

**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: October 31, 2013

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Director:

Table 1

Drug Names,
 Dosage Form
 and Sponsor:

Drug Name	Dosage Form and Route	Application Type/Number	Sponsor
Abstral (fentanyl)	Sublingual tablet	NDA 22-510	Galenya BioPharma
Actiq (fentanyl citrate)	Oral transmucosal lozenge	NDA 20-747	Cephalon, Inc.
Fentora (fentanyl citrate)	Buccal tablet	NDA 21-947	Cephalon, Inc.
Lazanda (fentanyl)	Nasal spray	NDA 22-569	DepoMed, Inc.
Onsolis (fentanyl)	Buccal soluble film	NDA 22-266	Meda Pharmaceuticals
Subsys (fentanyl)	Sublingual spray	NDA 202-788	Insys Therapy

Therapeutic class: Opioid Agonist

Dosage forms: Transmucosal Immediate release Fentanyl (TIRF)

OND Review Division: Division of Anesthesia, Analgesia and Addiction Products (DAAAP)

Table 2

Drug Name	Application Type & Number	FDA Received Date	Supplement Number	FDA Amendment Received Date
Abstral [®]	NDA 22-510	September 28, 2012	7	October 18, 2013
Actiq [®]	NDA 20-747	September 26, 2012	37	October 17, 2013
Fentora [®]	NDA 21-947	September 26, 2012	17	October 17, 2013
Lazanda [®]	NDA 22-569	September 28, 2012	15	October 29, 2013
Onsolis [®]	NDA 22-266	September 26, 2012	12	October 16, 2013
Subsys [®]	NDA 202-788	September 25, 2012	10	October 17, 2013

OSE RCM #: 2012-2313

TSI #: 290

n/a = not applicable

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EXECUTIVE SUMMARY

This is a review of the proposed Risk Evaluation and Mitigation Strategy (REMS) modification for the TIRF REMS Single Shared System initially received between September 25 and September 28, 2012 into the individual sponsors applications and amended through one joint submission into the drug master file (DMF) (027320) on September 24, 2013.

The REMS for the TIRF products was originally approved on December 28, 2011 to address the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors, and a REMS modification was approved on June 30, 2012. The most recently approved REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The TIRF SSS REMS Sponsors submitted a proposed modification to the REMS in response to an e-mail from Mark Libertore, OSE Project Manager on June 28, 2012, requesting modifications to incorporate information about the closed system pharmacies into the REMS document and the appended REMS materials. In addition, proposed modification to the TIRF REMS, including appended REMS materials as applicable, consist of the following:

- Revised terminology, processes, and definitions for outpatient pharmacies
- Revised terminology and definitions for wholesalers/distributors
- Revised attestations for physicians and patients to address concerns regarding patient access
- Revised Program Overview and Frequently Asked Questions to improve clarity and content
- Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program

DRISK finds the proposed modifications to the TIRF REMS to be acceptable.

1. INTRODUCTION

This is a review of the TIRF REMS Industry Group's (TRIG) proposed Risk Evaluation and Mitigation Strategy (REMS) modification #2 for all Transmucosal Immediate Release Fentanyl (TIRF) products (see Table 2) initially received between September 25 and September 28, 2012 into the individual sponsors applications and amended through one joint submission into the drug master file (DMF) (027320) on September 24, 2013.

1.1 BACKGROUND

TIRF medicines are short-acting fentanyl products indicated for the management of breakthrough pain in adults with cancer who are routinely taking other opioid pain medicines around-the-clock for pain.

The approved TIRF medicines 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, and
- Approved generic equivalents of these products

As described in DRISKS December 2, 2011 REMS review, FDA determined that all TIRF products were required to have a REMS to ensure that the benefits of the drug outweighed the increased risk(s) of misuse, abuse, addiction, overdose and serious complications due to medication errors. The TIRF REMS was originally approved on December 28, 2011, and a REMS modification was approved on June 30, 2012.

The most recently approved TIRF REMS (approved June 30, 2012) consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The TIRF medicines are approved under a single shared system REMS that has the following goal and objectives:

The goal of the TIRF REMS Access program is 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 elements included in the program are Medication Guides 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 Access Program assessments is at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.

1.2 REGULATORY HISTORY

Following is an overview of the regulatory history for the TIRF REMS modification, initially received on July 18, 2012.

- 07/18/12: TRIG emailed Modification #2 documents to FDA
- 09/25/12 – 9/28/12: TIRF Sponsors submitted Supplements to their individual NDA (see Table 2)
- 02/4/13: FDA emailed comments and revised documents to the TRIG.
- 03/11/13: TRIG emailed revised materials to FDA.
- 04/16/13: FDA emailed Information Request to TRIG.
- 5/6/2013: TRIG emailed the response to the April 16, 2013 IR to the FDA which contained revised TIRF REMS materials.
- 7/2/2013: FDA comments and revised documents emailed to the TRIG.
- 7/10/2013: TRIG emailed clarifying questions about the documents in the July 2, 2013 email. FDA responded the same day and provided correct versions of the Education Program and Knowledge Assessment.
- 8/13/2013: FDA emailed comments and final TIRF REMS document, appended materials and the supporting document to the TRIG.
- 9/24/2013: TRIG submitted final documents to the DMF for the TIRF REMS Access Program.
- 10/16/2013 - 10/29/2013: TRIG sponsors submitted amendments to individual applications which referenced the DMF and the appropriate Medication Guides.

2.1 SUBMISSIONS

The following submissions were reviewed for the proposed TIRF REMS modification:

- Final TIRF REMS Access Program submission to the DMF, September 24, 2013

Drug Name	Application Type & Number	Supplement Received Date	Supplement Number (Sequence No.)	Letter of Authorization for DMF received date (Sequence No.)	Amendment received date (referencing DMF submission)	Supplement Number (Sequence No.)
Abstral [®]	NDA 22-510	September 28, 2012	7 (61)	September 11, 2013 (96)	October 18, 2013	7 (81)
Actiq [®]	NDA 20-747	September 26, 2012	37 (21)	September 11, 2013 (29)	October 17, 2013	37 (31)
Fentora [®]	NDA 21-947	September 26, 2012	17 (23)	September 11, 2013 (36)	October 17, 2013	17 (37)
Lazanda [®]	NDA 22-569	September 28, 2012	15 (79)	September 11, 2013 (100)	October 29, 2013	15 (105)
Onsolis [®]	NDA 22-266	September 26, 2012	12 (107)	September 11, 2013 (114)	October 16, 2013	12 (117)
Subsys [®]	NDA 202-788	September 25, 2012	10 (41)	September 11, 2013 (62)	October 17, 2013	10 (66)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- *DRISK TIRF REMS Review (K. Lehrfeld February 1, 2013)*
- *Fentora DRISK Review(K. Lehrfeld February 21, 2013)*
- *Abstral DRISK Review(K. Lehrfeld July 5, 2013)*
- *Subsys DRISK Review(K. Lehrfeld July 5, 2013)*
- *DRISK TIRF REMS Review (K. Lehrfeld August 22, 2013)*

2. RATIONALE FOR PROPOSED REMS MODIFICATIONS

On June 5, 2013, FDA approved the TIRF REMS modification #1, which added a reference to closed system pharmacies to the TIRF REMS document and created a Closed System Pharmacy Enrollment Form. However, this modification did not incorporate any closed system information into any other TIRF REMS materials.

On June 28, 2012, FDA requested a modification to the TIRF REMS to incorporate information about the closed system pharmacies into the appended REMS materials. The TRIG was sent the following request via email:

I. Create the following document:

1. *TIRF REMS Program Overview for Closed System Pharmacies*

II. Modify the following documents:

1. REMS Document

Minor modification on page 11 to add the new Overview to the list

2. FAQ

Add the following or a similar question: What if our pharmacy's management system cannot communicate with the TIRF REMS Access program (e.g. does not electronically transmit claims information)? You will need to contact the TIRF REMS Access program at 1-866-822-1483 to see if you qualify to enroll as a "closed system pharmacy".

3. *Website*

Please provide feedback and/or a proposal as to what closed system pharmacy information and/or which documents will be posted on the TIRF REMS Website (we note your e-mail to Kimberly Compton on 6/22/2012 that stated that the enrollment form will not be posted, given that a pharmacy needs to be validated as being a closed system pharmacy prior to their enrollment). For example, closed-system pharmacies that are seeking to enroll in the TIRF REMS should understand that there is a mechanism for them to participate in the REMS; however, it also needs to be clear this mechanism is not an option for pharmacies that can process through their pharmacy management system.

4. Supporting Document

- Update to include information and a section on 'Closed System Pharmacies'
- Update your REMS Assessment Plan and TIRF REMS Access Non-Compliance Plan

3. PROPOSED REMS MODIFICATIONS

The proposed modifications to the REMS elements (received September 24, 2013) are described below.

4.1 GOALS

The applicant did not propose changes to the goals of the REMS.

4.2 REMS ELEMENTS

4.2.1 Medication Guide

The Medication Guides for the individual TRIG products are maintained in the individual applications, not in the DMF. The following products' MGs changed during this review cycle and were reviewed under separate cover by the Office of Medical Policy Patient Labeling Team.

Subsys: On July 31, 2013, an efficacy supplement (S-005) for Subsys (fentanyl sublingual spray) was approved. The MG was revised to include new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys.

Abstral: On July 26, 2013, a labeling supplement (S-010) for Abstral (fentanyl sublingual tablets) was approved. The MG was revised to include the change in ownership from ProStrakan to Galena BioPharma.

Fentora: On February 21, 2013, efficacy supplement (S-008) for Fentora (fentanyl buccal tablet), which proposed the addition of the sublingual route of administration for Fentora, was approved. The MG was revised to include the new route of administration.

Lazanda: Along with the approval of TIRF REMS Modification 2, Lazanda's MG was revised to include the change in ownership from Archimedes Pharma US, Inc. to Depomed, Inc. (S-017) and to revise the shelf-life for the product after first use to 60 days (S-012).

4.2.2 Elements to Assure Safe Use

REMS document

1. Clarification of types of Outpatient pharmacies

- **Outpatient Pharmacies**

- Chain Outpatient Pharmacy:** Retail, mail order or institutional outpatient pharmacies having a chain headquarters that is responsible for ensuring enrollment and training of pharmacy staff within all associated outpatient pharmacies. The chain headquarters will enroll multiple locations (i.e.: chains stores) in TIRF REMS Access.
- Independent Outpatient Pharmacy:** Retail, mail order, or institutional outpatient pharmacies having an authorized pharmacy representative that is responsible for ensuring enrollment and training of pharmacy staff within an individual outpatient pharmacy. Each store will individually enroll in TIRF REMS Access as a single pharmacy location.
- Closed System Outpatient Pharmacy:** Institutional or mail order outpatient pharmacies that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information.

- **Inpatient pharmacies** (e.g., hospitals, in-hospital hospices, and long-term care facilities that dispense for inpatient use)
2. As requested by FDA, a reference to the Closed System Pharmacy Overview document was added to page 11. Additionally, a Closed System Pharmacy Overview document was added as an appended REMS material.

REMS Appended Materials

The titles of the following REMS appended materials were revised as a result of the proposed clarifications to the REMS document described above.

Previous Title	Proposed New Title
Outpatient Pharmacy Enrollment Form	Independent Outpatient Pharmacy Enrollment Form
Chain Pharmacy Enrollment Form	Chain Outpatient Pharmacy Enrollment Form
Closed System Pharmacy Enrollment Form	Closed System Outpatient Pharmacy Enrollment Form
Inpatient Pharmacy Enrollment Form	Inpatient Pharmacy Enrollment Form
Outpatient Pharmacy Overview Document Chain Pharmacy Overview Document	Independent Outpatient Pharmacy Overview Document Chain Outpatient Pharmacy Overview Document

Patient Prescriber Agreement Form

1. Revision to the Patient Privacy Notice statement on the PPAF.

I allow the TIRF REMS Access program to receive, use, and share my Health Information, using a unique, encrypted identifier instead of my name, in order to:

- a. *Evaluate and report to the FDA about the proper use of TIRF medicines and the effectiveness of the TIRF REMS Access program.*
 - b. *Report to the FDA, about side effects from TIRF medicines and the TIRF REMS Access program effectiveness.*
2. Revised PPAF to remove the patient phone number as a mandatory field necessary for patient enrollment.
 3. Revised prescriber attestations #1 - #3 on the PPAF, as indicated below.
 1. ~~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.

2. I understand that TIRF medicines are contraindicated for use in opioid non-tolerant patients, and know that fatal overdose can occur at any dose.
3. ~~My patient is opioid tolerant. I understand that p~~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; or an equianalgesic dose of another opioid for one week or longer.

4. Revised patient attestation #2 on the PPAF, as indicated below.

- 2) I understand that TIRF medications should only be taken by patients who are regularly using another opioid, around-the-clock, for constant pain. opioid pain medications. I understand that before I can take any TIRF medicine, I must be opioid tolerant. If I am not taking around-the-clock opioid pain medicine, my prescriber and I have discussed the risks of only taking TIRF medicines. whether I am opioid tolerant.

Prescriber and Pharmacy Enrollment Forms

1. Enrollment forms modified to state that the Knowledge Assessment should be submitted with the enrollment form.

Dear Healthcare Provider Letter

TRIG agreed to remove the DHCP letters from the TRIF REMS Access website.

Frequently Asked Questions (FAQ) document

1. TRIG removed all reference to the transition from individual TIRF REMS programs to the shared system TIRF REMS Access Program. Furthermore, they added a section titled “*How long is my enrollment effective in the TIRF REMS Access program?*” which describes the reenrollment process to the following sections:
 - outpatient pharmacies
 - inpatient pharmacies
 - prescribers
 - distributor (wholesaler)
2. As requested by FDA, the following language was added:

“What if our pharmacy’s management system cannot communicate with the TIRF REMS Access program (e.g. does not electronically transmit claims information)? You will need to contact the TIRF REMS Access program at 1-866-822-1483 to see if you qualify to enroll as a “closed system pharmacy.”

TIRF REMS Overview documents

1. As requested by the FDA, a Closed System Outpatient Pharmacy Overview document, modeled after existing TIRF REMS overview documents, was created for this modification. This document was revised during the review period to improve clarity and flow. After revisions were agreed upon, TRIG subsequently revised the overview documents for Prescribers, Inpatient Pharmacies and Independent and Chain Outpatient Pharmacies to follow the same format as the Closed System Outpatient Pharmacy Overview.
2. The closed pharmacy overview document was revised to indicate during prescription verification a DEA number will not be required, if applicable, in order to validate a prescription. This was necessary due to a newly instituted process for enrolling a small number of closed system prescribers who do not require an individual DEA number in order to prescribe CII medicines. This process allows enrollment of these closed system prescribers and validation of a prescription written by these prescribers with only an NPI number. However, the affected prescribers can only enroll via fax.
3. TRIG provided additional minor edits to the stakeholder overview documents which do not impact the goals of the REMS or operations.

TIRF REMS Education Program

On July 31, 2013, an efficacy supplement (S-005) for Subsys (fentanyl sublingual spray) (NDA 202788) which included new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys was approved. Accordingly, slides 15 and 19 of the TIRF REMS Education Program were revised to reflect this change. (see K Lehrfeld REMS Review, July 5, 2013)

TIRF REMS Knowledge Assessment

On July 31, 2013, an efficacy supplement (S-005) for Subsys (fentanyl sublingual spray) (NDA 202788) which included new recommendations for safely switching from Actiq (fentanyl oral transmucosal lozenge) to Subsys was approved. Accordingly, the following question in the TIRF REMS Knowledge Assessment was revised to reflect this change. (see K Lehrfeld REMS Review, July 5, 2013)

Question 11: Conversion between ~~specific only two~~ TIRF medicines has been established and is described in the Prescribing Information for which ~~two~~ products? *Select one option.*

- A. Lazanda to Actiq
- B. Actiq to Fentora
- C. ~~Abstral to Fentora~~ Actiq to Subsys
- D. ~~Fentora to Actiq~~ Both B & C

Global changes to the TIRF REMS appended materials resulting from a non-safety related labeling change to an individual TIRF products NDA:

1. Changes to the following TIRF REMS product names were globally applied to all REMS materials:
 - “FENTORA® (fentanyl citrate) buccal tablet” was changed to “FENTORA® (fentanyl buccal tablet)”
 - “Onsolis® (fentanyl) buccal soluble film” was changed to “Onsolis® (fentanyl buccal soluble film)”
 - Replaced the TM symbol after Subsys with ®.
 - “SubsysTM (fentanyl) sublingual spray” was changed to “Subsys® (fentanyl sublingual spray)”
2. Addition of the following TIRF REMS products new NDCs to the Chain and Independent Outpatient Pharmacy enrollment forms

Subsys	Abstral	Par Pharmaceutical
20482-001-10	57881-331-12	49884-459-55
20482-002-10	57881-331-32	49884-460-55
20482-004-10	57881-332-12	49884-461-55
20482-006-10	57881-332-32	49884-462-55
20482-008-10	57881-333-12	49884-463-55
20482-001-01	57881-333-32	49884-464-55
20482-002-01	57881-334-12	
20482-004-01	57881-334-32	
20482-006-01	57881-336-32	
20482-008-01	57881-338-32	

3. Changes to the following Subsys NDCs:
 - Replaced 20482-012-30 with 20482-012-15
 - Replaced 20482-016-30 with 20482-016-15

4.2.3 Implementation System

The applicant did not propose changes to the implementation system of the REMS.

4.2.4 Timetable for Submission of Assessments

The timetable for submission of assessments of the REMS will remain the same as that approved on December 28, 2011.

4.3 SUPPORTING DOCUMENT

1. As requested by FDA, the REMS Supporting Document was updated to add a specific section, "Closed System Pharmacies".
2. TRIG proposed adding the closed system pharmacies to the assessment plan in the REMS supporting document. However, the second REMS Assessment submitted on December 21, 2012 is currently under review. Therefore, the TRIG's proposed changes to the REMS Assessment plan and any future changes will be reviewed under separate cover.
3. Clarification of the definition for wholesaler distributors in the REMS supporting document.

TIRF Sponsors will ensure that wholesaler distributors who take title to or direct the sale or disposition of TIRF medicines to persons other than a consumer or patient are enrolled in the TIRF REMS Access program and comply with the program requirements for wholesale distributors.

4. The *TIRF REMS Prescription Authorization Request Form* for closed system outpatient pharmacies was added to the TIRF REMS Supporting Document as an appended material.
5. On May 1, 2013, Abstral ownership transitioned from ProStrakan to Galena BioPharma. In order to support this transition, the REMS Supporting document (Table 1 on page 4) was updated to reflect Galena as the new Applicant/Sponsor.
6. On September 9, 2013, Lazanda ownership transitioned from Archimedes Pharma US, Inc. to Depomed, Inc. The REMS Supporting document (Table 1 on page 4) was updated to reflect Depomed, Inc. as the new Applicant/Sponsor.

3. REMS ASSESSMENT PLAN

The Second REMS Assessment submitted on December 21, 2012 is currently under review. Therefore, the TRIG's proposed changes to the REMS Assessment plan and any future changes will be reviewed under separate cover.

4. CONCLUSION

DRISK finds the proposed TIRF REMS modification as received on September 24, 2013 acceptable. The revisions were proposed in response to an email dated June 28, 2012 by

the applicant to update TIRF REMS appended materials with Closed System Outpatient Pharmacy information. In addition, the following revisions were discussed and agreed upon during this review cycle.

- Revised terminology, processes, and definitions for outpatient pharmacies
- Revised terminology and definitions for wholesalers/distributors
- Revised attestations for physicians and patients to address concerns regarding patient access
- Revised Program Overview and Frequently Asked Questions to improve clarity and content
- Updated REMS materials to reflect the completion of the transition phase for the TIRF REMS Access Program

The timetable for submission of assessments of the REMS will remain the same as that approved on December 28, 2011.

The REMS assessment plan did not change, and will remain the same as that that described in the December 28, 2011 Approval letter.

5. RECOMMENDATIONS

The OSE, DRISK recommends approval of the TIRF REMS Modification, received between September 25-28, 2012 (see Table 2) and last amended through one joint submission into the drug master file (DMF) (027320) on September 24, 2013, and appended to this review.

ATTACHMENTS

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

/s/

KIMBERLY LEHRFELD

10/31/2013

TIRF SSS REMS Modification 2 Final review. Review is also attached to DMF 27320 on October 31, 2013.

CLAUDIA B MANZO

10/31/2013

concur