Questions and Answers: FDA approves a class Risk Evaluation and Mitigation Strategy (REMS) for transmucosal immediate-release fentanyl (TIRF) medicines

On December 23, 2020, FDA approved modifications for the transmucosal immediate-release fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of these drugs continue to outweigh the risks. The Agency required this modification based on information from the REMS assessment reports suggesting many patients prescribed a TIRF medicine may not have been opioid-tolerant when they received a new prescription for a TIRF medicine.

FDA initially approved a shared system REMS for the entire class of TIRF medicines on December 28, 2011. The TIRF REMS was the first approved shared system REMS for drugs in the opioid class. TIRF medicines are used to manage breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. 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 person who is not opioid tolerant. TIRF medicines also carry the risks associated with other opioid medications including the risk of misuse, abuse, addiction, and overdose.

The modified TIRF REMS consists of a restricted distribution program for TIRF medicines to ensure safe use of these medicines, including use only in opioid-tolerant patients. This program was strengthened to:

- Require that prescribers document a patient's opioid tolerance with each prescription of a TIRF medicine for outpatient use.
- Require outpatient pharmacies dispensing TIRF medicines to document and verify a patient's opioid tolerance before dispensing.
- Require inpatient pharmacies to develop internal policies and procedures to verify opioid tolerance in patients who require TIRF medicines while hospitalized.
- Require a new patient registry for use, along with other data sources to monitor for accidental exposure, misuse, abuse, addiction, and overdose.

The following questions and answers provide an overview of the modified shared system REMS for TIRF medicines.

Q1. What are transmucosal immediate-release fentanyl (TIRF) medicines?

A. TIRF medicines contain fentanyl, a prescription opioid pain reliever. TIRF medicines are used to manage breakthrough pain in cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain. Breakthrough pain is pain that comes on suddenly for short periods of time and is not alleviated by a patient's normal pain management plan.

The current list of TIRF medicines include Actiq (fentanyl citrate) oral transmucosal lozenge and its generic equivalents, Fentora (fentanyl citrate) buccal tablet and its generic equivalents, Lazanda (fentanyl citrate) nasal spray, Onsolis (fentanyl citrate) buccal, Subsys (fentanyl) sublingual spray and fentanyl citrate sublingual tablets.

Q2. What is a Risk Evaluation and Mitigation Strategy (REMS)?

A. A REMS is a risk management plan that uses risk minimization strategies beyond approved labeling to manage serious risks associated with a drug. Under the Food and Drug Administration Amendments Act of 2007, FDA has the authority to require Applicants or Application holders to develop and comply with REMS programs if FDA determines a REMS is necessary to ensure that the benefits of a drug outweigh its risks.

A REMS can include a Medication Guide or patient package insert, communication plan for healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, one or more elements to assure safe use, an implementation system, and a timetable for submission of the REMS assessments.

Q3. Why did the FDA require modifications to the TIRF REMS?

A. The Agency required this modification based on information from the REMS assessment reports suggesting many patients prescribed a TIRF medicine may not have been opioid-tolerant when they received a new prescription for a TIRF medicine as well as recommendations from the August 3, 2018 joint meeting of the Drug Safety and Risk Management and the Anesthetic and Analgesic Drug Products Advisory Committees (/advisory-committees/advisory-committee-calendar/august-3-2018-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and). The risk of life-threatening respiratory depression is greatest in patients who are not opioid tolerant and are taking a TIRF medicine. In order to ensure benefits outweigh the risks of the TIRF medicines, modifications to the TIRF REMS were necessary to ensure that patients are opioid-tolerant with every prescription dispensed for outpatient use.

As described in approved labeling for these products, patients are considered opioid tolerant if they are currently taking (exclusive of a TIRF medicine) one or more of the following opioid regimens daily and have been on the regimen(s) for one week or longer:

- ≥ 60 mg oral morphine/day
- ≥ 25 mg oral oxymorphone/day
- ≥ 25 mcg transdermal fentanyl/hour
- ≥ 60 mg oral hydrocodone/day
- ≥ 30 mg oral oxycodone/day
- ≥ 8 mg oral hydromorphone/day
- an equianalgesic dose of another opioid

Q4. What should patients know about the new requirements in the TIRF REMS program?

A. Recent changes to the TIRF REMS require that healthcare providers enroll patients into the REMS who are prescribed TIRF medicines for outpatient use. Prescribers are required to document opioid tolerance for each patient prior to each prescription. Patients should be counseled by their prescriber about the safe use of TIRF medicines, including proper storage, and safe disposal. The prescriber will provide the patient a Medication Guide for the TIRF

he/she is prescribed as well as a Patient Counseling Guide. Patients will be asked to read the Medication Guide and Patient Counseling Guide provided to them by their prescriber. Patients must remain opioid tolerant to continue using a TIRF medicine. Patients must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.

Patients can then take their prescription to an enrolled pharmacy. Patients can locate an enrolled pharmacy by consulting their prescriber or calling the TIRF REMS program at 1-866-822-1483. This phone number will be available in March 2021 when the TIRF REMS Access program "goes live."

There are no changes for patients who receive TIRF medicines in an inpatient setting. In the inpatient setting, patients are not required to enroll in the TIRF REMS program.

Q5. What should prescribers know about the new requirements in the TIRF REMS program?

A. Healthcare providers who prescribe TIRF medicines for outpatient use will be required to enroll each patient into a registry and document opioid tolerance with every outpatient prescription for a TIRF medicine. Healthcare providers must counsel patients on the risks and safe use of TIRF medicines, including proper storage and safe disposal and provide patients with a copy of the Medication Guide and the new Patient Counseling Guide. The healthcare provider must also report when a patient discontinues treatment and any adverse events related to misuse, abuse, addiction, or overdose.

Information about co-prescribing with naloxone for opioid overdose as well as information on proper storage and safe disposal of TIRF medicines have been added to the REMS educational materials and the Patient Counseling Guide.

Because of the changes to the requirements for prescribers and updated REMS educational materials, likely prescribers and previously enrolled healthcare providers who prescribe TIRF medicines for outpatient use are required to complete new training, complete the knowledge assessment, and enroll or re-enroll into the modified REMS. Additional information about the enrollment process can be found on the TIRF REMS program website: www.TIRFREMSaccess.comExternal Link Disclaimer. This website will be available in March 2021 when the TIRF REMS program "goes live".

There are no changes to healthcare providers who prescribe TIRF medicines for inpatient use. In the inpatient setting, healthcare providers are not required to enroll in the TIRF REMS program.

Q6. What should pharmacists and authorized representatives of pharmacies know about the new requirements in the TIRF REMS program?

A. Both outpatient and inpatient pharmacies that dispense TIRF medicines are required to be enrolled in the TIRF REMS, however, the requirements are different for the two settings.

Outpatient pharmacies will be required to ensure that prescribers and patients are enrolled in the REMS, that the prescriber has documented that patient is opioid tolerant with every prescription and assess patient's medication use for a change in patient's opioid tolerance prior to each prescription. Outpatient pharmacies can ensure these requirements are met by reviewing data from various sources, such as available state Prescription Drug Monitoring Programs, the patient's records in the pharmacy's management system, information provided by the TIRF REMS, and/or by speaking with the prescriber. Once these safe use conditions have been met, a REMS dispense authorization will be provided to the pharmacist and the TIRF medicine can be dispensed.

Inpatient pharmacies will be required to develop policies and procedures to ensure that inpatients who require a TIRF medicine are opioid tolerant.

Previously enrolled pharmacies who wish to continue to dispense TIRF medicines will need to designate an authorized representative to complete the new training, complete the knowledge assessment, and reenroll into the TIRF REMS. The authorized representative will be responsible for training other pharmacy staff in the appropriate dispensing of TIRF medicines according to the modified TIRF REMS program.

Additional information about the enrollment process can be found on the TIRF REMS program website (http://www.TIRFREMSaccess.com) (http://www.fda.gov/about-fda/website-policies/website-disclaimer). This website will be available in March 2021 when the TIRF REMS program "goes live."

Q7. When does the modified TIRF REMS Program go into effect?

A. The modified TIRF REMS Program will "go live" in March 2021.

Related Information

- Transmucosal Immediate-Release Fentanyl (TIRF) Medicines (/drugs/information-drug-class/transmucosal-immediate-release-fentanyl-tirf-medicines)
- Approved Risk Evaluation and Mitigation Strategies (REMS) (http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm)
- FDA approves shared system REMS for TIRF products (https://wayback.archive-it.org/7993/20170112031936/http:/www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm285345.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)