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

REMS MODIFICATION REVIEW

Date:	July 12, 2017
Reviewer(s):	LaShaun Washington-Batts, Pharm.D. Risk Management Analyst Division of Risk Management (DRISK) Kate Oswell, M.A. Health Communication Specialist DRISK
Team Leader:	Selena Ready, Pharm.D. DRISK
Division Director:	Cynthia LaCivita, Pharm.D. DRISK
Subject:	REMS Modification
Therapeutic Class:	Opioid Analgesic
OND Review Division:	Division of Anesthetics, Analgesia, and Addiction Products
OSE RCM #:	2017-1183
DMF #:	027320

Drug Name, Dosage Form, NDA Number and Sponsor Name:

Drug Name	Dosage Form and Route	NDA Number	Sponsor
Abstral (fentanyl)	Sublingual tablet	022510	Galenya BioPharma
Actiq (fentanyl citrate)	Oral transmucosal lozenge	020747	Cephalon, Inc.
Fentora and Authorized Generic (fentanyl citrate)	Buccal tablet	021947	Cephalon, Inc.
Lazanda (fentanyl)	Nasal spray	022569	DepoMed, Inc.
Onsolis	Buccal soluble	022266	Meda Pharmaceuticals

(fentanyl)	film		
Subsys (fentanyl)	Sublingual spray	202788	Insys Therapy
fentanyl buccal	Buccal tablet	ANDA 079075	Watson Laboratories, Inc.
fentanyl citrate	Oral transmucosal lozenge	ANDA 078907	Mallinckrodt, Inc.
fentanyl citrate	Oral transmucosal lozenge	ANDA 077312	Par Pharmaceutical, Inc.

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1. INTRODUCTION

This review by the Division of Risk Management (DRISK) provides an evaluation of the proposed modification of the transmucosal immediate-release fentanyl (TIRF) risk evaluation and mitigation strategy (REMS) Access Program (TIRF REMS) received on June 9, 2017. This REMS modification is required to conform to safety labeling changes (SLC) approved on December 16, 2016 that address the addition of language related to the risks of misuse, abuse, addiction, overdose, death, and neonatal opioid withdrawal syndrome (NOWS), serotonin syndrome with concomitant use of serotonergic drugs, adrenal insufficiency, androgen deficiency, and risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants to the Prescribing Information.

Thus, the primary purpose of this proposed TIRF REMS modification is to incorporate the approved safety labeling changes within the TIRF REMS document and materials.

This review is written by the DRISK, in consultation with the Office of Prescription Drug Promotion (OPDP).

2. BACKGROUND

TIRF products are used for the management of breakthrough cancer pain in patients already receiving and who are tolerant to around the clock opioid therapy for their underlying persistent cancer pain.

The approved TIRF products include:

- Abstral (fentanyl) sublingual tablet
- Actiq (fentanyl citrate) oral transmucosal lozenge
- Fentora (fentanyl citrate) buccal tablet
- Lazanda (fentanyl) nasal spray,
- Onsolis (fentanyl) buccal soluble film
- Subsys (fentanyl) sublingual spray
- Approved generic equivalents of these products

The TIRF products are approved under a single, shared system REMS and all Sponsors with approved products in the TIRF REMS are members of the TIRF REMS Industry Group (TRIG). The goals of the TIRF REMS are to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

- Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in 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.

The REMS is comprised of Medication Guides (MG) for each individual TIRF medicine and the following elements to assure safe use (ETASU):

- Healthcare providers who prescribe TIRF medicines for outpatient use are specially certified
- TIRF medicines will only be dispensed by pharmacies that are specially certified
- TIRF medicines will only be dispensed for outpatient use with evidence or other documentation of safe-use conditions.

The timetable for submission of TIRF REMS assessments is at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.

The TIRF REMS was approved by the Agency on December 28, 2011 and was launched on March 12, 2012. The TIRF REMS was modified June 5, 2012, November 7, 2013 and December 24, 2014.

3. REGULATORY HISTORY

March 22, 2016: The Agency issued SLC notification letters to Sponsors of the TIRF product new drug applications (NDAs). The new safety information to be included in the labeling pertains 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.

August 31, 2016: The Agency issued SLC notification letters to the Sponsors of the TIRF product NDAs. The new safety information to be included in the labeling pertains to the risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants.

December 16, 2016: The Agency approved the SLCs for all TIRF products. The new safety information included the following: Updating the warning to include misuse, abuse, addiction, overdose, death, and NOWS, Serotonin Syndrome with concomitant use of serotonergic drugs, adrenal insufficiency, androgen deficiency, and risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants.

June 9, 2017: The TRIG point of contact submitted the TIRF Access Program REMS Modification to the Drug Master File (DMF).

June 12, 2017: All TRIG sponsors submitted individual cover letters for the TIRF Access Program REMS Modification to their applications, referencing the DMF Submission.

4. MATERIALS REVIEWED

4.1. SUBMISSIONS

- DMF # 027320 eCTD Sequence No. 029 TIRF Access Program REMS Modification received on June 9, 2017. These materials are the subject of this review.

Submission Date	Product Name	Application Number	Supplement Number
June 12, 2017	Abstral (fentanyl)	NDA 022510	17

June 12, 2017	Actiq (fentanyl citrate)	NDA 020747	47
June 12, 2017	Fentora and Authorized Generic (fentanyl citrate)	NDA 021947	27
June 12, 2017	Lazanda (fentanyl)	NDA 022569	26
June 12, 2017	Onsolis(fentanyl)	NDA 022266	19
June 12, 2017	Subsys (fentanyl)	NDA 202788	18
June 12, 2017	Fentanyl buccal tablet	ANDA 079075	13
June 12, 207	Fentanyl citrate lozenge	ANDA 078907	16
June 12, 207	Fentanyl citrate lozenge	ANDA 077312	9

4.2. Other Materials Informing Our Review

- Safety label change notification letters for all TIRF products issued on March 22, 2016
- Safety label change notification letters for all TIRF products issued on August 31, 2016
- Approval letters for all TIRF product prior approval supplement safety labeling changes issued December 16, 2016.
- Washington-Batts L. DRISK REMS Modification Rationale Review for TIRFs. March 6, 2017
- Toombs, L. Shenee'. OPDP REMS Consult Review. June 27, 2017

5. Rationale for the REMS Modification

The proposed TIRF REMS modification was in response to the SLC Approval Letter dated December 16, 2016 that included the addition of language related to the risks of misuse, abuse, addiction, overdose, death, and NOWS, serotonin syndrome with concomitant use of serotonergic drugs, adrenal insufficiency, androgen deficiency, and risks of concomitant use of opioid analgesics with benzodiazepines or other central nervous system depressants to the Prescribing Information. This REMS modification is necessary to align the TIRF REMS document and materials with the SLC.

6. Review of the Proposed REMS Modification

6.1. Medication Guide

There were no changes proposed for this element.

6.2. REMS Document

The TRIG proposed changes to the REMS Document as described below (modifications in red text and underlined).

On page 3, Prescriber Enrollment Form, paragraph iic: –

I understand that TIRF medicines are indicated only for the management of breakthrough pain in ***cancer*** patients, ***18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older)***, who are already receiving and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.

Reviewer Comment: *The Agency agrees with this change as it aligns with the prescribing information.*

On page 3, Prescriber Enrollment Form, paragraph iie:

I understand that TIRF medicines ***are not for use in the management of*** acute or postoperative pain, including headache/migraine ***and dental pain, or in the emergency room***.

Reviewer Comment: *The Agency disagrees with this change and proposes the following language:*

I understand that TIRF ***medicines must not be used to treat acute or postoperative pain, including headache/migraine and dental pain, or acute pain in the emergency department.***

On page 3, Prescriber Enrollment Form, paragraph if:

Changes to the TIRF REMS Access website URL to
be www.tirfremsaccess.com/TirfUI/rems/products.action

Reviewer Comment: The Agency agrees with the change to the TIRF REMS Access website, here and throughout the document.

On page 4, Patient Prescriber Agreement Form, paragraph 1):

I understand that TIRF medicines are indicated only for the management of breakthrough pain in ***cancer*** patients, ***18 years of age or older (Actiq and its generic equivalents are approved for 16 years of age and older)***, who are already receiving and who are tolerant to, around-the-clock opioid therapy for their underlying persistent pain.

Reviewer Comment: *The Agency agrees with this change as it aligns with the prescribing information.*

On page 4, Patient Prescriber Agreement Form, paragraph 3):

I understand that TIRF medicines are not for use in the management of acute or postoperative pain, including headache/migraine and dental pain, or in the emergency room.

Reviewer Comment: *The Agency agrees with this addition to the attestation for the Patient-Prescriber Agreement Form, but proposes the following language:*

I understand that TIRF ***medicines must not be used to treat acute or postoperative pain, including headache/migraine and dental pain, or acute pain in the emergency department.***

On page 4, Patient Prescriber Agreement Form, paragraph 4):

I understand that patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; ***60 mg oral hydrocodone/day***; or an equianalgesic dose of another opioid daily for one week or longer.

Reviewer Comment: *The Agency agrees with this change, but proposes the following language:*

I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; ***60 mg oral hydrocodone/day***; or an equianalgesic dose of another opioid daily ~~***for one week or longer.***~~

On page 5, Patient Prescriber Agreement Form, paragraph 8):

I will store my TIRF medicine ***securely out of reach of*** children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

Reviewer Comment: *The Agency disagrees with this change, but proposes the following language:*

I will store my TIRF medicine ***in a safe place, out of reach of*** children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death.

On page 8, Chain and Independent Outpatient Enrollment Form, paragraph iiid and page 11, Inpatient Pharmacy Enrollment Form, paragraph iid:

I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients; ***in the management of acute or postoperative pain, including headache/migraine and dental pain, or in the emergency department; acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment; or in known or suspected gastrointestinal obstruction, including paralytic ileus.***

Reviewer Comment: *The Agency disagrees with this change and proposes that the language remain as originally approved to read: "I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients."*

6.3. ELEMENTS TO ASSURE SAFE USE

6.3.1. REMS MATERIALS

The TRIG proposed changes to the REMS Materials to include safety language for the SLCs in the Education Program for Prescribers and Pharmacists. In addition, the TRIG proposed changes to the Patient-Prescriber Agreement Form, Prescriber Enrollment Form, Inpatient Pharmacy Enrollment Form, Independent Outpatient Enrollment Form, Closed Outpatient Enrollment Form, and Chain Outpatient Enrollment Form.

Reviewer Comments: *The Agency reviewed all changes to the REM Materials and proposes edits as stated below:*

Patient-Prescriber Agreement Form:

Prescriber Acknowledgments:

Revise bullet #3 to state: “I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.”

Revised bullet #4 to state: “I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.

Patient Acknowledgments:

Revise bullet #8 state: “I will store my TIRF medicine in a safe place, out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. “

Prescriber Enrollment Form:

Revise bullet #5 to better reflect the label: “I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.”

Remove bullet#6: “I understand that TIRF medicines must not be used to treat any contraindicated conditions described in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.”

Inpatient Pharmacy Enrollment Form, Independent Outpatient Enrollment Form, Closed Outpatient Enrollment Form, Chain Outpatient Enrollment Form:

Remove added language to bullet # 4. Language should remain unchanged so that bullet reads, “I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.”

Education Program for Prescribers and Pharmacists:

Page 7- The presentation of this information under the Indication minimizes the importance of this risk information. Remove the last bullet: “TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids”

Page 8- Revise last sub bullet to read: “OR an equianalgesic dose of another oral opioid daily

Page 9- Revise sub-bullet #1 under Contraindications section to better reflect the label: “Acute or postoperative pain including headache/migraine and dental pain, or acute pain in the emergency department.”

Page 10- Revise last statement under Contraindication section to read: “Deaths have occurred in opioid non-tolerant patients treated with fentanyl products.”

Page 12- Add the following bullet to the subheading “Risk of Misuse, Abuse, Addiction, and Overdose”: “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction.

Page14- Revise subheading to state: “2. Accidental Ingestion or Exposure” to reflect the label.

Page 14- Revise bullet #3 under Accidental Ingestion or Exposure” to read: “Instruct patients to take steps to store TIRF medicines in a safe place out of reach of children.

Page15- Revise bullet to state: Any accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Talk with your patients about safe and appropriate storage and disposal of TIRF Medicines.”

Page15- Revise the second bullet to mirror label under section 7. “Concomitant use of TIRF medicines with CYP3A4 inhibitors (e.g., certain protease inhibitors, ketoconazole, fluconazole, diltiazem, erythromycin, verapamil) may increase plasma concentrations of fentanyl and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression.”

Page 18- Include the following information to address neonatal opioid withdrawal syndrome.

“Determine Patient-Specific Risk Factors

4. Pregnancy

Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. “

Page 22- Revise bullet #4 to read: “If the prescribed dose no longer adequately manages the breakthrough cancer pain for several consecutive episodes, increase the dose as described in the titration section of the prescribing information.

Pharmacists: Instruct patients to consult with their prescriber.

Page 28- Revise bullet 3# under “Tell the Patient cont.):” to read: “Accidental ingestion or exposure, especially in children, may result in respiratory depression or death. Always store your TIRF medicine in a safe place away from children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. Use the child safety kit if one is provided with your TIRF medicine.

Pages 29/30- The bullets do not flow with the initial subheading, “Tell the Patient:” Remove the redundant phrase “Inform patients that” or “Inform patients and caregivers that” from these bullets.

Page 30- Include the bullet: “Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated.”

TIRF REMS Access Website:

Apply our comments on the REMS materials to similar presentations in the Web Prototype REMS document. Final website screenshots should also incorporate these changes.

7. IMPLEMENTATION SYSTEM

There were no changes proposed for this element.

8. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

There were no changes proposed for this element.

9. REMS SUPPORTING DOCUMENT

There were minor editorial revisions proposed for the REMS Supporting Document.

Reviewer Comment: The Agency agrees with the revisions to the REMS Supporting Document.

10. RECOMMENDATIONS FOR THE REVIEW DIVISION

The comments for the sponsor provided below should be sent to the TRIG with a request to resubmit the TIRF REMS document and materials with the requested changes by July 26, 2017.

11. COMMENTS FOR THE SPONSOR

The Agency reviewed the modifications proposed for the TIRF REMS Access Program. We provide the following comments below and redlined versions of the REMS Document and Education Program in the attachments.

REMS Supporting Document: The Agency agrees with the minor revisions to the REMS Supporting Document. Further, the Sponsor must make changes to any language impacted by the proposed changes in the REMS Document and Materials provided below.

REMS Document: See the attached redline version for agency comments and proposed changes.

REMS Materials: See the comments provided below and incorporate changes.

Patient-Prescriber Agreement Form:

Prescriber Acknowledgments:

Revise bullet #3 to state: “I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.”

Revised bullet #4 to state: “I understand that patients considered opioid-tolerant are those who are taking, for one week or longer, at least: 60 mg oral morphine/day; 25 micrograms transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; 60 mg oral hydrocodone/day; or an equianalgesic dose of another opioid daily.

Patient Acknowledgments:

Revise bullet #8 state: “I will store my TIRF medicine in a safe place, out of reach of children and teenagers because accidental use by a child, or anyone for whom it was not prescribed, is a medical emergency and can cause death. “

Prescriber Enrollment Form:

Revise bullet #5 to better reflect the label: “I understand that TIRF medicines must not be used to treat acute or postoperative pain, including headache/migraine, dental pain, or acute pain in the emergency department.”

Remove bullet#6: “I understand that TIRF medicines must not be used to treat any contraindicated conditions describer in the full Prescribing Information, such as acute or postoperative pain, including headache/migraine.”

Inpatient Pharmacy Enrollment Form, Independent Outpatient Enrollment Form, Closed Outpatient Enrollment Form, Chain Outpatient Enrollment Form:

Remove added language to bullet # 4. Language should remain unchanged so that bullet reads, “I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients.”

Education Program for Prescribers and Pharmacists:

We have made edits to align the Education Program with the label. See the Education Program for Prescribers and Pharmacists (attached) for suggested track changes. Please note: Page numbers were added to WORD document to help with the review process only.

Page 7- The presentation of this information under the Indication minimizes the importance of this risk information. Remove the last bullet: “TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression and death could occur at any dose in patients not taking chronic opioids”

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Page 30- Include the bullet: “Prolonged use of TIRF medicines during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated.”

TIRF REMS Access Website:

Apply our comments on the REMS materials to similar presentations in the Web Prototype REMS document. Final website screenshots should also incorporate these changes.

Submit the following TIRF REMS Access Program materials with proposed changes to your application no later than COB July 26, 2017:

1. Redlined and Clean, Word REMS Supporting Document
2. Redlined and Clean, Word versions of REMS Document and all materials, submitted as separate files
3. Clean, Final PDF versions of the REMS Document and all materials, submitted as separate files
4. A compiled document containing clean, final formatted PDF versions of the REMS Document and materials for posting on the FDA REMS Website

12. ATTACHMENTS

1. Redlined PDF versions with Agency Comments
    a. REMS Document
    b. REMS Education Program

Initial REMS approval: 12/2011

Most recent modification: XX/2017

TRANSMUCOSAL IMMEDIATE RELEASE FENTANYL (TIRF)
RISK EVALUATION AND MITIGATION STRATEGY (REMS)

FOLLOWING THIS PAGE, FDA_7183 TO FDA_7231 WITHHELD IN FULL AS B(4)/CCI (PROPOSED/DRAFT REMS WEB MATERIALS)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SELENA D READY on behalf of LASHAUN WASHINGTON-BATTS
07/11/2017

CYNTHIA L LACIVITA
07/11/2017
Concur