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 FINAL REVIEW

Date:	December 16, 2014
Reviewer(s)	Cathy A. Miller, MPH, BSN, Risk Management Analyst Division of Risk Management (DRISK) Joan Blair, MPH, Health Communication Analyst, DRISK
Team Leader	Kimberly Lehrfeld, Pharm.D., DRISK
Acting Division Director:	Reema Mehta, Pharm.D., M.P.H., DRISK

Drug Names, Dosage Form and Sponsor:

Table 1

Drug Name	Dosage Form and Route	NDA/ANDA Number	Sponsor
Abstral (fentanyl)	Sublingual tablet	022510	Galenya BioPharma
Actiq (fentanyl citrate)	Oral transmucosal lozenge	020747	Cephalon, Inc.
Fentora and	Buccal tablet	021947	Cephalon, Inc.
Lazanda (fentanyl)	Nasal spray	022569	DepoMed, Inc.
Onsolis (fentanyl)	Buccal soluble film	022266	Meda Pharmaceuticals
Subsys (fentanyl)	Sublingual spray	202788	Insys Therapy
Fentanyl Citrate	Transmucosal Troche/Lozenge	078907	Mallinckrodt
Fentanyl Citrate	Transmucosal Troche/Lozenge	077312	Par Pharm

Therapeutic class:	Opioid Agonist
Dosage forms:	Transmucosal Immediate release Fentanyl (TIRF)

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

OSE RCM: 2014-2057
TSI #: 290

Table 2: TIRF REMS Modification #3 DMF 27320 Seq. No. 0009 received May 20, 2014; amended November 25, 2014 Seq. No. 012 and December 10, 2014 Seq. No. 013

Drug Name	Applicant Holder Numbers	Suppl. Submitted Date; Amendment Submitted Date	Suppl. Number (Seq. No.)
Abstral	NDA 022510	March 12, 2014; amended July 25, 2014; December 9, 2014 May 21, 2014; amended December 1, 2014 and December 15, 2014	S-013 (0086; 0091 and 0098 S-014 (0089; 0097 and 0099)
Actiq	NDA 020747	May 21, 2014; amended November 26, 2014 and December 11, 2014	S-041 (0041; 0045 0046)
Fentora	NDA 021947	May 21, 2014; amended November 26, 2014 December 11, 2014	S-022 (0048; 0056 and 0057)
Lazanda	NDA 022569	May 21, 2014; amended November 26, 2014 and December 11, 2014	S-020 (0115; 0120 0123)
Onsolis	NDA 022266	May 21, 2014; amended November 26, 2014 and December 11, 2014	S-014 (0120; 0124 and 0125)
Subsys	NDA 202788	May 20, 2014; amended November 26, 2014 and December 11, 2014	S-012 (0081; 0090 and 0092)
Fentanyl Citrate	ANDA 077312	May 21, 2014; amended November 26, 2014 and December 11, 2014	S-006 (0021; 0025 and 0026)
Fentanyl Citrate	ANDA 078907	May 20, 2014; November 26, 2014 and December 11, 2014	S-012 (0055; 0059 and 0061

1 INTRODUCTION

This is a review of the proposed risk evaluation and mitigation strategy (REMS) modification for the Transmucosal Immediate-Release Fentanyl (TIRF) REMS Single Shared System (SSS) originally submitted by the Transmucosal REMS Industry Group (TRIG) between March 12 and May 21, 2014, and amended between November 25-26, 2014, December 10, 2014 and between December 15, 2014. See Table 2 for detailed submission information.

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
- Approved generic equivalents of these products

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

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 (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 Access Program assessments is at 6 and 12 months from the date of the initial REMS approval, and annually thereafter.

1.2 REGULATORY HISTORY

- On May 20, 2014, the TRIG submitted a proposed REMS modification to the SSS TIRF REMS. The regulatory history for the proposed TIRF REMS Modification #3 is detailed in the DRISK TIRF REMS Modification Interim Comments review by Cathy Miller dated October 20, 2014.
- On March 12, 2014, Galena Biopharma submitted a prior approval supplement (S-013) Abstral (fentanyl) sublingual tablets, proposing the conversion from Actiq (fentanyl citrate) transmucosal lozenge, to Abstral, including a proposed TIRF REMS modification. It was determined that this proposed revision would affect select TIRF REMS material.
- On July 29, 2014, DRISK completed the review of Abstral S-013/Proposed REMS Modification. As cited above, these modifications affected the TIRF REMS, and therefore, would be incorporated into the TIRF REMS modification #3 currently under review.
- On November 4, 2014, DAAAP approved Abstral S-013 including revised TIRF REMS documents.
- On November 5, 2014, Galena BioPharma sent an email notification to all TRIG TIRF product applicant holders, notifying them of S-013 approval for the conversion of Actiq to Abstral.
- On November 5, 2014, the TRIG sent an email communication to OSE (project manager Vaishali Jarral) confirming the approval of Abstral S-013 and the requesting three additional business days to make the changes to the TIRF REMS to incorporate Abstral conversion information. The TRIG proposed the following submission timeline:

Action Item	Current Plan:	Date of submission allowing TRIG to incorporate Galena's changes:
Submit finalized documents by e-mail to VJ	November 12, 2014	November 17, 2014
Submit all documents to DMF	November 18, 2014	November 21, 2014
Submit notification of DMF submission to each individual sponsors' applications	November 19, 2014	November 24, 2014

- On November 6, 2014, OSE (project manager Vaishali Jarral) sent an email communication to the TRIG agreeing to the TRIG's requested revision to the timeline and requested that the TRIG submit all final TIRF REMS documents via email in advance of the final submission to the DMF to provide DRISK an opportunity to review all documents for accuracy.
- On November 7, 2014, the TRIG sent an email communication to OSE/DRISK (project manager Vaishali Jarral) with clarifying questions related to our November 6, 2014 email communication. They requested that our proposed modification to the TIRF REMS Access Program Knowledge Assessment Question 11 be modified slightly so that there were only four multiple choice answer options due to program issues with formatting that requires only four rather than five options to multiple choice questions. Their proposal read:

  Select one option
  a) Actiq to Abstral *Lazanda to Actiq*
  b) Actiq to Fentora
  c) Actiq to Subsys
  d) All of the above ~~Both B&C~~
- On November 7, 2014, OSE/DRISK replied to the TRIG's email and requested clarification on the formatting of the TIRF REMS Access Program Knowledge Assessment Question 11, specifically, whether they inadvertently failed to strike through "Lazanda to Actiq" in option 'a'
- On November 10, 2014, the TRIG replied to OSE/DRISK November 7, 2014 email and indicated that they failed to strike through "Lazanda to Actiq" in option 'a'.
- On November 13, 2014, DRISK was notified by Office of Generic Drugs that there were inconsistencies in the dosage titration information contained in the Abstral U.S. Prescribing Information (USPI) Section 2.2, which were also reflected in relevant TIRF REMS materials.[1]
- On November 14, DAAAP notified Galena of the inconsistencies identified in the Abstral USPI.
- On November 17, 2014, the TRIG emailed OSE the revised TIRF REMS material, as previously agreed upon, which incorporated revisions to all the TIRF REMS materials made as a result of DRISK TIRF REMS Modification Interim comments #1 and #2 reviews (C. Miller).
- On November 18, 2014, the Office of Surveillance and Epidemiology (OSE) (project manager Vaishali Jarral) notified the TRIG via email to correct the error contained in the TIRF REMS Access Education Program Products Covered Under

[1] Gierhart, Brenda, Office of Generic Drugs, email communication to OSE and DAAAP dated November 13, 2014.

this Program table for Abstral in their final TIRF Modification Submission #3 due to be submitted to the DMF on Friday, November 21, 2014.

- On November 25, 2014, the TRIG submitted the final TIRF REMS Modification #3 to drug master file (DMF 27320) Seq. No. 0012, incorporating all previously communicated revisions to the TIRF REMS
- Between November 25, 2014 and December 1, 2014 , all TIRF applicant holders submitted amendments to their prior approval supplements for the current TIRF REMS modification (See Table 2 for detailed submission information).
- On November 26, 2014, DRISK noted that the TRIG submission of the complete TIRF REMS did not include all the appended material and subsequently, the OSE PM requested, via email, that the TRIG resubmit their final TIRF REMS to include all appended material. OSE also requested that the TRIG notify all applicant holders of the need for their resubmission cover letters referencing the DMF and to assure that all of their submissions included the current Medication Guide (MG) or reference to their current MG in the cover letters.
- On December 2, 2014, the TRIG notified OSE via email, that their resubmission of the complete TIRF REMS, as directed above, would be submitted to the DMF on December 10, 2014 and applicant holders would subsequently submit their cover letters to their applications referencing the DMF submission on the following date, December 11, 2014. The TRIG confirmed that they would provide directives to the applicant holders to include their most currently approved MG or reference as such in their cover letters.
- On December 9, 2014, Galena submitted the requested Abstral correction to the TIRF REMS Education Program Products Covered document in the TIRF REMS, for prior approval supplement (S-013) (Seq. No. 0098)
- On December 10, 2014, the TRIG submitted their final TIRF REMS and all appended material (DMF 27320) (Seq. No. 0013) as a "replace for Seq. No. 0012" which reflects the correct and final TIRF REMS for Modification #3.
- Between December 11 – December 15, 2014, the TIRF REMS applicant holders submitted their cover letters referencing the December 10, 2014 submission of the final TIRF REMS reflecting Modification #3 to the (DMF 27320), along with reference to their current MGs. (see Table 2 on Page 2 for detailed submission information)

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- TIRF REMS Industry Group (TRIG) Drug Master File (DMF 27320) Transmucosal Immediate Release (TIRF) Access Program REMS Modification received May 20, 2014 (Seq. No. 0099) and submitted to individual applicant holders (see table on page 2)

- TIRF REMS Industry Group (TRIG) Drug Master File (DMF 27320) Transmucosal Immediate Release (TIRF) Access Program REMS Modification Amendment received November 25, 2014 (Seq. No. 012) and to individual applicant holders (see table on page 2)
- TIRF REMS Industry Group (TRIG) Drug Master File (DMF 27320) Transmucosal Immediate Release (TIRF) Access Program REMS Modification Amendment received December 10, 2014 (Seq. No. 013) and to individual applicant holders (see table on page 2)

- Galena's Abstral Prior Amendment to Approval Supplement (S-013) REMS Modification dated December 9, 2014 (Seq. No. 0098)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Miller, C. DRISK REMS Modification Review for Abstral (NDA 22510) DARRTS dated July 29, 2014
  - Miller, C. DRISK REMS Modification Addendum Review for Abstral (NDA 22510) DARRTS dated December 10, 2014
- Miller, C. DRISK TIRF REMS Modification Review #1 of the TIRF REMS dated October 20, 2014.
- Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Prior Approval Labeling Supplement (S-013) for Abstral (fentanyl) sublingual tablets approval letter dated November 4, 2014.
- Miller, C. DRISK TIRF REMS Modification Review #2 of TIRF REMS dated November 5, 2014.
- All email communications as referenced in Section 1.2 Regulatory History.

3 PROPOSED REMS MODIFICATION

The following information below outlines the Proposed TIRF REMS Modification #3. Details and prior regulatory history for these proposed modifications can be found in DRISK Abstral REMS Modification Review (dated July 29, 2014) DRISK TIRF REMS Modification Review#1 (dated October 20, 2014), and DRISK TIRF REMS Modification Review #2 (dated November 5, 2014).

3.1 REMOVAL OF NDC NUMBERS

This modification proposes updates of select REMS materials to eliminate product specific information NDC numbers and replace with a link on the TIRF REMS Access Program website that references the information for interested stakeholders. The revision was made to reduce Sponsor and Agency administrative burden for multiple modifications to incorporate this product specific information. Agreement was made that removal of this information did not impact the safe use of the TIRF products and

minimizes the need for repeated modifications as the program continues to grow. The impacted REMS materials include:

- Independent Outpatient Pharmacy Enrollment Form
- Chain Outpatient Pharmacy Enrollment Form
- TIRF REMS Website Prototype

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.2 REMOVAL OF REFERENCE TO GENERICS

This modification proposes updates of select REMS materials to eliminate reference to generics which does not impact the safe use of TIRF, and replace the reference generics with (**) beside the trade name drug, and an accompanying footnote stating "This includes approved generic equivalents of these products". The revision was made to reduce Sponsor and Agency administrative burden for originated from internal discussions about certain aspects of the TIRF REMS program that prompt repeated administrative process and multiple modifications to incorporate this product specific information.. Agreement was made that removal of this information and replacing with the referenced (**) and footnote did not impact the safe use of the TIRF products and minimizes the need for repeated modifications as the program continues to grow. Impacted REMS materials include:

- Education Program for Prescribers and Pharmacists

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.3 REMOVAL OF ATTACHMENT 1' LIST OF TIRF MEDICINES/REPLACE WITH HYPERLINK TO FDA APPROVED REMS WEBSITE

This modification proposes the removal of 'Attachment 1' list of TIRF medicines in select REMS documents while replacing the list with a hyperlink that redirects the user to FDA Approved Risk Evaluation and Mitigation Strategy (REMS) website. As discussed above in Section 3.1, this revision was made to reduce Sponsor and Agency administrative burden for originated from internal discussions about certain aspects of the TIRF REMS program that prompt repeated administrative process and multiple modifications to incorporate this product specific information.. Agreement was made that removal of this information did not impact the safe use of the TIRF products and minimizes the need for repeated modifications as the program continues to grow. The impacted REMS materials include:

- TIRF REMS Document
- TIRF REMS Supporting 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
- TIRF Website Prototype and TIRF Website Landing Page

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.4 CRITERIA FOR INACTIVATION OF PATIENT-PRESCRIBER AGREEMENT FORM (PPAF)

This modification proposes revisions to the criteria for the description of triggers that will inactive a patient's PPAF, including the removal of the criteria of 'patients who receive prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame, that is suggestive of misuse, abuse, or addiction'. The modification also proposes the addition of criteria that will trigger inactivation of a patient PPAF. The current TIRF REMS has only one criteria listed which is "the patient has not filled a prescription for more than six (6) months. This revision resulted in the addition of the following 3 criteria:

- PPAF has expired
- Patient is deceased
- Patient chooses to no longer participate in the TIRF REMS Access Program

The impacted REMS materials include:

- TIRF REMS Document
- TIRF REMS Supporting Document

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.5 REVISION OF REMS ASSESSMENT METRICS

As a result of the 24-month TIRF REMS Assessment (submitted December 30, 2013), and subsequent DRISK 24-Month TIRF REMS Assessment review (dated June 19, 2014), changes to the TIRF REMS Assessment were communicated to the TRIG in the TIRF REMS Assessment Acknowledgement letter dated August 21, 2014. The REMS Assessment Plan changes are reflected in the TIRF REMS Supporting document submitted as part of this TIRF REMS Modification.

Reviewer Comments: The REMS Assessment Plan changes communicated to the TRIG on August 21, 2014 are accurately reflected in the TIRF REMS Supporting Document. See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.6 REVISIONS TO ENHANCE KNOWLEDGE ABOUT CONVERSION OF TIRF MEDICINES

The TRIG is proposed a modification to emphasize and strengthen risk messaging about the conversion of TIRF medicines based on prescriber survey and knowledge assessment results that demonstrated low comprehension of this concept. The impacted REMS materials and proposed revisions include:

- Education Program for Prescribers and Pharmacists
- TIRF REMS Access Website

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.7 INFORMATION ABOUT THE TIRF REMS CASH CLAIM TRANSACTION PROCESS

This revision, proposed by the TRIG, added information to select TIRF REMS material to enhance understanding about the correct TIRF REMS Cash Claim transaction process. The TRIG states that these revisions are proposed based on several pharmacies' acknowledgement that they are unaware of the cash claim processing requirements, and is documented as part of the TIRF REMS 24-Month Assessment Report (Table 29, Non-Compliance Activity Reports by Stakeholders). The impacted REMS materials and proposed revisions include:

- TIRF REMS Access Program Frequently Asked Questions (FAQ) Document
- Independent Outpatient Pharmacy Overview
- Chain Outpatient Pharmacy Overview
- Closed System Outpatient Pharmacy Overview

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.8 UPDATE THE TIRF REMS WEB PROTOTYPE DOCUMENT AND WEBSITE LANDING PAGE

This modification proposes revisions to the TIRF REMS Access Web Prototype and Website Landing Page, that incorporations all changes outlined above, where identified, along with the following additional revisions, along with updates to the Resources for Prescribers, Resources for Patients and Resources for Distributors Tabs to add a link for the appropriate products list, as requested in DRISK TIRF REMS Modification Interim comments1 review.

Reviewer Comments: See REMS Modification #3 Interim Comments 1 review (C. Miller) dated November 4, 2014 for discussion.

3.9 ADDITIONAL MODIFICATIONS PROPOSED RELATED TO ABSTRAL (NDA 22510) PRIOR APPROVAL SUPPLEMENT (S-013)

The TIRF REMS Access Program Education Program for Prescribers and Pharmacists

Galena's amended PAS/Proposed REMS Modification submission for S-013 (NDA 22510), as discussed above in Section 1.2 Regulatory History, includes the following proposed revision to Section 2.2 of the Abstral PI:

2.2 Conversion from Actiq

The initial dose of Abstral is always 100 mcg with the only exception being patients already using Actiq.

a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patients on Actiq. See Table 1 for initial dosing recommendations. 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 Abstral Dose (mcg)
200	100 mcg
400	200 mcg
600	200 mcg
800	200 mcg
1200	200 mcg
1600	400 mcg

b. For patients converting from Actiq doses ~~400~~ 200 mcg ~~and below~~, initiate titration with 100 mcg Abstral and proceed using multiples of this strength.

As a result, the TIRF REMS Access Program Education Program for Prescribers and Pharmacists – Products Covered Under this Program Table (Abstral) was revised as indicated below:

Products Covered Under this Program:**

Product	Dosage and Administration			Titration
	Initial Dose	Max Dose Per Episode	Frequency	
Abstral® (fentanyl) sublingual tablets	Abstral is aAlways 100 mcg. (unless the patient is being converted from ≥400 mcg ACTIQ - please see Full Prescribing Information).	If adequate analgesia is not obtained the patient may use a second ABSTRAL dose (after 30 minutes) as directed by their healthcare provider. No more than two doses of ABSTRAL may be used to treat an episode of breakthrough pain.	Patients must wait at least 2 hours before treating another episode of breakthrough pain with ABSTRAL.	If adequate analgesia was not obtained with the first 100mgc dose, continue dose escalation in a stepwise manner over consecutive breakthrough episodes until adequate analgesia with tolerable side effects is achieved. During titration, patients can be instructed to use multiples of 100 mcg tablets and/or 200 mcg tablets for any single dose. Instruct patients not to use more than 4 tablets at one time.
Actiq® (fentanyl citrate) oral transmucosal lozenge	Always 200 mcg.	If the breakthrough pain episode is not relieved after 30 minutes, patients may take 1 additional dose using the same strength. Patients should not take more than 2 doses of ACTIQ per breakthrough pain episode.	Patients must wait at least 4 hours before treating another breakthrough pain episode with ACTIQ.	Closely follow patients and change the dosage level until adequate analgesia with tolerable side effects is achieved with a single unit.

Note: This table is also available to print for use as a quick reference guide. Please visit www.TIRFREMSaccess.com for further information and resources.

** This includes approved generic equivalents of these products.

Reviewer Comments: DRISK confirmed in consultation with DAAAP via email on November 14, 2014, that the Abstral dose begins to titrate above 100 mcg when a patient is being converted from greater than or equal to 400 mcg of ACTIQ, not 600 mcg. Subsequently, the language contained in the TIRF REMS Access Program for Prescribers and Pharmacists table for Abstral should read: (unless the patient is being converted from ≥ 400 mcg of ACTIQ – please see Full Prescribing Information).

4 CONCLUSION

The REMS Modification to the TIRF REMS Access Program is acceptable to the Office of Surveillance and Epidemiology, Division of Risk Management (OSE/DRISK).

All revisions as cited above, were incorporated into the attached TIRF REMS document and appended materials.

5 RECOMMENDATIONS

OSE/DRISK recommends approval of the TIRF REMS Modification, received on May 20, 2014, last amended through one joint submission into drug master file (DMF) 27320 on November 25, 2014 and amended December 10, 2014 (see Table 2 for detailed submission information for TIRF product applicant holders), and appended to this review.

ATTACHMENTS

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Initial REMS approval: 12/2011

Most recent modification: XX/2014

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

FOLLOWING THIS PAGE, FDA_7025 TO FDA_7155 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/

CATHY A MILLER
12/16/2014

REEMA J MEHTA
12/16/2014
I concur.