

Risk Evaluation and Mitigation Strategy (REMS) Document

Transmucosal Immediate Release Fentanyl (TIRF)

Shared System REMS Program

I. Administrative Information

Initial Shared System REMS Approval: 12/2011
Most Recent REMS Update: 12/2020

II. REMS Goals

The goals of the TIRF REMS are to:

1. Mitigate the risk of overdose by:
 - a) Requiring documentation of opioid tolerance with every TIRF prescription for outpatient use.
 - b) Requiring inpatient pharmacies to develop policies and procedures to verify opioid tolerance in inpatients who require TIRF medicines while hospitalized.
 - c) Educating prescribers, pharmacists and patients that the safe use of TIRF medicines requires patients to be opioid-tolerant throughout treatment.
2. Mitigate the risk of accidental exposure by educating prescribers, pharmacists and patients about proper storage and disposal of TIRF medicines.
3. Monitor for accidental exposure, misuse, abuse, addiction, and overdose by enrolling all patients who receive a TIRF medicine for outpatient use into a registry and using surveillance systems and other data sources.

III. REMS Requirements

TIRF Applicants must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe TIRF medicines for outpatient use must:

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| To become certified to prescribe | <ol style="list-style-type: none">1. Review each drug's Prescribing Information.2. Review the following: Prescriber Education.3. Successfully complete the Prescriber Knowledge Assessment and submit it to the REMS program.4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS program. |
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Before treatment initiation	<ol style="list-style-type: none"> 5. Assess the patient for risk factors of opioid addiction, abuse, and misuse. 6. Counsel the patient on the safe use of TIRF medicines using the Medication Guide for the prescribed TIRF medicine and the Patient Counseling Guide. Provide a copy of the materials to the patient. 7. Assess the patient’s opioid tolerance. Document and submit to the REMS program using the Patient Enrollment Form. 8. Enroll the patient by completing and submitting the Patient Enrollment Form to the REMS program.
During treatment, before each prescription	<ol style="list-style-type: none"> 9. Assess the patient’s health status for opioid tolerance, appropriateness of dose, misuse, abuse, addiction, and overdose. Document and submit to the REMS program using the Patient Status and Opioid Tolerance Form.
During treatment, every 2 years	<ol style="list-style-type: none"> 10. Counsel the patient on the safe use of TIRF medicines using the Medication Guide for the prescribed TIRF medicine and the Patient Counseling Guide. Provide a copy of the materials to the patient. 11. Re-enroll the patient in the REMS by completing the Patient Enrollment Form and submitting it to the REMS program.
Before treatment re-initiation, lapse in treatment of 6 months or longer	<ol style="list-style-type: none"> 12. Counsel the patient on the safe use of TIRF medicines using the Medication Guide for the prescribed TIRF medicine and the Patient Counseling Guide. Provide a copy of the materials to the patient.
To maintain certification to prescribe, every 2 years	<ol style="list-style-type: none"> 13. Review the Prescribing Information for the TIRF medicines. 14. Review the following: Prescriber Education. 15. Successfully complete the Prescriber Knowledge Assessment and submit it to the REMS program. 16. Re-enroll in the REMS by completing the Prescriber Enrollment Form.
At all times	<ol style="list-style-type: none"> 17. Counsel the patient using the Medication Guide for any new TIRF medicine not previously prescribed. Provide a copy to the patient. 18. Report serious adverse events of accidental exposure, misuse, abuse, addiction, and overdose to the REMS program using the Adverse Events of Special Interest Reporting Form. 19. Report treatment discontinuations to the REMS Program using the Patient Discontinuation Form.

2. Patients who are prescribed TIRF medicines for outpatient use:

Before treatment initiation	<ol style="list-style-type: none">1. Receive counseling from the prescriber on the safe use of TIRF medicines using the Medication Guide and the Patient Counseling Guide.2. Enroll in the REMS program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS program.
Before treatment re-initiation, lapse in treatment of 6 months or longer	<ol style="list-style-type: none">3. Receive counseling from the prescriber on the safe use of TIRF medicines using the Medication Guide and the Patient Counseling Guide.
During treatment, every 2 years	<ol style="list-style-type: none">4. Receive counseling from the prescriber on the safe use of TIRF medicines using the Medication Guide and the Patient Counseling Guide.5. Re-enroll in the REMS program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS program.
At all times	<ol style="list-style-type: none">6. Adhere to safe use conditions: taking around-the-clock opioid pain medicine when using TIRF medicines, not sharing TIRF medicines, properly storing and disposing your TIRF medicines.7. Inform the prescriber if your TIRF medicine does not relieve your pain. Do not change your dose or take a TIRF medicine more often than your prescriber directed.8. Receive counseling from the prescriber on the safe use of each new TIRF medicine you are prescribed.9. Inform the prescriber of serious adverse events of accidental exposure, abuse, misuse, addiction, and overdose.

3. Pharmacies that dispense TIRF medicines for outpatient use must:

To become certified to dispense	<ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS program on behalf of the pharmacy.2. Have the authorized representative review the Pharmacy Education.3. Have the authorized representative successfully complete the Pharmacy Knowledge Assessment and submit it to the REMS program.4. Establish processes and procedures to assess the patient's medication use for a change in opioid tolerance.
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	<ol style="list-style-type: none"> 5. Have the authorized representative enroll in the REMS Program by completing and submitting the Outpatient Pharmacy Enrollment Form. 6. Train all relevant staff involved in dispensing of TIRF medicines on the risks associated with TIRF medicines and the requirements of the REMS program using the Pharmacy Education.
Before dispensing	<ol style="list-style-type: none"> 7. Provide the patient with the product-specific Medication Guide. 8. Assess the patient's medication use for a change in opioid tolerant status. Document and submit the results to the REMS Program. 9. Obtain authorization to dispense each prescription by contacting the REMS program to verify that the prescriber and the patient are enrolled, and the patient is opioid tolerant.
To maintain certification to dispense	<ol style="list-style-type: none"> 10. Have any new authorized representative enroll in the REMS Program by reviewing the Pharmacy Education, successfully completing the Pharmacy Knowledge Assessment and the Outpatient Pharmacy Enrollment Form and submitting both to the REMS Program.
At all times	<ol style="list-style-type: none"> 11. Not distribute, transfer, loan, or sell TIRF medicines. 12. Maintain records of staff training. 13. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed. 14. Report serious adverse events of accidental exposure, misuse, abuse, addiction, and overdose to the REMS program using the Adverse Events of Special Interest Reporting Form.

4. Pharmacies that dispense TIRF medicines for inpatient use must:

To become certified to dispense	<ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS program on behalf of the pharmacy.2. Have the authorized representative review the Pharmacy Education.3. Have the authorized representative successfully complete the Pharmacy Knowledge Assessment and submit it to the REMS program.4. Have the authorized representative enroll in the REMS program by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS program.5. Train all relevant staff involved in dispensing of TIRF medicines on the risks associated with TIRF medicines and the requirements of the REMS program using the Pharmacy Education.6. Establish processes and procedures to verify that the patient is opioid tolerant.
Before dispensing	<ol style="list-style-type: none">7. Verify the patient is opioid tolerant through the processes and procedures established as a requirement of the REMS program.
To maintain certification to dispense	<ol style="list-style-type: none">8. Have any new authorized representative enroll in the REMS Program by reviewing Pharmacy Education, successfully completing the Pharmacy Knowledge Assessment and the Inpatient Pharmacy Enrollment Form and submitting both to the REMS Program.
At all times	<ol style="list-style-type: none">9. Not distribute, transfer, loan, or sell TIRF medicines.10. Maintain records of staff training.11. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.12. Not dispense TIRF medicines for outpatient use.

5. Wholesalers-Distributors that distribute TIRF medicines must:

To be able to distribute	<ol style="list-style-type: none"> 1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies. 2. Train all relevant staff involved in distributing TIRF medicines on the procedures and the REMS program requirements.
At all times	<ol style="list-style-type: none"> 3. Distribute only to certified pharmacies. 4. Maintain records of shipments to certified pharmacies. 5. Comply with audits carried out by TIRF Applicants or a third party acting on behalf of the TIRF Applicants to ensure that all processes and procedures are in place and are being followed.

TIRF Applicants must provide training to healthcare providers who prescribe TIRF medicines. The training includes the following educational material: [Prescriber Education](#). The training must be made available on a website and by calling the REMS program.

TIRF Applicants must provide training to pharmacies that dispense TIRF medicines. The training includes the following educational material: [Pharmacy Education](#). The training must be made available on a website and by calling the REMS program.

To inform healthcare providers about the REMS program and the risks and safe use of TIRF medicines, TIRF Applicants must disseminate REMS communication materials according to the table below:

Target Audience	Communication Materials & Dissemination Plans
Inpatient and outpatient pharmacies that dispense Schedule II drugs and may be involved in dispensing TIRF medicines	<p>REMS Letter: Inpatient Pharmacy Letter with attachment Pharmacy Education; Outpatient Pharmacy Letter with attachment Pharmacy Education.</p> <ol style="list-style-type: none"> a. Email within 30 calendar days of the approval of the REMS modification and again 1 month later. <ol style="list-style-type: none"> a. Send by mail or fax within 45 calendar days of the date the second email was sent if email was undeliverable or unopened. b. Disseminate through the following professional societies and request the letter or content be provided to their members: <ol style="list-style-type: none"> b. American Association of Colleges of Pharmacy (AACP), American College of Clinical Pharmacy (ACCP), Accreditation Council for Pharmacy Education (ACPE), Academy of Managed Care Pharmacy (AMCP), American Pharmacists Association (APhA), American Society of Consultant Pharmacists (ASCP), American Society of Health-System Pharmacists (ASHP), Board of Pharmacy Specialties (BPS), Board Certified Oncology Pharmacists (BCOP), National Association of Boards of Pharmacy (NABP), National Community Pharmacists Association (NCPA), National Alliance of State Pharmacy Associations (NASPA)

Inpatient and outpatient pharmacies previously enrolled in the TIRF REMS	REMS Letter: Inpatient Pharmacy Letter with attachment Pharmacy Education ; Outpatient Pharmacy Letter with attachment Pharmacy Education 1. Mail or fax within 45 calendar days of approval of the REMS modification (12/23/2020).
Inpatient and outpatient pharmacies, and wholesaler-distributors previously enrolled in the TIRF REMS	REMS Letter: Urgent Notification Regarding TIRF Products Stock Letter Mail or fax within 120 calendar days of approval of the REMS modification (12/23/2020).
Healthcare providers who are likely to prescribe TIRF medicines	REMS Letter: Healthcare Provider Letter with attachment Prescriber Education 1. Email within 30 calendar days of the approval of the REMS modification and again 1 month later. a. Send by mail or fax within 45 calendar days of the date the second email was sent if email was undeliverable or unopened. 2. Disseminate through the following professional societies and request the letter or content be provided to their members: a. American Academy of Hospice and Palliative Medicine, American Academy of Pain Management, American Academy of Pain Medicine, American Association of Poison Control Centers, American College of Physicians, American Chronic Pain Association, American Pain Society, American Society of Pain Educators, National Hospice and Palliative Care Organization
Prescribers previously enrolled in the TIRF REMS	REMS Letter: Healthcare Provider Letter with attachment Prescriber Education 1. Mail or fax within 45 calendar days of approval of the REMS modification (12/23/2020).

To support REMS program operations, TIRF Applicants must:

1. Authorize dispensing for each patient based on receipt of the [Patient Status and Opioid Tolerance Form](#) and pharmacy assessment for a change in opioid tolerance. The authorization is valid for one dispensing for up to 30 calendar days from date the prescriber initiates the authorization.
2. Establish and maintain a REMS program website, www.TIRFREMSaccess.com. The REMS program website must include the capability to complete prescriber, pharmacy, and patient enrollment online, document Adverse Events of Special Interest, document opioid tolerance, obtain authorization to dispense, and the option to print the Prescribing Information, [Medication Guide](#), and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS program website. The REMS program website must not link back to the promotional product website(s).
3. Make the REMS program website fully operational and all REMS materials available through the website and coordinating center within 180 calendar days of the REMS modification (12/23/2020).
4. Establish and maintain a REMS program coordinating center for REMS participants at 1-866-822-1483.

5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the TIRF REMS program. The database must contain information on their enrollment status.
6. Ensure that prescribers and pharmacies are able to complete enrollment by fax and online.
7. Ensure prescribers are able to document opioid tolerance using the [Patient Status and Opioid Tolerance Form](#) by fax and online.
8. Ensure prescribers are able to report serious adverse events of accidental exposure, misuse, abuse, addiction, and overdose using the [Adverse Events of Special Interest Reporting Form](#) by fax and online.
9. Ensure pharmacies are able to report serious adverse events of accidental exposure, misuse, abuse, addiction, and overdose using the [Adverse Events of Special Interest Reporting Form](#) by phone, fax, and online.
10. Ensure pharmacies are able to enroll as an inpatient pharmacy (hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use) or as an outpatient pharmacy.
11. Ensure outpatient pharmacies are able to document changes in opioid tolerance by phone and online.
12. Ensure outpatient pharmacies are able to obtain authorization to dispense TIRF medicines by phone and online.
13. Provide [Prescriber Enrollment Form](#), [Patient Enrollment Form](#), [Outpatient Pharmacy Enrollment Form](#), [Inpatient Pharmacy Enrollment Form](#), [Prescriber Education](#), [Prescriber Knowledge Assessment](#), [Patient Counseling Guide](#), [Pharmacy Education](#), [Pharmacy Knowledge Assessment](#), and the Prescribing Information to REMS participants who (1) attempt to prescribe/dispense/distribute TIRFs and are not yet certified or (2) inquire about how to become certified.
14. Notify prescribers and pharmacies within three business days after they become certified in the REMS program.
15. Notify REMS participants 30 calendar days before their enrollment expires and of the need to re-enroll.
16. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
17. Provide certified outpatient pharmacies access to the database of certified prescribers and enrolled patients.
18. Establish and maintain a registry which includes a reporting and collection system for all outpatients to provide information on serious adverse events including accidental exposure, abuse, misuse, addiction, and overdose.
19. Follow up with the healthcare provider to obtain the reason for discontinuation if the patient is not dispensed a TIRF medicine after 2.5 times the days' supply of their last prescription's days' supply.
20. Ensure that once a report suggestive of accidental exposure, abuse, misuse, addiction, or overdose is received, TIRF Applicants follow up with the healthcare provider to obtain all required data for complete adverse event reporting related to accidental exposure, abuse, misuse, addiction, and overdose under the REMS.
21. Report any overdose that results in a death associated with a TIRF medicine, as soon as possible to FDA but no later than 15 calendar days from the initial receipt of the information by the TIRF Applicants. This requirement does not affect the applicants' other reporting and follow-up requirements under FDA regulations.

To ensure REMS participants' compliance with the REMS program, TIRF Applicants must:

22. Ensure a [Patient Status and Opioid Tolerance Form](#) is received, and the pharmacy assesses for a change in opioid tolerance for each patient for each dispensing.

23. Verify every two years that the pharmacy's authorized representative's name and information correspond to the designated authorized healthcare for the certified pharmacy, and if different, require the pharmacy to recertify with a new authorized representative.
24. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: TIRF distribution and dispensing; certification of prescribers, pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
25. Establish a plan for addressing noncompliance with REMS program requirements.
26. Monitor prescribers, pharmacies, and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
27. Annually audit all certified outpatient pharmacies and 10% but no less than 50 certified inpatient pharmacies no later than 90 calendar days after they have become certified/re-certified in the TIRF REMS to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Similarly, annually audit all wholesalers-distributors no later than 90 calendar days after they become authorized to distribute TIRFs to ensure that all REMS processes and procedures are in place, functioning, and support the REMS program requirements.
28. Take reasonable steps to improve operations of and compliance with the requirements in the TIRF REMS program based on monitoring and evaluation of the TIRF REMS program.

IV. REMS Assessment Timetable

TIRF NDA Applicants must submit REMS Assessments at 12 months from 12/23/2020, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. TIRF NDA Applicants must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the TIRF REMS program:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Outpatient Pharmacy Enrollment Form](#)
4. [Inpatient Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

5. [Prescriber Education](#)
6. [Prescriber Knowledge Assessment](#)

Patient:

7. [Patient Counseling Guide](#)

8. [Medication Guides](http://www.TIRFREMSaccess.com) (available at www.TIRFREMSaccess.com)

Pharmacy:

9. [Pharmacy Education](#)
10. [Pharmacy Knowledge Assessment](#)

Patient Care Forms

11. [Patient Status and Opioid Tolerance Form](#)
12. [Adverse Events of Special Interest Reporting Form](#)
13. [Patient Discontinuation Form](#)

Communication Materials

14. [Healthcare Provider Letter](#)
15. [Outpatient Pharmacy Letter](#)
16. [Inpatient Pharmacy Letter](#)
17. [Urgent Notification Regarding TIRF Products Stock Letter](#)

Other Materials

18. [Website](http://www.TIRFREMSaccess.com) (www.TIRFREMSaccess.com)