitude relative to that of comparators. The increase in abuse rates in PC data concur with the findings from TCPC and NAVIPPRO. The rise in major medical outcomes and deaths may be linked to the increase in exposure calls for TIRF medicine abuse, given that its relative change is more aligned with the change in major medical outcomes and deaths than the

patterns in unintentional general exposures, unintentional therapeutic errors, and misuse. There were no data to assess whether the rise in major medical outcomes/deaths was linked to the rise in abuse, and further data are needed on the reason for these outcomes.

However, the interpretation was less clear for the pre- to post-REMS change in TIRF medicine exposure calls resulting in ED visits and hospitalizations, as well as for misuse calls, unintentional therapeutic error calls, and unintentional general exposure calls. Means in number of calls per quarter and population-adjusted rate decreased, yet, there were suggestive increases in the prescription-adjusted rates of these calls. For comparators, both population-adjusted and prescription-adjusted rates tended to decrease or remain constant. In contrast, unintentional general TIRF medicine exposures calls, overall and among children age <6 years, decreased on both the population-adjusted and prescription-adjusted scales, and to as great an extent or greater than decreases in rates of comparator unintentional general exposures. Pediatric exposure calls were extremely rare events, pre-REMS and post-REMS, and additional data are needed to decide whether the REMS is effective at preventing pediatric exposure.

Limitations:

- For TIRF medicines, the low number of calls in both pre- and post-REMS periods yielded imprecise estimates of percentage change in call rates.
- Poison center calls represent a small fraction of the total number of events of interest. It is uncertain what fraction of events result in a poison center call, and to what extent this fraction varies over time. This complicates the interpretation of trends in poison center call rates to population-level trends in outcomes.

Strengths:

- Numerous features support data accuracy: data are reported by people seeking medical advice or intervention, often with the package available, with a trained medical interviewer. Data collection procedures are standardized nationwide. False-positive reports are therefore less of a concern than they are in treatment center data. RADARS® staff review the case notes of calls for prescription opioid exposure to identify inconsistent information.
- There is less of a chance of changing sampling fraction over time for pediatric exposures.

4.4 AMERICAN ASSOCIATION OF POISON CONTROL CENTERS (AAPCC), NATIONAL POISON DATA SYSTEM (NPDS)

We found that calls in the post-REMS period were mainly for either Actiq/generic fentanyl lozenge, Subsys, or Fentora; while fewer calls reported exposure to Lazanda or Abstral; and no calls were received reporting Onsolis exposure. Enough calls were made involving exposure to either Actiq or Fentora to run a product-specific analysis of ED visits/hospitalizations, which aided our understanding of the results of the TIRF aggregated data in the RADARS® PCP. Specifically, both Actiq and Fentora exhibited increases in the prescription-adjusted rate of ED visits/ hospitalizations from the pre- to post-REMS periods, consistent with the results of the TIRF medicines aggregated data analysis in the RADARS® PCP.

Limitations:

- The number of calls per TIRF medicine was small, as expected, which limited the statistical analyses that could be conducted feasibly and resulted in imprecise estimates.

- Poison center calls represent a small fraction of the total number of events of interest. It is uncertain what fraction of events result in a poison center call, and to what extent this fraction varies over time. This complicates the interpretation of trends in poison center call rates to population-level trends in outcomes.

Strengths:

- Numerous features support data accuracy: data are reported by people seeking medical advice or intervention, often with the package available, with a trained medical interviewer. Data collection procedures are standardized nationwide. False-positive reports are therefore less of a concern than they are in treatment center data.
- Product-specific data clarified what products were contributing to changes in the pre- to post-REMS periods.

4.5 PERSISTENCY ANALYSIS

Switching TIRF therapy was not uncommon among patients who filled two or more prescriptions for TIRFs during 2012 – 2014. Prescribing patterns appeared to change over time, as patients who were prescribed an index TIRF regimen in late 2013 – 2014 were less likely to switch regimens and more likely to discontinue their TIRF therapy completely, compared to patients prescribed their index TIRF regimen in earlier years.

The presentation of results is clearer in the revised analysis, addressing the recommendations from FDA's prior review. These results provide basic information to satisfy FDA's original request and prior review. To evaluate whether the REMS is achieving its goal of preventing inappropriate product conversions, more detailed data about the regimens are needed. The prior review also expressed the need for data on product strength and dosing instructions to characterize the changes in regimens.

Analysis of patient outcomes following a switch in TIRF regimens may be warranted due to the substantial proportion of patients who switched regimens, and the lack of data on patient outcomes following a switch. Because the intended dose of each product is a critical factor in considering the appropriate conversion and patient safety, the analysis of patient outcomes must incorporate data on product strength and prescriber instructions.

Limitations:

- These data were collected three to six years ago, and they indicate that prescribing patterns shifted during 2012-2015. Therefore, generalizability to current patients is uncertain.
- These data reflect prescriptions dispensed, not actual consumption.
- TIRF regimens were defined by the product, but there were no data on dose (e.g., prescriber instructions).

Strengths:

- Presenting results in the overall population and stratified by index prescribing date enable us to draw general interpretations while noting changes in apparent prescribing practices.
- There were enough patients in the analysis to make stable estimates of persisting and switching.

- The counts of the various, blinded TIRF regimens indicate that each product was represented.
- The results were not sensitive to alternative definitions of the grace period, or to outlier values.

4.6 SURVEY OF NON-MEDICAL USE OF PRESCRIPTION DRUGS (NMURX)

NMURx initiated data collection in the third quarter of 2016, and so it cannot evaluate the effectiveness of the TIRF REMS as there was no observation period prior to the REMS implementation. DEPI's interpretation of NMURx results differs from the TRIG's interpretations provided in the 72 month REMS Assessment Report. The point where the DEPI reviewer differs from the TRIG's interpretation is that we noted substantial variability in their results over time, which they did not mention.

There have been only three survey periods, and prevalence estimates for TIRF medicine non-medical use were highly variable between survey periods. To understand issues of instrument validity, more information is needed on survey development and validation, and demographic variable distributions in the unweighted sample. A promising indicator is that the introduction of randomizing the order of product groups on the Q3 2017 survey coincided with a steep decline in the estimated prevalence of TIRF non-medical use, from levels that appeared too high both in an absolute sense and relative to comparators' levels. Provided questions about the validity and generalizability are answered, a general-population survey of non-medical use of specific opioid analgesic products would be useful for surveillance data.

NMURx data were stratified by college student status, as college student surveys were among the components of TIRF REMS surveillance data requested by FDA. Considering the low TIRF medicine utilization and AEs and the importance of evaluating product-specific data to determine the REMS effectiveness, it is preferable to discontinue stratification in favor of enhancing precision of the results. Therefore, future surveillance work for TIRF REMS Assessment does not need to stratify non-medical use by college-student status.

5 CONCLUSION

Observed increases in the prescription-adjusted rates of abuse of TIRF medicines are concerning. TIRF medicines aggregate data from several data streams suggested that the prescription-adjusted rate of TIRF abuse increased from the pre- to post-REMS period, or, that there was an upward trend in the prescription-adjusted abuse rate post-REMS through 2016, although the abuse rate appeared to decline starting in Q1 2017. These patterns in abuse are concerning giving that prescription-adjusted abuse rates of comparators showed either contemporaneous declines or no change. The TIRF product-specific data generally showed that individual product trends mainly tracked with the TIRF medicines aggregate trend.

Rates of major medical outcomes/ deaths attributed to TIRF medicine exposure in poison control center data also increased, which is also concerning. There were no data to assess whether the rise in major medical outcomes/deaths was linked to the rise in abuse, and further data are needed on the reason for these major medical outcomes/deaths.

The results of other adverse outcomes are difficult to interpret due to low numbers of events. Prescription-adjusted rates of unintentional therapeutic errors, intentional misuse, and ED visits and hospitalizations increased from pre- to post-REMS, although estimates were imprecise.

Product-specific analyses of poison control center calls involving Fentora or Actiq/generic oral transmucosal lozenge also suggested their respective prescription-adjusted rates of ED visits and hospitalizations increased from pre- to post-REMS. In contrast, rates of poison center calls for unintentional general TIRF medicine exposures decreased among adults and children, but these events were extremely rare pre-REMS and post-REMS. FDA has requested additional data sources from the TRIG to generate a more robust evidence base, and the process of obtaining these data is ongoing.

Finally, we conclude that TIRF product-specific data are useful for understanding potential contributing factors to trends in aggregated TIRF medicines data and limitations of the data.

6 REFERENCES

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7 APPENDICES

7.1 RADARS® TREATMENT CENTER PROGRAMS COMBINED

Details of the Poisson regression model

Quoting from the Surveillance Data Monitoring report in the 72-month TIRF REMS Assessment:

> Two models are fit to the data, a comparison of means model and a comparison of trends model. In the comparison of means model, separate means are fit to the pre and post TIRF REMS periods. The pre to post changes in the mean outcome rates are calculated for each drug group. In the comparison of trends model, separate trend lines are fit to the pre and post TIRF REMS periods. Times are divided into two periods: Pre (3rd quarter 2010 through 2nd quarter 2012), and Post (3rd quarter 2012 through 2nd quarter 2017).
>
> The total number of events within each product group in the three-digit ZIP codes covered by the RADARS System each quarter are computed and used as the dependent variable in the Poisson regression models. The denominators of the rates (population, prescriptions dispensed, or dosage units dispensed) enter the model as an offset variable. A drug group-specific variance structure is fit, thus allowing for different variances in the TIRF REMS opioid group versus the comparators. The link function is the log link.
>
> For the means model, the Poisson regression model includes a period by drug group effect which is used to test whether:
>
> 1. The Pre to Post period means are equal for the TIRF REMS group.

2. The change in means from the Pre to Post period for the TIRF REMS group is equal to the change in means for the comparator group.

The Poisson regression piecewise linear models include separate intercepts for the interaction of drug group and period, and separate slopes for the interaction of drug group, period, and time. This model is used to test whether:

1. The Pre and Post period slopes are equal for the TIRF REMS group.

2. The change in slopes from the Pre to Post period for the TIRF REMS group is equal to the change in slopes for the comparator groups.

Table A1. RADARS® Treatment Center Programs Combined trend in past month abuse cases per 100,000 population, Q3 2010- Q2 2017

Drug Group	Time Period	Parameter	Estimate (95% CI)	Percentage Change (95% CI)	Ratio of Rate Ratios (95% CI)
TIRF Medicines	Pre TIRF REMS	Intercept	0.0226 (0.0177, 0.0288)	Reference	
		Slope	0.8554 (0.8190, 0.8934)	Reference	
	Post TIRF REMS	Intercept	0.0301 (0.0261, 0.0347)	33.31% (0.47%, 76.89%)	
		Slope	0.9871 (0.9739, 1.0004)	15.39% (10.26%, 20.76%)	
IR Oxycodone	Pre TIRF REMS	Intercept	0.1236 (0.0820, 0.1864)	Reference	
		Slope	0.8188 (0.7627, 0.8790)	Reference	
	Post TIRF REMS	Intercept	0.3077 (0.2567, 0.3690)	148.90% (58.86%, 289.98%)	1.8671 (1.0982, 3.1743)
		Slope	1.0026 (0.9864, 1.0191)	22.45% (13.86%, 31.70%)	1.0612 (0.9739, 1.1563)
ER Oxycodone	Pre TIRF REMS	Intercept	0.2876 (0.2469, 0.3349)	Reference	
		Slope	0.8796 (0.8556, 0.9043)	Reference	
	Post TIRF REMS	Intercept	0.2901 (0.2621, 0.3211)	0.88% (-15.99%, 21.15%)	0.7568 (0.5403, 1.0600)
		Slope	0.9750 (0.9654, 0.9846)	10.84% (7.63%, 14.15%)	0.9605 (0.9099, 1.0140)
IR Hydromorphone	Pre TIRF REMS	Intercept	0.2380 (0.2064, 0.2743)	Reference	
		Slope	0.9642 (0.9377, 0.9915)	Reference	
	Post TIRF REMS	Intercept	0.2558 (0.2361, 0.2771)	7.48% (-8.71%, 26.54%)	0.8062 (0.5816, 1.1176)
		Slope	0.9795 (0.9720, 0.9871)	1.59% (-1.31%, 4.57%)	0.8804 (0.8342, 0.9291)
IR Oxymorphone	Pre TIRF REMS	Intercept	0.1529 (0.1198, 0.1951)	Reference	
		Slope	0.9665 (0.8980, 1.0402)	Reference	
	Post TIRF REMS	Intercept	0.1221 (0.1085, 0.1373)	-20.16% (-39.12%, 4.71%)	0.5989 (0.4048, 0.8862)
		Slope	0.9821 (0.9711, 0.9932)	1.61% (-5.67%, 9.45%)	0.8806 (0.8071, 0.9608)

Source: RADARS® Surveillance Monitoring Report, 72-month TIRF REMS Assessment

Table A2. RADARS® Treatment Center Programs Combined trend in past month abuse cases per 10,000 prescriptions, Q3 2010- Q2 2017

Drug Group	Time Period	Parameter	Estimate (95% CI)	Percentage Change (95% CI)	Ratio of Rate Ratios (95% CI)
TIRF Medicines	Pre TIRF REMS	Intercept	23.7039 (18.5973, 30.2127)	Reference	
		Slope	0.9131 (0.8743, 0.9535)	Reference	
	Post TIRF REMS	Intercept	26.8632 (23.1895, 31.1188)	13.33% (-14.67%, 50.51%)	
		Slope	1.0413 (1.0268, 1.0560)	14.04% (8.97%, 19.36%)	
IR Oxycodone	Pre TIRF REMS	Intercept	0.2754 (0.1793, 0.4232)	Reference	
		Slope	0.8201 (0.7614, 0.8832)	Reference	
	Post TIRF REMS	Intercept	0.7367 (0.6087, 0.8916)	167.48% (67.18%, 327.95%)	2.3602 (1.3631, 4.0866)
		Slope	1.0036 (0.9865, 1.0210)	22.38% (13.41%, 32.07%)	1.0731 (0.9820, 1.1727)
ER Oxycodone	Pre TIRF REMS	Intercept	7.3304 (6.1152, 8.7870)	Reference	
		Slope	0.9377 (0.9074, 0.9691)	Reference	
	Post TIRF REMS	Intercept	6.6556 (5.8822, 7.5306)	-9.21% (-27.09%, 13.06%)	0.8012 (0.5597, 1.1467)
		Slope	0.9926 (0.9807, 1.0046)	5.85% (2.21%, 9.63%)	0.9282 (0.8763, 0.9831)
IR Hydromorphone	Pre TIRF REMS	Intercept	8.6586 (7.4282, 10.0928)	Reference	
		Slope	0.9491 (0.9209, 0.9781)	Reference	
	Post TIRF REMS	Intercept	9.4644 (8.6744, 10.3262)	9.31% (-8.36%, 30.38%)	0.9645 (0.6906, 1.3470)
		Slope	0.9904 (0.9821, 0.9987)	4.36% (1.15%, 7.67%)	0.9150 (0.8659, 0.9670)
IR Oxymorphone	Pre TIRF REMS	Intercept	118.6908 (76.9347, 183.1099)	Reference	
		Slope	1.1041 (0.9672, 1.2603)	Reference	
	Post TIRF REMS	Intercept	81.4473 (66.5219, 99.7216)	-31.38% (-57.47%, 10.73%)	0.6055 (0.3472, 1.0561)
		Slope	0.9711 (0.9523, 0.9902)	-12.05% (-23.06%, 0.55%)	0.7712 (0.6696, 0.8883)

Source: RADARS® Surveillance Monitoring Report, 72-month TIRF REMS Assessment

7.2 NATIONAL ADDICTIONS VIGILANCE INTERVENTION AND PREVENTION PROGRAM (NAVIPPRO™)

Table A3. Change in Mean of Quarterly Abuse Rate from Pre-REMS to Post-REMS, National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), Q3 2010 – Q2 2017

	Abuse cases, n		% Change in means	
Drug group	**Pre-period**	**Post-period**	**Per 100,000 assessments**	**Per 1,000,000 prescriptions**
TIRF (any product)	111	277	16.80	177.95
Actiq and generic lozenge	54	123	6.59	309.75
Fentora	41	119	35.82	204.88
Onsolis	25	55	2.97	
Oxycodone ER	8,457	13,272	-27.71	-3.58
Oxycodone IR	12,454	30,936	14.45	13.49
Oxymorphone IR	384	1,301	58.77	69.92
Hydromorphone IR	2,537	7,296	34.36	32.01
Fentanyl, unknown	196	665	58.77	NA

ER, extended-release; IR, immediate-release; NA, Not Applicable; TIRF, transmucosal immediate-release fentanyl

Source: Analysis and table by Inflexxion® through an FDA-conducted contract.

7.3 RADARS® POISON CENTER PROGRAM

Table A4. Rates of abuse exposure calls, RADARS® Poison Center Program (Q3 2010 – Q2 2017).

		Population-adjusted rate			Prescription-adjusted rate		
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
Abuse							
TIRF medicines	Pre TIRF REMS	0.0002 (0.0001,0.0005)	Reference		0.1929 (0.0793, 0.4694)	Reference	
	Post TIRF REMS	0.0003 (0.0002,0.0005)	38 (-45, 248)	Reference	0.5181 (0.3283, 0.8176)	169 (-1, 630)	Reference
IR oxycodone	Pre TIRF REMS	0.0894 (0.0841, 0.0951)	Reference		0.2320 (0.2175, 0.2475)	Reference	
	Post TIRF REMS	0.0641 (0.0613,0.0669)	-28 (-34, -23)	0.52 (0.20, 1.31)	0.1695 (0.1619, 0.1775)	-27 (-32, -21)	0.27 (0.10, 0.74)
ER oxycodone	Pre TIRF REMS	0.0409 (0.0351, 0.0477)	Reference		0.8477 (0.7648, 0.9396)	Reference	
	Post TIRF REMS	0.0190 (0.0166, 0.0217)	-54 (-62, -43)	0.34 (0.13, 0.87)	0.5501 (0.5022, 0.6025)	-35 (-43, -26)	0.24 (0.09, 0.66)
IR hydromorphone	Pre TIRF REMS	0.0111 (0.0091, 0.0135)	Reference		0.4657 (0.3937, 0.5509)	Reference	
	Post TIRF REMS	0.0105 (0.0093, 0.0119)	-45 (-24, 20%)	0.69 (0.26, 1.79)	0.4587 (0.4134, 0.5089)	-2 (-19, 20)	0.37 (0.13, 1.05)
IR oxymorphone	Pre TIRF REMS	0.0011 (0.0007, 0.0016)	Reference		0.6571 (0.4275, 1.0102)	Reference	
	Post TIRF REMS	0.0004 (0.0003, 0.0006)	-65 (-80, -38)	0.25 (0.08, 0.75)	0.2605 0.1679, 0.4042)	-60 (-78, -27)	0.15 (0.05, 0.48)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-**	**Ratio of Rate Ratios**

		Population-adjusted rate			Prescription-adjusted rate		
			REMS period			**REMS period**	
Intentional Misuse							
TIRF medicines	Pre TIRF REMS	0.0003 (0.0001, 0.0006)	Reference		0.2315 (0.1025, 0.5229)	Reference	
	Post TIRF REMS	0.0002 (0.0001, 0.0003)	-27 (-71, 81)		0.3272 (0.1839, 0.5822)	41 (-48, 283)	
IR oxycodone	Pre TIRF REMS	0.0998 (0.0935, 0.1065)	Reference		0.2589 (0.2433, 0.2754)	Reference	
	Post TIRF REMS	0.0779 (0.0745, 0.0814)	-22 (-27, -16)	1.08 (0.43, 2.68)	0.2060 (0.1975, 0.2149)	-20 (-26, -14)	0.56 (0.21, 1.53)
ER oxycodone	Pre TIRF REMS	0.0211 (0.0177, 0.0250)	Reference		0.4366 (0.3866, 0.4930)	Reference	
	Post TIRF REMS	0.0119 (0.0104, 0.0137)	-43 (-55, -29)	0.78 (0.30, 1.99)	0.3454 (0.3133, 0.3808)	-21 (-32, -8)	0.56 (0.20, 1.54)
IR hydromorphone	Pre TIRF REMS	0.0115 (0.0099, 0.0133)	Reference		0.4830 (0.4233, 0.5510)	Reference	
	Post TIRF REMS	0.0087 (0.0078, 0.0096)	-24 (-37, -10)	1.04 (0.41, 2.63)	0.3772 (0.3442, 0.4133)	-22 (-33, -8)	0.55 (0.20, 1.52)
IR oxymorphone	Pre TIRF REMS	0.0003 (0.0002, 0.0007)	Reference		0.1917 (0.0926, 0.3968)	Reference	
	Post TIRF REMS	0.0002 (0.0001, 0.0004)	-37.71 (-75.75, 60.04)	0.86 (0.23, 3.19)	0.1359 (0.0780, 0.2369)	-29.08 (-71.61, 77.16)	0.50 (0.13, 1.94)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
Unintentional Therapeutic Errors							

		Population-adjusted rate			Prescription-adjusted rate		
TIRF medicines	Pre TIRF REMS	0.0005 (0.0003, 0.0008)	Reference		0.4244 (0.2337, 0.7708)	Reference	
	Post TIRF REMS	0.0004 (0.0003, 0.0006)	-21 (-57, 47)		0.6544 (0.4370, 0.9801)	54 (-25, 217)	
IR oxycodone	Pre TIRF REMS	0.1454 (0.1371, 0.1543)	Reference		0.3772 (0.3564, 0.3993)	Reference	
	Post TIRF REMS	0.1390 (0.1340, 0.1442)	-4 (-11, 2)	1.21 (0.65, 2.24)	0.3677 (0.3551, 0.3808)	-2 (-9, 4)	0.63 (0.31, 1.30)
ER oxycodone	Pre TIRF REMS	0.0558 (0.0495, 0.0629)	Reference		1.1558 (1.0801, 1.2368)	Reference	
	Post TIRF REMS	0.0381 (0.0349, 0.0415)	-32 (-4, -21)	0.86 (0.46, 1.62)	1.1030 (1.0498, 1.1589)	-5 (-12, 4)	0.62 (0.30, 1.28)
IR hydromorphone	Pre TIRF REMS	0.0219 (0.0196, 0.0244)	Reference		0.9180 (0.8298, 1.0156)	Reference	
	Post TIRF REMS	0.0215 (0.0201, 0.0230)	-2 (-14, 12)	1.24 (0.66, 2.33)	0.9361 (0.8804, 0.9954)	2 (-9, 15)	0.66 (0.32, 1.37)
IR oxymorphone	Pre TIRF REMS	0.0008 (0.0005, 0.0014)	Reference		0.4929 (0.2957, 0.8215)	Reference	
	Post TIRF REMS	0.0006 (0.0004, 0.0009)	-25 (-61, 42)	0.94 (0.39, 2.29)	0.4191 (0.2935, 0.5985)	-15 (-55, 58)	0.55 (0.21, 1.43)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
Unintentional General Exposures							
TIRF medicines	Pre TIRF REMS	0.0004 (0.0002, 0.0008)	Reference		0.3473 (0.1699, 0.7097)	Reference	
	Post TIRF REMS	0.0001 (<0.0001,	-63.66 (-86.76, -0.30)		0.2454 (0.1201, 0.5016)	-29.33 (-74.28, 94.19)	

		Population-adjusted rate			Prescription-adjusted rate		
		0.0003)					
IR oxycodone	Pre TIRF REMS	0.0848 (0.0788, 0.0913)	Reference		0.2200 (0.2041, 0.2372)	Reference	
	Post TIRF REMS	0.0675 (0.0642, 0.0709)	-20.43 (-27.16, -13.07)	2.1899 (0.7951, 6.0318)	0.1786 (0.1697, 0.1879)	-18.85 (-25.90, -11.14)	1.1482 (0.4162, 3.1681)
ER oxycodone	Pre TIRF REMS	0.0152 (0.0131, 0.0177)	Reference		0.3156 (0.2833, 0.3516)	Reference	
	Post TIRF REMS	0.0095 (0.0084, 0.0106)	-37.99 (-48.63, -25.14)	1.7066 (0.6113, 4.7647)	0.2738 (0.2521, 0.2974)	-13.25 (-24.27, -0.62)	1.2276 (0.4427, 3.4041)
IR hydromorphone	Pre TIRF REMS	0.0059 (0.0049, 0.0070)	Reference		0.2472 (0.2083, 0.2935)	Reference	
	Post TIRF REMS	0.0050 (0.0044, 0.0056)	-15.78% (-32.02%, 4.34%)	2.3178 (0.8260, 6.5041)	0.2156 (0.1927, 0.2414)	-12.78 (-28.96, 7.09)	1.2342 (0.4400, 3.4621)
IR oxymorphone	Pre TIRF REMS	0.0003 (0.0001, 0.0005)	Reference		0.1643 (0.0814, 0.3316)	Reference	
	Post TIRF REMS	0.0002 (<0.0001, 0.0003)	-39.44 (-74.58, 44.26)	1.6667 (0.4403, 6.3094)	0.1133 (0.0657, 0.1952)	-31.05 (-71.64, 67.64)	0.9756 (0.2540, 3.7476)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
Unintentional General Pediatric Exposures							
TIRF medicines	Pre TIRF REMS	0.0004 (0.0002, 0.0008)	Reference		0.3473 (0.1705, 0.7071)	Reference	
	Post TIRF REMS	0.0001 (<0.0001, 0.0003)	-63.66 (-86.76, -0.28)		0.2454 (0.1205, 0.4997)	-29.33 (-74.15, 93.18)	

		Population-adjusted rate			Prescription-adjusted rate		
IR oxycodone	Pre TIRF REMS	0.0876 (0.0816, 0.0939)	Reference		0.2272 (0.2116, 0.2439)	Reference	
	Post TIRF REMS	0.0755 (0.0722, 0.0791)	-13.73 (-20.65, -6.21)	2.3742 (0.8622, 6.5378)	0.1998 (0.1908, 0.2093)	-12.03 (-19.17, -4.25)	1.2448 (0.4538, 3.4151)
ER oxycodone	Pre TIRF REMS	0.0152 (0.0131, 0.0176)	Reference		0.3147 (0.2841, 0.3486)	Reference	
	Post TIRF REMS	0.0093 (0.0083, 0.0104)	-38.57 (-48.93, -26.10)	1.6907 (0.6058, 4.7181)	0.2705 (0.2500, 0.2926)	-14.06 (-24.47, -2.21)	1.2161 (0.4412, 3.3520)
IR hydromorphone	Pre TIRF REMS	0.0059 (0.0049, 0.0072)	Reference		0.2491 (0.2074, 0.2993)	Reference	
	Post TIRF REMS	0.0052 (0.0046, 0.0059)	-12.79 (-30.56, 9.52)	2.4000 (0.8526, 6.7556)	0.2250 (0.1999, 0.2533)	-9.69 (-27.40, 12.35)	1.2780 (0.4567, 3.5763)
IR oxymorphone	Pre TIRF REMS	0.0003 (0.0001, 0.0005)	Reference		0.1643 (0.0814, 0.3316)	Reference	
	Post TIRF REMS	0.0002 (<0.0001, 0.0003)	-39.44 (-74.58, 44.26)	1.6667 (0.4402, 6.3102)	0.1133 (0.0657, 0.1952)	-31.05 (-71.64, 67.64)	0.9756 (0.2550, 3.7329)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
ED Visits / Hospitalizations							
TIRF medicines	Pre TIRF REMS	0.0015 (0.0011, 0.0020)	Reference		1.2478 (1.2093, 1.2876)	Reference	
	Post TIRF REMS	0.0012 (0.0009, 0.0014)	-20.51 (-44.91, 14.69)		1.2275 (1.2042, 1.2514)	55% (-1%, 141%)	
IR oxycodone	Pre TIRF REMS	0.4810 (0.4650, 0.4975)	Reference		2.7992 (2.6552, 2.9510)	Reference	

		Population-adjusted rate			Prescription-adjusted rate		
	Post TIRF REMS	0.4640 (0.4545, 0.4737)	-3.53% (-7.28, 0.36)	1.2136 (0.8393, 1.7549)	2.5082 (2.4104, 2.6099)	-1.63 (-5.18, 2.06)	0.5796 (0.3698, 0.9086)
ER oxycodone	Pre TIRF REMS	0.1351 (0.1214, 0.1504)	Reference		2.3995 (2.2354, 2.5757)	Reference	
	Post TIRF REMS	0.0866 (0.0799, 0.0938)	-35.95 (-43.99, -26.76)	0.8058 (0.5453, 1.1906)	2.5199 (2.4153, 2.6290)		0.6793 (0.4322, 1.0678)
IR hydromorphone	Pre TIRF REMS	0.0571 (0.0520, 0.0627)	Reference		1.3690 (1.0377, 1.8062)	Reference	
	Post TIRF REMS	0.0579 (0.0548, 0.0613)	1.41 (-9.08, 13.10)	1.2758 (0.8702, 1.8703)	0.8608 (0.6876, 1.0778)	5 (-3, 14)	0.4067 (0.2300, 0.7193)
IR oxymorphone	Pre TIRF REMS	0.0023 (0.0017, 0.0030)	Reference		1.2478 (1.2093, 1.2876)	Reference	
	Post TIRF REMS	0.0013 (0.0010, 0.0016)	-44.77 (-61.14, -21.50)	0.6949 (0.4181, 1.1548)	1.2275 (1.2042, 1.2514)	-37 (-56, -10)	0.6363 (0.4073, 0.9942)
Drug Group	**Time Period**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**	**Rate (95% CI)**	**Percentage change from Pre- to Post-REMS period**	**Ratio of Rate Ratios**
Major Medical Outcomes and Deaths							
TIRF medicines	Pre TIRF REMS	0.0002 (<0.0001, 0.0004)	Reference		0.1543 (0.0702, 0.3396)	Reference	
	Post TIRF REMS	0.0003 (0.0002, 0.0004)	54.43 (-31.00, 245.65)		0.4636 (0.3162, 0.6795)	200.35 (25.04, 621.44)	
IR oxycodone	Pre TIRF REMS	0.0413 (0.0383, 0.0445)	Reference		0.1071 (0.0993, 0.1156)	Reference	
	Post TIRF REMS	0.0424 (0.0406, 0.0443)	2.71 (-5.87, 12.06)	0.6651 (0.2957, 1.4956)	0.1122 (0.1072, 0.1174)	4.74 (-4.15, 14.44)	0.3487 (0.1445, 0.8414)

		Population-adjusted rate			Prescription-adjusted rate		
ER oxycodone	Pre TIRF REMS	0.0165 (0.0141, 0.0193)	Reference		0.3412 (0.3013, 0.3863)	Reference	
	Post TIRF REMS	0.0107 (0.0095, 0.0120)	-35.28 (-46.82, -21.24)	0.4191 (0.1829, 0.9604)	0.3089 (0.2815, 0.3390)	-9.46 (-22.47, 5.74)	0.3015 (0.1238, 0.7341)
IR hydromorphone	Pre TIRF REMS	0.0073 (0.0065, 0.0083)	Reference		0.3086 (0.2793, 0.3409)	Reference	
	Post TIRF REMS	0.0061 (0.0056, 0.0066)	-16.72 (-28.14, -3.49)	0.5393 (0.2377, 1.2233)	0.2661 (0.2492, 0.2842)	-13.75 (-23.47, -2.81)	0.2872 (0.1186, 0.6954)
IR oxymorphone	Pre TIRF REMS	0.0002 (0.0001, 0.0005)	Reference		0.1369 (0.0626, 0.2994)	Reference	
	Post TIRF REMS	0.0001 (<0.0001, 0.0003)	-34.59 (-75.21, 72.57)	0.4235 (0.1200, 1.4948)	0.1019 (0.0569, 0.1827)	-25.54 (-71.94, 97.59)	0.2479 (0.0668, 0.9203)

CI, confidence interval; ED, emergency department; ER, extended-release; IR, immediate-release; REMS, Risk Evaluation and Mitigation Strategy; TIRF, transmucosal immediate-release fentanyl

Source: RADARS® TIRF REMS Surveillance Monitoring Report, Table Numbers: 13.2.1.1, 13.2.1.2, 13.2.2.1, 13.2.2.2, 13.2.3.1, 13.2.3.2, 13.2.4.1, 13.2.4.2, 13.2.5.1, 13.2.5.2, 13.2.6.1, 13.2.6.2, 13.2.7.1, 13.2.7.2.

7.4 American Association of Poison Control Centers (AAPCC), National Poison Data System (NPDS)

Table A5. Number of exposure calls by transmucosal immediate release fentanyl (TIRF) product and Calendar Quarter, American Association of Poison Control Centers, National Poison Data System, Q3 2010 – Q2 2017.

	Abstral	Actiq and generics	Fentora	Lazanda	Onsolis	Subsys
2010 Q3	0	9	1	0	0	0
2010 Q4	0	7	1	0	0	0
2011 Q1	0	11	1	0	0	0
2011 Q2	0	2	4	0	0	0
2011 Q3	0	3	2	0	0	0
2011 Q4	0	4	4	0	0	0
2012 Q1	0	5	2	0	0	0
2012 Q2	0	2	1	0	0	0
2012 Q3	1	5	3	0	0	0
2012 Q4	0	4	0	0	0	0
2013 Q1	0	6	0	0	0	0
2013 Q2	0	2	0	1	0	2
2013 Q3	0	5	0	0	0	0
2013 Q4	0	2	0	0	0	1
2014 Q1	0	1	1	1	0	2
2014 Q2	1	4	2	0	0	0
2014 Q3	0	3	3	0	0	1
2014 Q4	0	5	0	0	0	3
2015 Q1	0	1	1	0	0	2
2015 Q2	0	2	1	1	0	3
2015 Q3	0	1	0	0	0	2
2015 Q4	0	2	1	0	0	3
2016 Q1	0	1	0	1	0	2
2016 Q2	0	6	0	1	0	0
2016 Q3	0	1	0	1	0	1
2016 Q4	0	2	0	0	0	2
2017 Q1	1	1	0	1	0	0
2017 Q2	0	3	0	1	0	2

Source: Table and Analysis by American Association of Poison Control Centers through an FDA contract; shading added by DEPI reviewer.

7.5 PERSISTENCY ANALYSIS

Excerpt from 72-month TIRF REMS Assessment Report, page 954:

"*Data source*
"The pharmacy switch database served as the data source of the persistency analysis and contains complete outpatient TIRF prescription data collected since the inception of the REMS (March 12, 2012). The TIRF REMS Access program is an ongoing effort, and the data cut-off for the persistency analysis is October 28, 2015. The data cut-off date was selected to correspond with the specification for the 48-month FDA Assessment Report. The dataset used for this analysis included anonymized data for paid claims only; rejected transactions and reversed claims were not included in the analysis. The following data elements were provided for each paid TIRF claim:

- Unique patient identification (ID)
- Date of birth
- Prescription number
- Prescription process date (filled date)
- Product name (brand or generic, as dispensed)
- National Drug Code (NDC) code
- Product strength
- Quantity dispensed
- Days' supply (As recorded in the pharmacy switch database, this may not equal actual days' supply since TIRF medicines are commonly used on an as needed basis and pharmacists ascribe the days' supply amount at the time of medication fill."

Table A6. Characteristics of Patients Enrolled in the REMS, by Number of TIRFs Filled: TIRF REMS Pharmacy Switch Database, March 12, 2012 – October 28, 2015

	Patients with only 1 Prescription Filled[1] (N=8,113)	Patients with >1 Prescription Filled[2] (N=18,160)	Total Patients (N=26,273)
Age (years)[3]			
Mean	55.4	52.6	53.5
SD	13.43	11.88	12.44
Median	56.0	53.1	53.9
Min, Max	0, 101	10, 104	0, 104
Year of entering REMS (n, %)			
2012	2,627 (32.4%)[6]	9,456 (52.1%)[7]	12,083 (46.0%)[8]
2013	2,764 (34.1%)[6]	4,282 (23.6%)[7]	7,046 (26.8%)[8]
2014	2,722 (33.6%)[6]	4,422 (24.4%)[7]	7,144 (27.2%)[8]
Total number of prescriptions filled (n)			
2012	2,627	80,090	82,717
2013	2,764	102,960	105,724
2014	2,722	108,860	111,582
2015[5]	N/A	67,195	67,195
Number of prescriptions filled per patient			
Mean	1.0	19.8	14.0
SD	0.00	26.22	23.46
Median	1.0	11.0	4.0
Min, Max	1, 1	2, 1074	1, 1074
Duration of follow-up (months) per patient[4]			
Median	27.6	35.0	32.2
Min, Max	12, 44	12, 44	12, 44

1 Patients with a single prescription filled for one TIRF medicine.

2 Patients with more than one prescription for a single TIRF medicine, or one or more prescriptions for multiple TIRF medicines.

3 (First prescription fill date – Date of birth) ÷ 365.25.

4 (Observation period end date – first prescription fill date + 1) × 12 ÷ 365.25.

5 Prescriptions filled until October 28, 2015, the date of data cut corresponding to the end of the observation period.

6 Denominator, n=8,113. Patients with a single prescription filled within the eligibility period, without a second prescription filled to confirm continuous use of TIRF therapy.

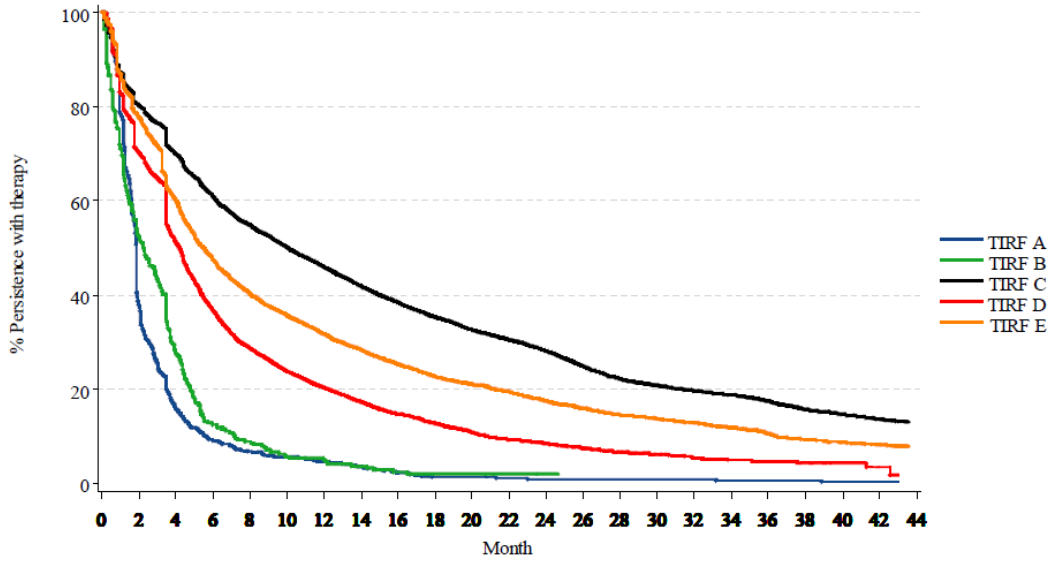
7 Denominator, n=18,160. Patients with at least two prescriptions filled for TIRF therapy, the analysis set for persistency analysis.

Source: 72-Month REMS Assessment Report, Persistency Analysis, Appendix 12.9, Table 1.

Product-level analysis

An analysis compared the percent of patients persistent with therapy by index product. While the products were blinded by random-letter assignment, it was evident that median time to discontinuation varied substantially by product.

Figure A1. Plot of percent of patients who were persistent with index TIRF regimen over time, TIRF REMS Pharmacy Switch Database, March 2012 – October 2014.



Kaplan-Meier Analysis where patients who are still on the TIRF regimen at the end of the follow-up period are counted as censored observations. TIRF products have been randomized to letter codes to maintain product blind. A separate randomization of product codes was performed for each table.

Source: 72-Month REMS Assessment Report, Persistency Analysis, Appendix 12.9, Figure 1a.

7.6 SURVEY OF NON-MEDICAL USE OF PRESCRIPTION DRUGS

Details of the weighting method used

National prevalence estimates were calculated by using post-stratification weights to represent the approximate age and gender distribution of the US adult population (ages 18 – 110). The 2015 U.S. Census Bureau residential population estimates were used to calculate weights in 48 strata defined by:

- U.S. Census region (Northeast, South, Midwest, West)
- Gender (female, male)
- Age categories (there were six, but the ranges were not given)

The formula for weighted national prevalence estimates was:

$$\sum_i cases_i * w_i / \sum_i population_i * 100$$

Table A7. Prevalence of Recent Non-Medical Use by College Student Status

Source: TIRF REMS Surveillance Monitoring Report, Table 13.2.9.1

	3rd Quarter 2016		1st Quarter 2017		3rd Quarter 2017	
Recent Non-Medical Use	**College Student % (95% CI)**	**Non-College Student % (95% CI)**	**College Student % (95% CI)**	**Non-College Student % (95% CI)**	**College Student % (95% CI)**	**Non-College Student % (95% CI)**
TIRF Medicines						
Last 12 Months			7.3 (6.29, 8.22)	2.9 (2.70, 3.13)	2.1 (1.55, 2.57)	0.5 (0.44, 0.61)
Last 90 Days	2.9 (2.26, 3.54)	2.5 (2.28, 2.68)	2.5 (1.87, 3.05)	1.3 (1.13, 1.42)	0.4 (0.20, 0.68)	0.1 (0.10, 0.20)
Last 30 Days	2.6 (1.97, 3.16)	2.3 (2.16, 2.54)	2.3 (1.76, 2.89)	1.2 (1.09, 1.38)	0.4 (0.18, 0.62)	0.1 (0.10, 0.19)
Last 7 Days	2.5 (1.89, 3.07)	2.1 (1.96, 2.33)	2.0 (1.48, 2.56)	1.1 (0.96, 1.23)	0.4 (0.18, 0.62)	0.1 (0.09, 0.18)
IR Oxycodone						
Last 12 Months			3.9 (3.18, 4.69)	1.5 (1.35, 1.66)	4.1 (3.40, 4.81)	1.6 (1.46, 1.76)
Last 90 Days	1.6 (1.06, 2.08)	0.9 (0.81, 1.05)	1.0 (0.61, 1.34)	0.5 (0.38, 0.56)	1.1 (0.75, 1.51)	0.6 (0.50, 0.68)
Last 30 Days	1.2 (0.80, 1.69)	0.8 (0.67, 0.89)	0.7 (0.43, 1.06)	0.4 (0.33, 0.50)	0.9 (0.60, 1.30)	0.5 (0.42, 0.59)
Last 7 Days	1.1 (0.66, 1.46)	0.6 (0.53, 0.72)	0.7 (0.39, 0.99)	0.3 (0.27, 0.42)	0.7 (0.43, 1.03)	0.4 (0.32, 0.47)
ER Oxycodone						
Last 12 Months			3.2 (2.50, 3.82)	1.3 (1.15, 1.44)	3.7 (3.04, 4.41)	1.2 (1.09, 1.36)
Last 90 Days	1.4 (0.93, 1.95)	0.7 (0.57, 0.77)	0.6 (0.31, 0.89)	0.4 (0.31, 0.48)	0.7 (0.38, 0.95)	0.4 (0.34, 0.50)
Last 30 Days	1.3 (0.82, 1.81)	0.6 (0.47, 0.65)	0.5 (0.27, 0.83)	0.3 (0.26, 0.41)	0.5 (0.28, 0.78)	0.4 (0.30, 0.44)
Last 7 Days	1.1 (0.62, 1.52)	0.5 (0.39, 0.56)	0.5 (0.22, 0.73)	0.3 (0.21, 0.34)	0.5 (0.23, 0.71)	0.3 (0.21, 0.34)
IR Hydromorphone						
Last 12 Months			1.0 (0.66, 1.34)	0.3 (0.21, 0.34)	1.9 (1.41, 2.38)	0.5 (0.46, 0.63)
Last 90 Days	0.3 (0.12, 0.50)	0.3 (0.23, 0.37)	0.2 (0.07, 0.39)	0.1 (0.05, 0.13)	0.5 (0.27, 0.77)	0.2 (0.14, 0.24)
Last 30 Days	0.3 (0.10, 0.45)	0.3 (0.21, 0.35)	0.2 (0.05, 0.34)	0.1 (0.05, 0.13)	0.5 (0.25, 0.74)	0.2 (0.11, 0.21)

	3rd Quarter 2016		1st Quarter 2017		3rd Quarter 2017	
Last 7 Days	0.2 (0.07, 0.41)	0.3 (0.19, 0.32)	0.2 (0.03, 0.30)	0.1 (0.05, 0.12)	0.5 (0.23, 0.68)	0.1 (0.08, 0.17)
Recent Non-Medical Use	**College Student % (95% CI)**	**Non-College Student % (95% CI)**	**College Student % (95% CI)**	**Non-College Student % (95% CI)**	**College Student % (95% CI)**	**Non-College Student % (95% CI)**
IR Oxymorphone						
Last 12 Months			1.6	0.3	2.0	0.5
Last 90 Days	0.5 (0.24, 0.77)	0.3 (0.27, 0.41)	0.4 (0.12, 0.59)	0.1 (0.07, 0.16)	0.7 (0.39, 0.95)	0.2 (0.11, 0.21)
Last 30 Days	0.5 (0.21, 0.73)	0.3 (0.25, 0.39)	0.4 (0.12, 0.59)	0.1 (0.07, 0.15)	0.7 (0.39, 0.95)	0.1 (0.09, 0.18)
Last 7 Days	0.5 (0.21, 0.73)	0.3 (0.23, 0.36)	0.3 (0.10, 0.55)	0.1 (0.06, 0.14)	0.6 (0.37, 0.92)	0.1 (0.07, 0.15)

Table A8. Reported Non-Medical Use Odds Ratio, College Students Relative to Non-College Students: RADARS® Survey of Non-Medical Use of Prescription Drugs Program

Source TIRF REMS Surveillance Monitoring Report, Tables 13.3.9.2 – 13.2.9.4

	Odds Ratio (95% CI)		
Drug Group	**3rd Quarter 2016**	**1st Quarter 2017**	**3rd Quarter 2017**
TIRF Medicines	1.176 (0.924, 1.497)	1.952 (1.488, 2.561)	2.962 (1.582, 5.544)
IR Oxycodone	1.694 (1.187, 2.417)	2.100 (1.374, 3.211)	1.917 (1.319, 2.788)
ER Oxycodone	2.166 (1.466, 3.198)	1.532 (0.906, 2.590)	1.585 (0.992, 2.533)
IR Hydromorphone	1.029 (0.530, 1.997)	2.569 (1.132, 5.831)	2.741 (1.581, 4.751)
IR Oxymorphone	1.488 (0.836, 2.646)	3.117 (1.469, 6.615)	4.115 (2.455, 6.898)

Example of Approved PI for TIRF Medicine Product

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

See full prescribing information for complete boxed warning.

- **Serious, life-threatening, and/or fatal respiratory depression has occurred. Monitor closely, especially upon initiation or following a dose increase. Due to the risk of fatal respiratory depression, fentanyl buccal tablets are contraindicated in opioid non-tolerant patients (1) and in management of acute or postoperative pain, including headache/migraines. (5.1)**
- **Accidental ingestion of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl. Keep out of reach of children. Ensure proper storage and disposal. (5.2)**
- **Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of fentanyl. (5.3, 7, 12.3)**
- **Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.4, 7)**
- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl product to fentanyl buccal tablets. (5.5)**
- **When dispensing, do not substitute with any other fentanyl products. (5.5)**
- **Fentanyl buccal tablets expose users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor closely for these behaviors and conditions. (5.6)**
- **Fentanyl buccal tablets are available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program. (5.7)**
- **Prolonged use of fentanyl buccal tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.8)**

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

Boxed Warning	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

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

Fentanyl buccal tablets are an opioid agonist indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. (1)

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

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, or dental pain.
- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to patients enrolled in the TIRF REMS Access program. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

----------DOSAGE AND ADMINISTRATION----------

- Patients must require and use around-the-clock opioids when taking fentanyl buccal tablets. (1)
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initial dose of fentanyl buccal tablets: 100 mcg. (2.2)
- Initiate titration using multiples of 100 mcg fentanyl buccal tablets. Limit patient access to only one strength of fentanyl buccal tablets at any one time. (2.3)
- Individually titrate to a tolerable dose that provides adequate analgesia using single fentanyl buccal tablets. (2.4)
- No more than two doses can be taken per breakthrough pain episode. (2.2)
- Wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets. (2.2)
- Place entire tablet in buccal cavity or under the tongue; tablet is not to be split, crushed, sucked, chewed or swallowed whole. (2.5)
- When opioid therapy is no longer required, consider discontinuing fentanyl buccal tablets along with a gradual downward of other opioids to minimize possible withdrawal effects. (2.6)

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

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

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

- Opioid non-tolerant patients. (4)
- Management of acute or postoperative pain, including headache/migraine and dental pain. (4)
- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Known hypersensitivity to fentanyl or components of fentanyl buccal tablets. (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected. (5.10)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.11)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of fentanyl buccal tablets in patients with circulatory shock. (5.12)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of fentanyl buccal tablets in patients with impaired consciousness or coma. (5.13)
- Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding. (5.18)

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with fentanyl buccal tablets because they may reduce analgesic effect of fentanyl buccal tablets or precipitate withdrawal symptoms. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause fetal harm. (8.1)

- Lactation: Not recommended. (8 2)
- Renal and Hepatic Impairment: Administer fentanyl buccal tablets with caution. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; RISKS FROM CYTOCHROME P450 3A4 INTERACTION; RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS; RISK OF MEDICATION ERRORS; ADDICTION, ABUSE, AND MISUSE; REMS; and NEONATAL OPIOID WITHDRAWAL SYNDROME

Life-Threatening Respiratory Depression

Serious life-threatening and/or fatal respiratory depression has occurred in patients treated with fentanyl buccal tablets, including following use in opioid non-tolerant patients and improper dosing. Monitor for respiratory depression, especially during initiation of fentanyl buccal tablets or following a dose increase. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.1)]*.

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

Accidental Ingestion

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in a fatal overdose of fentanyl *[see Warnings and Precautions (5.2)]*.

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products. Fentanyl buccal tablets must be kept out of reach of children *[see Warnings and Precautions (5.2)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of fentanyl buccal tablets with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl buccal tablets and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- **Reserve concomitant prescribing of fentanyl buccal tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

Risk of Medication Errors

Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products that result in clinically important differences in the extent of absorption of fentanyl and that could result in fatal overdose *[see Dosage and Administration (2.1), Warnings and Precautions (5.5)]*.

- **When prescribing, do not convert patients on a mcg per mcg basis from any other fentanyl products to fentanyl buccal tablets *[see Dosage and Administration (2.1)]*.**
- **When dispensing, do not substitute a fentanyl buccal tablets prescription for other fentanyl products.**

Addiction, Abuse, and Misuse

Fentanyl buccal tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing fentanyl buccal tablets, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.6)]*.

Risk Evaluation and Mitigation Strategy (REMS) Access Program

Because of the risk for misuse, abuse, addiction, and overdose, fentanyl buccal tablets are available only through a restricted program required by the Food and Drug Administration, called a Risk Evaluation and Mitigation Strategy (REMS). Under the Transmucosal Immediate Release Fentanyl (TIRF) REMS Access program, outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors must enroll in the program *[see Warnings and Precautions (5.7)]*. Further information is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.8)]*.

1 INDICATIONS AND USAGE

Fentanyl buccal tablets are indicated for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

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

Limitations of Use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, and dental pain *[see Contraindications (4)]*.

- As a part of the TIRF REMS Access program, fentanyl buccal tablets may be dispensed only to outpatients enrolled in the program *[see Warnings and Precautions (5.7)]*. For inpatient administration of fentanyl buccal tablets (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- Healthcare professionals who prescribe fentanyl buccal tablets on an outpatient basis must enroll in the TIRF REMS Access program and comply with the requirements of the REMS to ensure safe use of fentanyl buccal tablets *[see Warnings and Precautions (5.7)]*.
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- It is important to minimize the number of strengths available to patients at any time to prevent confusion and possible overdose.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.6)]*.
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with fentanyl buccal tablets and adjust the dosage accordingly *[see Warnings and Precautions (5.1)]*.
- Instruct patients and caregivers to take steps to store fentanyl buccal tablets securely and to properly dispose of unused fentanyl buccal tablets as soon as no longer needed *[see Warnings and Precautions (5.2, 5.6), Patient Counseling Information (17)]*.
- Fentanyl buccal tablets are not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. There are no conversion directions available for patients on any other fentanyl products other than ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Warnings and Precautions (5.5)]*.
- Fentanyl buccal tablets are NOT a generic version of any other transmucosal fentanyl product *[see Warnings and Precautions (5.5)]*.

2.2 Initial Dosage

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

Patients on ACTIQ

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

Table 1. Initial Dosing Recommendations for Patients on ACTIQ

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

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

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

Repeat Dosing

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

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

2.3 Dose Titration

a. From an initial dose, closely follow patients and change the dosage strength until the patient reaches a dose that provides adequate analgesia with tolerable side effects. Patients should record their use of fentanyl buccal tablets over several episodes of breakthrough pain and discuss their experience with their healthcare provider to determine if a dosage adjustment is warranted.

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

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

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

e. Patients should be strongly encouraged to use all of their fentanyl buccal tablets of one strength prior to being prescribed the next strength. If this is not practical, unused fentanyl buccal tablets should be disposed of safely *[see How Supplied/Storage and Handling (16)]*. Dispose of any unopened fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.

2.4 Maintenance Dosing

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

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

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

d. Dosage adjustment of fentanyl buccal tablets may be required in some patients.
Generally, the fentanyl buccal tablets dose should be increased only when a single administration of the current dose fails to adequately treat the breakthrough pain episode for several consecutive episodes.

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

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

2.5 Administration of Fentanyl Buccal Tablets

Opening the Blister Package:

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

Tablet Administration:

Once the tablet is removed from the blister unit, the patient should immediately place the entire fentanyl buccal tablet in the buccal cavity (above a rear molar, between the upper cheek and gum) or place the entire fentanyl buccal tablet under the tongue. Patients should not split the tablet.
The fentanyl buccal tablet should not be crushed, sucked, chewed or swallowed whole, as this will result in lower plasma concentrations than when taken as directed.
The fentanyl buccal tablet should be left between the cheek and gum or under the tongue until it has disintegrated, which usually takes approximately 14-25 minutes.
After 30 minutes, if remnants from the fentanyl buccal tablet remain, they may be swallowed with a glass of water.
It is recommended that patients alternate sides of the mouth when administering subsequent doses of fentanyl buccal tablets in the buccal cavity.

2.6 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing fentanyl buccal tablets along with a gradual downward titration of other opioids to minimize possible withdrawal effects. In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, fentanyl buccal tablets therapy can usually be discontinued immediately. *[see Drug Abuse and Dependence (9.3*

2.7 Disposal of Fentanyl Buccal Tablets

To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush fentanyl buccal tablets blister packages or cartons down the toilet. If you need additional assistance with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279.

3 DOSAGE FORMS AND STRENGTHS

Fentanyl buccal tablets are flat-faced, round, beveled-edge in shape; are white in color; and are available in 100 mcg, 200 mcg, 400 mcg, 600 mcg, and 800 mcg strengths as fentanyl base. Each tablet strength is marked with a unique identifier *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Fentanyl Buccal Tablets are contraindicated in:

- Opioid non-tolerant patients: Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients *[see Indications and Usage (1); Warnings and Precautions (5.1)]*.
- Significant respiratory depression *[see Warnings and Precautions (5.1)]*.
- Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department *[see Indications and Usage (1)]*.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.9)]*.
- Known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.14)]*.
- Known hypersensitivity (e.g. anaphylaxis) to fentanyl or components of fentanyl buccal tablets (e.g., anaphylaxis) *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of fentanyl buccal tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of fentanyl buccal tablets.

To reduce the risk of respiratory depression, proper dosing and titration of fentanyl buccal tablets are essential *[see Dosage and Administration (2.3)]*. Overestimating the fentanyl buccal tablets dosage can result in a fatal overdose with the first dose. The substitution of fentanyl buccal tablets for any other fentanyl product may result in fatal overdose *[see Warnings and Precautions (5.5)]*.

Fentanyl buccal tablets could be fatal to individuals for whom it is not prescribed and for those who are not opioid-tolerant.

Accidental ingestion of even one dose of fentanyl buccal tablets, especially by children, can result in respiratory depression and death due to an overdose of fentanyl.

5.2 Increased Risk of Overdose in Children Due to Accidental Ingestion or Exposure

Death has been reported in children who have accidentally ingested transmucosal immediate-release fentanyl products.

Patients and their caregivers must be informed that fentanyl buccal tablets contain a medicine in an amount which can be fatal to a child. Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure.

Patients and their caregivers must be instructed to keep both used and unused dosage units out of the reach of children. While all units should be disposed of immediately after use, partially consumed units represent a special risk to children. In the event that a unit is not completely consumed it must be properly disposed as soon as possible *[see Patient Counseling Information (17)]*.

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

5.3 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of fentanyl buccal tablets with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression *[see Warnings and Precautions (5.1)]*, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in fentanyl buccal tablets-treated patients may increase fentanyl plasma concentrations and prolong opioid adverse reactions. When using fentanyl buccal tablets with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in fentanyl buccal tablets-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved *[see Drug Interactions (7)]*.

Concomitant use of fentanyl buccal tablets with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease fentanyl plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. When using fentanyl buccal tablets with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur *[see Drug Interactions (7)]*.

5.4 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants (including Alcohol)

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of fentanyl buccal tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics *[see Drug Interactions (7)]*.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when fentanyl buccal tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

5.5 Risk of Medication Errors

When prescribing, do not convert a patient to fentanyl buccal tablets from any other fentanyl product on a mcg per mcg basis as fentanyl buccal tablets and other fentanyl products are not equivalent on a microgram per microgram basis.

Fentanyl buccal tablets are not a generic version of other transmucosal immediate release fentanyl (TIRF) formulations. When dispensing, do not substitute a fentanyl buccal tablets prescription for any other TIRF formulation under any circumstances. Other TIRF formulations and fentanyl buccal tablets are not equivalent. Substantial differences exist in the pharmacokinetic profile of fentanyl buccal tablets compared to other fentanyl products including other TIRF formulations that result in clinically important differences in the rate and extent of absorption of fentanyl. As a result of these differences, the substitution of fentanyl buccal tablets or any other fentanyl product may result in a fatal overdose.

There are no safe conversion directions available for patients on any other fentanyl products except ACTIQ (Note: This includes oral, transdermal, or parenteral formulations of fentanyl.) *[see Dosage and Administration (2.1)]*.Therefore, for opioid tolerant patients, the initial dose of fentanyl buccal tablets should always be 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects *[see Dosage and Administration (2.3)]*.

5.6 Addiction, Abuse, and Misuse

Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance. As an opioid, fentanyl buccal tablets expose users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed fentanyl buccal tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing fentanyl buccal tablets, and monitor all patients receiving fentanyl buccal tablets for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as fentanyl buccal tablets, but use in such patients necessitates intensive counseling about the risks and proper use of fentanyl buccal tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing fentanyl buccal tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

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

Because of the risk for misuse, abuse, addiction, and overdose *[see Drug Abuse and Dependence (9)]*, fentanyl buccal tablets are available only through a restricted program called the TIRF REMS Access program. Under the TIRF REMS Access program, outpatients, healthcare professionals who prescribe for outpatient use, pharmacies, and distributors must enroll in the program. For inpatient administration (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use) of fentanyl buccal tablets, patient and prescriber enrollment is not required.

Required components of the TIRF REMS Access program are:

- Healthcare professionals, who prescribe fentanyl buccal tablets for outpatient use, must review the prescriber educational materials for the TIRF REMS Access program, enroll in the program, and comply with the REMS requirements.
- To receive fentanyl buccal tablets, outpatients must understand the risks and benefits and sign a Patient-Prescriber Agreement.
- Pharmacies that dispense fentanyl buccal tablets must enroll in the program and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute fentanyl buccal tablets must enroll in the program, and distribute only to authorized pharmacies.
- Further information, including a list of qualified pharmacies/distributors, is available at www.TIRFREMSAccess.com or by calling 1-866-822-1483.

5.8 Neonatal Opioid Withdrawal Syndrome

Prolonged use of fentanyl buccal tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1), Patient Counseling Information (17)]*.

5.9 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of fentanyl buccal tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: fentanyl buccal tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of fentanyl buccal tablets *[see Warnings and Precautions (5.1)]*.

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients *[see Warnings and Precautions (5.1)]*.

Monitor such patients closely, particularly when initiating and titrating fentanyl buccal tablets and when fentanyl buccal tablets are given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.1)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.10 Serotonin Syndrome with Concomitant Use of Serotonergic Drugs

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of fentanyl buccal tablets with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

Fentanyl buccal tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g. phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. Monitor these patients for signs of hypotension after initiating or titrating the dosage of fentanyl buccal tablets. In patients with circulatory shock, fentanyl buccal tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of fentanyl buccal tablets in patients with circulatory shock.

5.13 Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

In patients who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or brain tumors), fentanyl buccal tablets may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with fentanyl buccal tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of fentanyl buccal tablets in patients with impaired consciousness or coma.

5.14 Risks of Use in Patients with Gastrointestinal Conditions
Fentanyl buccal tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The fentanyl in fentanyl buccal tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

5.15 Increased Risk of Seizures in Patients with Seizure Disorders
The fentanyl in fentanyl buccal tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during fentanyl buccal tablets therapy.

5.16 Risks of Driving and Operating Machinery
Fentanyl buccal tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of fentanyl buccal tablets and know how they will react to the medication.

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

5.18 Application Site Reactions
Application site reactions occurred in 10% of patients in clinical trials and ranged from paresthesia to ulceration and bleeding *[see Adverse Reactions (6)]*.

5.19 MAO Inhibitors
Fentanyl buccal tablets are not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS
The following serious adverse reactions are described, or described in greater detail, in other sections:

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.1)]*
- Interactions with Benzodiazepines and Other CNS Depressants *[see Warnings and Precautions (5.4)]*
- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.6)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.8)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.11)]*
- Severe Hypotension *[see Warnings and Precautions (5.12)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.14)]*
- Seizures *[see Warnings and Precautions (5.15)]*

6.1 Clinical Studies Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of fentanyl. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders:

- Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.
Endocrine Disorders:
- Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.
- Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.
Immune System Disorders:
- Anaphylaxis: Anaphylaxis has been reported with ingredients contained in fentanyl buccal tablets.
General Disorders and Administration Site Conditions: Drug withdrawal syndrome

7 DRUG INTERACTIONS

Table 4 includes clinically significant drug interactions with fentanyl buccal tablets.

Table 4: Clinically Significant Drug Interactions with Fentanyl Buccal Tablets

Inhibitors of CYP3A4	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inhibitors can increase the plasma concentration of fentanyl, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of fentanyl buccal tablets is achieved *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the fentanyl plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to fentanyl.
Intervention	If concomitant use is necessary, consider dosage reduction of fentanyl buccal tablets until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), protease inhibitors (e.g., ritonavir), grapefruit juice
CYP3A4 Inducers	
Clinical Impact	The concomitant use of fentanyl buccal tablets and CYP3A4 inducers can decrease the plasma concentration of fentanyl *[see Clinical Pharmacology (12.3)]*, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to fentanyl *[see Warnings and Precautions (5.3)]*. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.
Intervention	If concomitant use is necessary, consider increasing the fentanyl buccal tablets dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider fentanyl buccal tablets dosage reduction and monitor for signs of respiratory depression.
Examples	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation *[see Warnings and Precautions (5.4)]*.
Examples	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.10)]*.
Intervention	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue fentanyl buccal tablets if serotonin syndrome is suspected.
Examples	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact	MAOI interactions with opioids may manifest as serotonin syndrome *[see Warnings and Precautions (5.10)]* or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.1)]*.
Intervention	The use of fentanyl buccal tablets is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples	Phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact	May reduce the analgesic effect of fentanyl buccal tablets and/or precipitate withdrawal symptoms.
Intervention	Avoid concomitant use.
Examples	Butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact	Fentanyl may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of fentanyl buccal tablets and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention	Monitor patients for signs of urinary retention or reduced gastric motility when fentanyl buccal tablets are used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.8)]*. Available data with fentanyl buccal tablets in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, fentanyl administration to pregnant rats during organogenesis was embryocidal at doses within the range of the human recommended dosing. When administered during gestation through lactation fentanyl administration to pregnant rats resulted in reduced pup survival at doses within the range of the human recommended dosing. No evidence of malformations were noted in animal studies completed to date *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset of neonatal withdrawal symptoms usually occurs in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.8)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. Fentanyl buccal tablets are not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including fentanyl buccal tablets, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Animal Data

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

Fentanyl has been shown to embryocidal in pregnant rats at doses of 30 mcg/kg intravenously (0.4 times the 800 mcg dose of fentanyl buccal tablets on a mg/m^2 basis) from GD 6 to 18 and 160 mcg/kg subcutaneously (2 times the 800 mcg dose of fentanyl buccal tablets based on a mg/m^2 basis). No evidence of teratogenicity was reported.

No evidence of malformations or adverse effects on the fetus was reported in a published study in which pregnant rats were administered fentanyl continuously via subcutaneously implanted osmotic minipumps at doses of 10, 100, or 500 mcg/kg/day starting 2-weeks prior to breeding and throughout pregnancy. The high dose was approximately 6 times the human dose of 800 mcg fentanyl buccal tablets per pain episode on a mg/m^2 basis and produced mean steady-state plasma levels that are approximately 5 times higher than the mean C_{max} observed following administration of 800 mcg dose of fentanyl buccal tablets in humans.

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

8.2 Lactation

Risk Summary

Fentanyl is present in breast milk. One published lactation study reports a relative infant dose of fentanyl of 0.024%. However, there is insufficient information to determine the effects of fentanyl on the breastfed infant and the effects of fentanyl on milk production.

Because of the potential for serious adverse reactions, including excess sedation and respiratory depression in a breastfed infant, advise patients that breastfeeding is not recommended during treatment with fentanyl buccal tablets.

Clinical Considerations

Monitor infants exposed to fentanyl buccal tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2) Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

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

8.5 Geriatric Use
Of the 304 patients with cancer in clinical studies of fentanyl buccal tablets, 69 (23%) were 65 years of age and older. Patients over the age of 65 years tended to titrate to slightly lower doses than younger patients. Patients over the age of 65 years reported a slightly higher frequency for some adverse events specifically vomiting, constipation, and abdominal pain. Therefore, caution should be exercised in individually titrating fentanyl buccal tablets in elderly patients to provide adequate efficacy while minimizing risk.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of fentanyl buccal tablets slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.9)]*.

Fentanyl is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Patients with Renal or Hepatic Impairment
Insufficient information exists to make recommendations regarding the use of fentanyl buccal tablets in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system and mostly eliminated in urine. If the drug is used in these patients, it should be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

8.7 Sex
Both male and female opioid tolerant patients with cancer were studied for the treatment of breakthrough cancer pain. No clinically relevant sex differences were noted either in dosage requirement or in observed adverse reactions.

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

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Fentanyl buccal tablets contain fentanyl, a Schedule II controlled substance.

9.2 Abuse
Fentanyl buccal tablets contain fentanyl, a substance with high potential for abuse similar to other opioids including hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol. Fentanyl buccal tablets can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.6)]*.
All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

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

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance *[see Drug Abuse and Dependence (9.3)]*. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Fentanyl buccal tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

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

Risks Specific to the Abuse of Fentanyl Buccal Tablets
Fentanyl buccal tablets are for oral transmucosal use only. Abuse of fentanyl buccal tablets poses a risk of overdose and death. This risk is increased with concurrent abuse of fentanyl buccal tablets with alcohol and other central nervous system depressants.

9.3 Dependence

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

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene) mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

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

10 OVERDOSAGE

Clinical Presentation

Acute overdose with fentanyl buccal tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to fentanyl overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to fentanyl overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of fentanyl in fentanyl buccal tablets, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

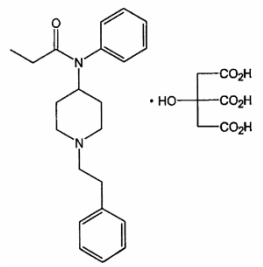
In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

11 DESCRIPTION

Fentanyl buccal tablets are an opioid agonist, intended for buccal mucosal administration.
Fentanyl buccal tablets are designed to be placed and retained within the buccal cavity for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa.

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

Active Ingredient: Fentanyl citrate, USP is N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The molecular weight of the free base is 336.5 (the citrate salt is 528.6). The pKa of the tertiary nitrogens are 7.3 and 8.4. The compound has the following structural formula:



All tablet strengths are expressed as the amount of fentanyl free base, e.g., the 100 microgram strength tablet contains 100 micrograms of fentanyl free base.
Inactive Ingredients: Mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid agonist whose principal therapeutic action is analgesia.

12.2 Pharmacodynamics

Effects on the Central Nervous System

The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu* opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug. Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem to both increases in carbon dioxide and to electrical stimulation.
Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System
Fentanyl produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating, and/or orthostatic hypotension.

Effects on the Endocrine System
Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon *[see Adverse Reactions (6.2)]*. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System
Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships
The analgesic effects of fentanyl are related to the blood level of the drug, if proper allowance is made for the delay into and out of the CNS (a process with a 3- to 5-minute half-life).

In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance with any and all opioids. The rate of development of tolerance varies widely among individuals *[see Dosage and Administration (2.1)]*.

The minimum effective analgesic concentration of fentanyl for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Reaction Relationships
There is a relationship between increasing fentanyl plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.2, 2.3, 2.4)]*.

Respiratory System
All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects. Peak respiratory depressive effects may be seen as early as 15 to 30 minutes from the start of oral transmucosal fentanyl citrate product administration and may persist for several hours.

Serious or fatal respiratory depression can occur even at recommended doses. Although not observed with oral transmucosal fentanyl products in clinical trials, fentanyl given rapidly by intravenous injection in large doses may interfere with respiration by causing rigidity in the muscles of respiration *[see Warnings and Precautions (5.1)]*.

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

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

In a study that compared the absolute and relative bioavailability of fentanyl buccal tablets and ACTIQ (oral transmucosal fentanyl citrate), the rate and extent of fentanyl absorption were considerably different (approximately 30% greater exposure with fentanyl buccal tablets) (Table 5).

Table 5. Pharmacokinetic Parameters* in Adult Subjects Receiving Fentanyl Buccal Tablets or ACTIQ

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

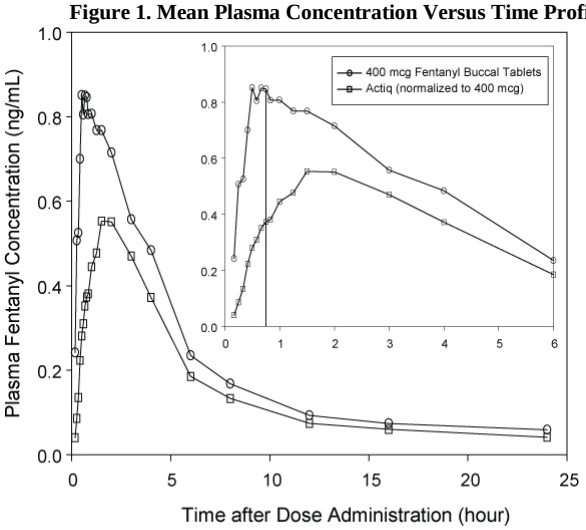
$AUC_{0\text{-}inf}$ (ng•hr/mL)	6.48 ± 2.98	4.79 ± 1.96

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

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

Due to differences in drug delivery, measures of exposure (C_{max}, $AUC_{0\text{-}tmax}$, $AUC_{0\text{-}inf}$) associated with a given dose of fentanyl buccal tablets compared to ACTIQ (see Figure 1). Therefore, caution must be exercised when switching patients from one product to another *[see Dosage and Administration (2.2) and Warnings and Precautions (5.5)]*. Figure 1 includes an inset which shows the mean plasma concentration versus time profile to 6 hours. The vertical line denotes the median T_{max} for fentanyl buccal tablets.

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



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

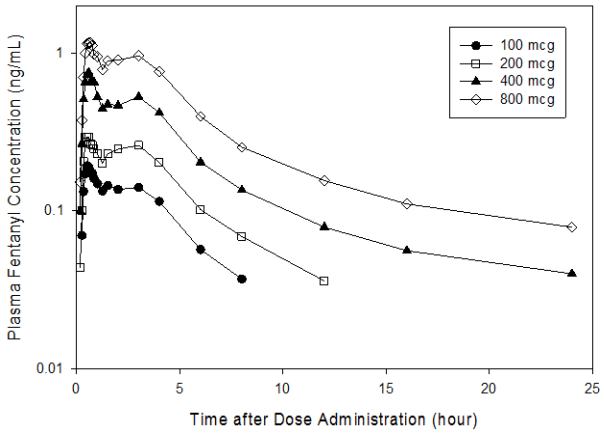
Mean pharmacokinetic parameters are presented in Table 6. Mean plasma concentration versus time profiles are presented in Figure 2.

Table 6. Pharmacokinetic Parameters* Following Single 100, 200, 400, and 800 mcg Doses of Fentanyl Buccal Tablets in Healthy Subjects

Pharmacokinetic Parameter (mean±SD)	100 mcg	200 mcg	400 mcg	800 mcg
C_{max} (ng/mL)	0.25 ± 0.14	0.40 ± 0 18	0.97 ± 0.53	1.59 ± 0.90
T_{max}, minute (range)**	45.0 (25.0 - 181.0)	40.0 (20.0 - 180.0)	35.0 (20.0 - 180.0)	40.0 (25.0 - 180.0)
$AUC_{0\text{-}inf}$ (ng•hr/mL)	0.98 ± 0.37	2.11 ± 1 13	4.72 ± 1.95	9.05 ± 3.72
$AUC_{0\text{-}tmax}$ (ng•hr/mL)	0.09 ± 0.06	0.13 ± 0.09	0.34 ± 0.23	0.52 ± 0.38
$T_{1/2}$, hr**	2.63 (1.47 - 13.57)	4.43 (1.85 - 20.76)	11.09 (4.63 - 20.59)	11.70 (4.63 - 28.63)

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

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



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

The effect of mucositis (Grade 1) on the pharmacokinetic profile of fentanyl buccal tablets was studied in a group of patients with (N = 8) and without mucositis (N = 8) who were otherwise matched. A single 200 mcg tablet was administered, followed by sampling at appropriate intervals. Mean summary statistics (standard deviation in parentheses, expected t_{max} where range was used) are presented in Table 7.

Table 7. Pharmacokinetic Parameters in Patients with Mucositis

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

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

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

Elimination

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

Excretion
Disposition of fentanyl following buccal administration of fentanyl buccal tablets has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Fentanyl was evaluated for carcinogenic potential in a 104-week rat study and in a 6-month Tg.AC transgenic mouse study. In rats, doses up to 50 mcg/kg in males and 100 mcg/kg in females were administered subcutaneously and no treatment-related neoplasms were observed (doses are equivalent to 2 3- and 3.4-times the exposure of a single human dose of 800 mcg per pain episode, respectively, based on an AUC comparison). In a 26-week transgenic mice model (Tg.AC), at topical doses up to 50 mcg/dose/day, no increase in the occurrence of treatment-related neoplasms was observed.

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

Impairment of Fertility

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

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg IV and 160 mcg/kg subcutaneously. Conversion to the human equivalent doses indicates that this is within the range of the human recommended dosing for fentanyl buccal tablets.

14 CLINICAL STUDIES

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

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

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

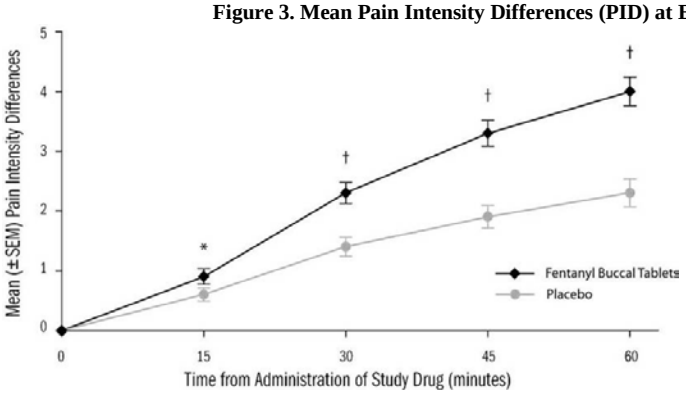
Sixty-five percent (65%) of patients who entered the study achieved a successful dose during the titration phase. The distribution of successful doses is shown in Table 8. The median dose was 400 mcg.

Table 8. Successful Dose of Fentanyl Buccal Tablets Following Initial Titration

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

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

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



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

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

Storage and Handling
Store at 20 to 25 C (68 to 77 F) with excursions permitted between 15 and 30 C (59 to 86 F) until ready to use. (See USP Controlled Room Temperature.)
Protect fentanyl buccal tablets from freezing and moisture. Do not use if the blister package has been tampered with.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Life-Threatening Respiratory Depression
Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting fentanyl buccal tablets or when the dosage is increased, and that it can occur even at recommended dosages *[see Warnings and Precautions (5.1)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Increased Risk of Overdose and Death in Children Due to Accidental Ingestion

- Healthcare providers and dispensing pharmacists must specifically question patients or caregivers about the presence of children in the home (on a full time or visiting basis) and counsel them regarding the dangers to children from inadvertent exposure *[see Warnings and Precautions (5.2)]*.
- Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.
- Instruct patients to take steps to store fentanyl buccal tablets securely and to dispose of unused fentanyl buccal tablets *[see Dosage and Administration (2.7), Patient Counseling Information; Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed (17)]*.
- Instruct patients and caregivers to keep both used and unused fentanyl buccal tablets out of the reach of children *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and Other CNS Depressants (including Alcohol)
Inform patients that potentially fatal additive effects may occur if fentanyl buccal tablets are used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

Addiction, Abuse, and Misuse
Inform patients that the use of fentanyl buccal tablets, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death *[see Warnings and Precautions (5.6)]*. Instruct patients not to share fentanyl buccal tablets with others and to take steps to protect fentanyl buccal tablets from theft or misuse.

Transmucosal Immediate-Release Fentanyl (TIRF) REMS
Advise patients of the following information pertaining to the TIRF REMS

- Inform outpatients that they must be enrolled in the TIRF REMS Access program before they can receive fentanyl buccal tablets.
- Allow patients the opportunity to ask questions and discuss any concerns regarding fentanyl buccal tablets or the TIRF REMS Access program.
- As required by the TIRF REMS Access program, review the contents of the fentanyl buccal tablets Medication Guide with every patient before initiating treatment with fentanyl buccal tablets.
- Advise the patient that fentanyl buccal tablets is available only from pharmacies that are enrolled in the TIRF REMS Access program, and provide them with the telephone number and website for information on how to obtain the drug.
- Advise the patient that only enrolled healthcare providers may prescribe fentanyl buccal tablets.
- Inform the patient that they must sign the Patient-Prescriber Agreement to acknowledge that they understand the risks of fentanyl buccal tablets.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the TIRF REMS Access program *[see Warnings and Precautions (5.7)]*.

Serotonin Syndrome
Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.10), Drug Interactions (7)]*.

MAOI Interaction
Inform patients to avoid taking fentanyl buccal tablets while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking fentanyl buccal tablets *[see Warnings and Precautions (5.10, 5.19); Drug Interactions (7)]*.

Adrenal Insufficiency
Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.11)]*.

Important Administration Instructions *[see Dosage and Administration (2)]*

- Instruct patients not to take fentanyl buccal tablets for acute pain, postoperative pain, pain from injuries, headache, migraine or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and that fentanyl buccal tablets are only to be used as a supplemental pain medication for patients with pain requiring around-the-clock opioids, who have developed tolerance to the opioid medication, and who need additional opioid treatment of breakthrough pain episodes.
- Instruct patients that, if they are not taking an opioid medication on a scheduled basis (around-the-clock), they should not take fentanyl buccal tablets.
- Instruct patients that the titration phase is the only period in which they may take more than ONE tablet to achieve a desired dose (e.g., two 100 mcg tablets for a 200 mcg dose).
- Instruct patients that, if the breakthrough pain episode is not relieved after 30 minutes, they may take ONLY ONE ADDITIONAL DOSE OF FENTANYL BUCCAL TABLETS USING THE SAME STRENGTH FOR THAT EPISODE. Thus, patients should take a maximum of two doses of fentanyl buccal tablets for any breakthrough pain episode.
- Instruct patients that they MUST wait at least 4 hours before treating another episode of breakthrough pain with fentanyl buccal tablets.
- Instruct patients NOT to share fentanyl buccal tablets and that sharing fentanyl buccal tablets with anyone else could result in the other individual's death due to overdose.
- Make patients aware that fentanyl buccal tablets contain fentanyl which is a strong pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Instruct patients not to open the blister until ready to use fentanyl buccal tablets and not to store the tablet in a temporary container such as a pill box, once it has been removed from the blister package.

- Instruct patients that fentanyl buccal tablets are not to be swallowed whole; this will reduce the effectiveness of the medication. Tablets are to be placed between the cheek and gum above a molar tooth or under the tongue and allowed to dissolve. After 30 minutes if remnants of the tablet still remain, patients may swallow it with a glass of water.
- Caution patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking fentanyl buccal tablets.
- Instruct patients to use fentanyl buccal tablets exactly as prescribed by their doctor and not to take fentanyl buccal tablets more often than prescribed.
- Provide patients and their caregivers with a Medication Guide each time fentanyl buccal tablets are dispensed because new information may be available.

Hypotension
Inform patients that fentanyl buccal tablets may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.12)]*.

Anaphylaxis
Inform patients that anaphylaxis have been reported with ingredients contained in fentanyl buccal tablets. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome
Inform patients that prolonged use of fentanyl buccal tablets can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity
Inform female patients of reproductive potential that fentanyl buccal tablets can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy *[see Use in Specific Populations (8.1)Nonclinical Toxicology (13.1)]*.

Lactation
Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility
Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Driving or Operating Heavy Machinery
Inform patients that fentanyl buccal tablets may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.16)]*.

Constipation
Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention *[see Adverse Reactions (6), Clinical Pharmacology (12.2)]*.

Disposal of Unopened Fentanyl Buccal Tablets Blister Packages When No Longer Needed
- Patients and members of their household must be advised to dispose of any unopened blister packages remaining from a prescription as soon as they are no longer needed.
- To dispose of unused fentanyl buccal tablets, remove fentanyl buccal tablets from blister packages and flush down the toilet. Do not flush the fentanyl buccal tablets blister packages or cartons down the toilet.
- Detailed instructions for the proper storage, administration, disposal, and important instructions for managing an overdose of fentanyl buccal tablets are provided in the fentanyl buccal tablets Medication Guide. Instruct patients to read this information in its entirety and provide an opportunity to have their questions answered.
- In the event that a caregiver requires additional assistance in disposing of excess unusable tablets that remain in the home after a patient has expired, instruct them to call the Teva Pharmaceuticals toll-free number (1-888-483-8279) or seek assistance from their local DEA office.

FBT-003

Distributed By:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454

Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:

Do not use fentanyl buccal tablets unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep fentanyl buccal tablets in a safe place away from children.

Get emergency help right away if:

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

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

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. Fentanyl buccal tablets are started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use fentanyl buccal tablets if you are not opioid tolerant.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using fentanyl buccal tablets. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
- Fentanyl buccal tablets are available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive fentanyl buccal tablets, you must:
  - talk to your healthcare provider
  - understand the benefits and risks of fentanyl buccal tablets
  - agree to all of the instructions
  - sign the Patient-Prescriber Agreement form
- Fentanyl buccal tablets are only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your fentanyl buccal tablets prescription filled.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take fentanyl buccal tablets if:

- You are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- You are allergic to any of the ingredients in fentanyl buccal tablets See the end of this Medication Guide for a complete list of ingredients in fentanyl buccal tablets.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.

- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Instructions for Use at the end of this Medication Guide for information about how to use fentanyl buccal tablets.**
- **Use fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- Wait 30 minutes after using fentanyl buccal tablets. If there is any of the fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- You must not use more than 2 doses of fentanyl buccal tablets for each episode of breakthrough cancer pain.
- Use **1** dose of fentanyl buccal tablets for an episode of breakthrough cancer pain.
- If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of fentanyl buccal tablets, you can use **only 1** more dose of fentanyl buccal tablets as instructed by your healthcare provider.
- If your breakthrough pain does not get better after the second dose of fentanyl buccal tablets, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tablets at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tablets.
- If you only need to take 1 dose of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.
- If you need to use 2 doses of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using fentanyl buccal tablets.
- Talk to your healthcare provider if your dose of fentanyl buccal tablets does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tablets needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.
- Do not stop taking fentanyl buccal tablets without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **DO NOT Switch from fentanyl buccal tablets to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tablets is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of fentanyl buccal tablets that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- Pain, irritation, or sores at the application site (on your gum, on the inside of your cheek, or under your tongue). Tell your healthcare provider if this is a problem for you.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not take any more fentanyl buccal tablets until you have talked to your healthcare provider.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

How should I store fentanyl buccal tablets?

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

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

- **Dispose of any unused fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 or call your local Drug Enforcement Agency (DEA) office.**

General information about fentanyl buccal tablets

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

This Medication Guide summarizes the most important information about fentanyl buccal tablets. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your pharmacist or healthcare provider for information about fentanyl buccal tablets that is written for health professionals.

For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients in fentanyl buccal tablets?
Active Ingredient: fentanyl citrate
Inactive Ingredients: mannitol, sodium starch glycolate, sodium bicarbonate, sodium carbonate, citric acid, and magnesium stearate.

Patient Instructions for Use

Before you use fentanyl buccal tablets, it is important that you read the Medication Guide and these Instructions for Use. Be sure that you read, understand, and follow these Instructions for Use so that you use fentanyl buccal tablets the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use fentanyl buccal tablets.

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

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

XXX mcg **(See Figure 1).**

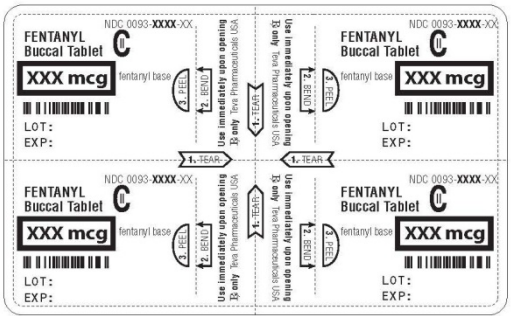


Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

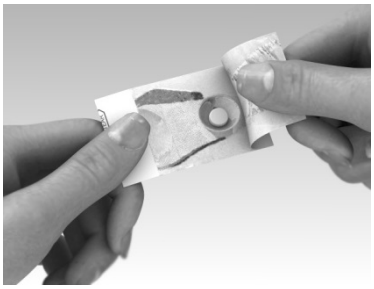


Figure 2

- **Do not push the tablet through the foil on the blister unit because this could damage the tablet.**
- **When removed from the blister unit, fentanyl buccal tablets must be used right away.**
- **Use fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- **You can place a fentanyl buccal tablet:**
  - **in your mouth above a rear molar tooth between the upper cheek and gum (See Figure 3). Switch (alternate) sides of your mouth for each dose.**

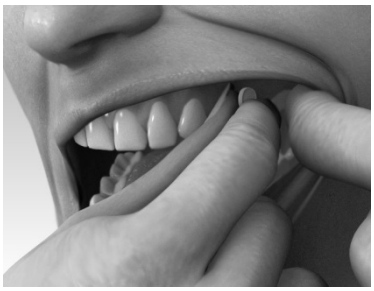


Figure 3

OR,

o **on the floor of your mouth, under your tongue (See Figures 4a, 4b, 4c, 4d).**

- **When placing the tablet under your tongue, first lift your tongue (4b), then place the tablet under your tongue (4c), and lower your tongue over the tablet (4d).**

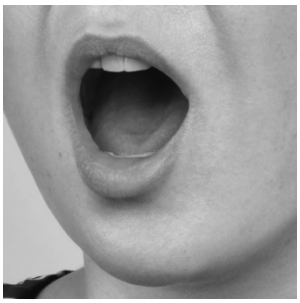


Figure 4a

Figure 4b

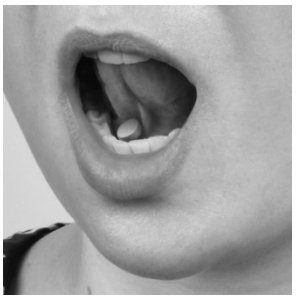


Figure 4c

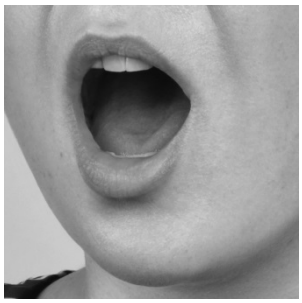


Figure 4d

- **Leave the tablet in place until it dissolves. A fentanyl buccal tablet generally takes between 14 to 25 minutes to dissolve.**
- **After 30 minutes, if there is any fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.**
- **If you cannot use fentanyl buccal tablets in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do.**

Distributed by:
Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454 call 1-888-483-8279

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Printed in USA

Medication Guide
Fentanyl Buccal Tablets, CII

IMPORTANT:

Do not use fentanyl buccal tablets unless you are regularly using another opioid pain medicine around-the-clock for at least one week or longer for your cancer pain and your body is used to these medicines (this means you are opioid tolerant). You can ask your healthcare provider if you are opioid tolerant.

Keep fentanyl buccal tablets in a safe place away from children.

Get emergency help right away if:

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

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

Fentanyl buccal tablets are:

- A strong prescription pain medicine that contain an opioid (narcotic) that is used to manage breakthrough pain in adults with cancer who are already routinely taking other opioid pain medicines around-the-clock for cancer pain. Fentanyl buccal tablets are started only after you have been taking other opioid pain medicines and your body has become used to them (you are opioid tolerant). Do not use fentanyl buccal tablets if you are not opioid tolerant.
- An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.

Important information about fentanyl buccal tablets:

- **Get emergency help right away if you take too much fentanyl buccal tablets (overdose).** When you first start taking fentanyl buccal tablets, when your dose is changed, or if you take too much (overdose), serious life-threatening breathing problems that can lead to death may occur.
- Taking fentanyl buccal tablets with other medicines that may make you sleepy, such as other pain medicines, anti-depressants, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers, or with alcohol or street drugs can cause severe drowsiness, confusion, breathing problems, coma, and death.
- Never give anyone else your fentanyl buccal tablets. They could die from taking it. Store fentanyl buccal tablets away from children and in a safe place to prevent stealing or abuse. Selling or giving away fentanyl buccal tablets is against the law.
- If you stop taking your around-the-clock opioid pain medicine for your cancer pain, **you must stop** using fentanyl buccal tablets. You may no longer be opioid tolerant. Talk to your healthcare provider about how to treat your pain.
- Fentanyl buccal tablets are available only through a program called the **T**ransmucosal **I**mmediate **R**elease **F**entanyl (TIRF) **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Access program. To receive fentanyl buccal tablets, you must:
  - talk to your healthcare provider
  - understand the benefits and risks of fentanyl buccal tablets
  - agree to all of the instructions
  - sign the Patient-Prescriber Agreement form
- Fentanyl buccal tablets are only available at pharmacies that are part of the TIRF REMS Access program. Your healthcare provider will let you know the pharmacy closest to your home where you can have your fentanyl buccal tablets prescription filled.
- Be very careful about taking other medicines that may make you sleepy, such as other pain medicines, anti-depressant medicines, sleeping pills, anti-anxiety medicines, antihistamines, or tranquilizers.
- Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Do not take fentanyl buccal tablets if:

- You are not opioid tolerant. Opioid tolerant means that you are already taking other opioid pain medicines around-the-clock for at least one week or longer for your cancer pain, and your body is used to these medicines.
- You have severe asthma, trouble breathing, or other lung problems.
- You have a bowel blockage or have narrowing of the stomach or intestines.
- You are allergic to any of the ingredients in fentanyl buccal tablets See the end of this Medication Guide for a complete list of ingredients in fentanyl buccal tablets.
- You have short-term pain that you would expect to go away in a few days, such as:
  - pain after surgery
  - headache or migraine
  - dental pain

Before taking fentanyl buccal tablets, tell your healthcare provider if you have a history of:

- Troubled breathing or lung problems such as asthma, wheezing, or shortness of breath
- head injury, seizures
- slow heart rate or other heart problems
- low blood pressure
- abuse of street or prescription drugs, alcohol addiction, or mental health problems
- mental problems [including major depression, schizophrenia or hallucinations (seeing or hearing things that are not there)]
- problems urinating
- liver, kidney, thyroid problems
- pancreas or gallbladder problem

Tell your healthcare provider if you are:

- **pregnant or planning to become pregnant.** Prolonged use of fentanyl buccal tablets during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Fentanyl buccal tablets pass into breast milk and may harm your baby.
- taking prescription over-the-counter medicines, vitamins, or herbal supplements. Taking fentanyl buccal tablets with certain other medicines can cause serious side effects that could lead to death.

When taking fentanyl buccal tablets:

- Do not change your dose. Take fentanyl buccal tablets exactly as prescribed by your healthcare provider.
- Your healthcare provider will change the dose until you and your healthcare provider find the right dose for you.
- **See the detailed Instructions for Use at the end of this Medication Guide for information about how to use fentanyl buccal tablets.**
- **Use fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**

- Wait 30 minutes after using fentanyl buccal tablets. If there is any of the fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.
- You must not use more than 2 doses of fentanyl buccal tablets for each episode of breakthrough cancer pain.
- Use **1** dose of fentanyl buccal tablets for an episode of breakthrough cancer pain.
- If your breakthrough cancer pain does not get better 30 minutes after taking the first dose of fentanyl buccal tablets, you can use **only 1** more dose of fentanyl buccal tablets as instructed by your healthcare provider.
- If your breakthrough pain does not get better after the second dose of fentanyl buccal tablets, call your healthcare provider for instructions. **Do not use another dose of fentanyl buccal tablets at this time.**
- Wait at least **4** hours before treating a new episode of breakthrough cancer pain with fentanyl buccal tablets.
- If you only need to take 1 dose of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours from the time of that dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.
- If you need to use 2 doses of fentanyl buccal tablets for an episode of breakthrough pain, you must wait 4 hours after the second dose to take a dose of fentanyl buccal tablets for a **new** episode of breakthrough pain.
- It is important for you to keep taking your around-the-clock opioid pain medicine while using fentanyl buccal tablets.
- Talk to your healthcare provider if your dose of fentanyl buccal tablets does not relieve your breakthrough cancer pain. Your healthcare provider will decide if your dose of fentanyl buccal tablets needs to be changed.
- Talk to your healthcare provider if you have more than 4 episodes of breakthrough cancer pain per day. The dose of your around-the-clock opioid pain medicine may need to be adjusted.
- If you begin to feel dizzy, sick to your stomach, or very sleepy before the tablet is completely dissolved, rinse your mouth with water and spit the remaining pieces of the tablet into a sink or toilet right away. Rinse the sink or flush the toilet to dispose of any remaining tablet pieces.
- Do not stop taking fentanyl buccal tablets without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependency is not the same as drug addiction.
- After you stop taking, or when fentanyl buccal tablets is no longer needed, see "**How should I dispose of unused fentanyl buccal tablets when they are no longer needed**?" for proper disposal of fentanyl buccal tablets.
- **DO NOT** Drive or operate heavy machinery, until you know how fentanyl buccal tablets affect you. Fentanyl buccal tablets can make you sleepy, dizzy, or lightheaded.
- **DO NOT** Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with fentanyl buccal tablets may cause you to overdose and die.
- **DO NOT Switch from fentanyl buccal tablets to other medicines that contain fentanyl without talking with your healthcare provider.** The amount of fentanyl in a dose of fentanyl buccal tablets is not the same as the amount of fentanyl in other medicines that contain fentanyl. Your healthcare provider will prescribe a starting dose of fentanyl buccal tablets that may be different than other fentanyl containing medicines you may have been taking.

The possible side effects of fentanyl buccal tablets:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, low red blood cell count, swelling of the arms, hands, legs and feet Call your healthcare provider if you have any of these symptoms and they are severe.
- Decreased blood pressure. This can make you feel dizzy or lightheaded if you get up too fast from sitting or lying down.
- Pain, irritation, or sores at the application site (on your gum, on the inside of your cheek, or under your tongue). Tell your healthcare provider if this is a problem for you.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- These symptoms can be a sign that you have taken too much fentanyl buccal tablets or the dose is too high for you. **These symptoms may lead to serious problems or death if not treated right away. If you have any of these symptoms, do not take any more fentanyl buccal tablets until you have talked to your healthcare provider.**

These are not all the possible side effects of fentanyl buccal tablets. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

How should I store fentanyl buccal tablets?

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

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

- **Dispose of any unused fentanyl buccal tablets remaining from a prescription as soon as they are no longer needed.**
  - **Remove the tablets from blister packages and flush them down the toilet.**
- **Do not flush the fentanyl buccal tablets packaging (card, blister units or cartons) down the toilet.**
- **If you need help with disposal of fentanyl buccal tablets, call Teva Pharmaceuticals at 1-888-483-8279 or call your local Drug Enforcement Agency (DEA) office.**

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

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For more information about the TIRF REMS Access program, go to www.TIRFREMSAccess.com or call 1-866-822-1483.

What are the ingredients in fentanyl buccal tablets?
Active Ingredient: fentanyl citrate

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

Patient Instructions for Use

Before you use fentanyl buccal tablets, it is important that you read the Medication Guide and these Instructions for Use. Be sure that you read, understand, and follow these Instructions for Use so that you use fentanyl buccal tablets the right way. Ask your healthcare provider or pharmacist if you have any questions about the right way to use fentanyl buccal tablets.

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

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

XXX mcg **(See Figure 1).**

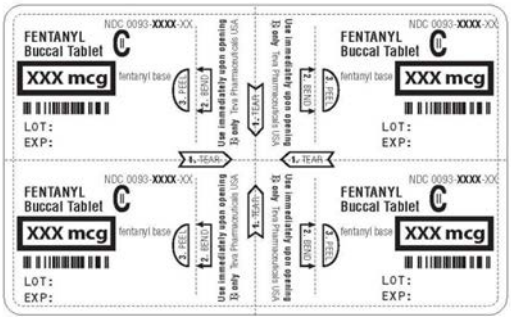

Figure 1

- **Peel back foil on blister unit to expose tablet (See Figure 2).**

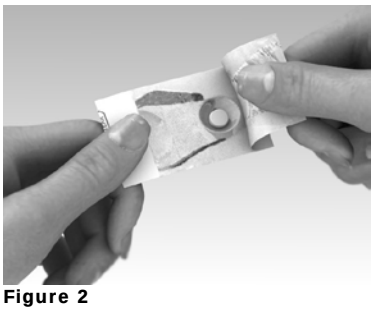

Figure 2

- **Do not push the tablet through the foil on the blister unit because this could damage the tablet.**
- **When removed from the blister unit, fentanyl buccal tablets must be used right away.**
- **Use fentanyl buccal tablets whole.**
- **Do not crush, split, suck, or chew fentanyl buccal tablets, or swallow the tablets whole. You will get less relief for your breakthrough cancer pain.**
- **You can place a fentanyl buccal tablet:**
  - **in your mouth above a rear molar tooth between the upper cheek and gum (See Figure 3). Switch (alternate) sides of your mouth for each dose.**

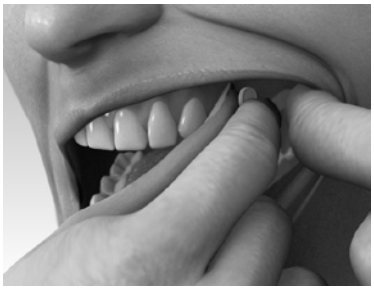

Figure 3

OR,

- **on the floor of your mouth, under your tongue (See Figures 4a, 4b, 4c, 4d).**

- **When placing the tablet under your tongue, first lift your tongue (4b), then place the tablet under your tongue (4c), and lower your tongue over the tablet (4d).**

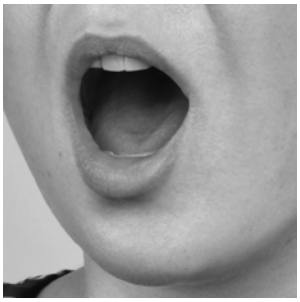
Figure 4a


Figure 4b

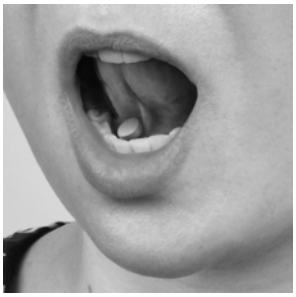
Figure 4c

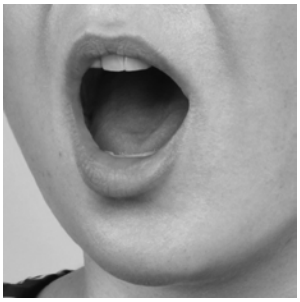
Figure 4d

- **Leave the tablet in place until it dissolves. A fentanyl buccal tablet generally takes between 14 to 25 minutes to dissolve.**
- **After 30 minutes, if there is any fentanyl buccal tablet left in your mouth, you may drink a glass of water to help you swallow the left over medicine.**
- **If you cannot use fentanyl buccal tablets in this manner, tell your healthcare provider. Your healthcare provider will tell you what to do.**

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