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
Interim Comments #1

Date: November 4, 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

Table 1

Drug Names, Dosage Form and Sponsor:

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 (fentanyl)	Buccal soluble film	022266	Meda Pharmaceuticals
Subsys (fentanyl)	Sublingual spray	202788	Insys Therapy

Therapeutic class: Opioid Agonist

Dosage forms: Transmucosal Immediate release Fentanyl (TIRF)

Table 2: TIRF REMS Modification #3 DMF 27320 Seq. No. 0009 received May 20, 2014			
Drug Name	**NDA Number**	**Suppl. Submitted Date; Amendment Submitted Date**	**Suppl. Number (Seq. No.)**
Abstral	022510	March 12, 2014; amended July 25, 2014 May 21, 2014	S-013 (0086; 0091) S-014 (0089)
Actiq	020747	May 21, 2014	S-041 (0041)
Fentora and AG	021947	May 21, 2014	S-022 (0048)
Lazanda	022569	May 21, 2014	S-020 (0115)
Onsolis	022266	May 21, 2014	S-014 (0120)
Subsys	202788	May 20, 2014	S-012 (0081)
Abbreviations: *Amend.=Amendment; AG=Authorized Generic; DMF=Drug Master File; LOA=Letter of Authorization; Seq. No.=Sequence Number; Suppl.=Supplement; NDA=New Drug Application*			

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

OSE RCM #: 2014-2057

TSI #: 290

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n/a = not applicable

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) submitted by the Transmucosal REMS Industry Group (TRIG) between March 12 and May 21, 2014 (see Table 2 on cover page 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 single shared system 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

- 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 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. The proposed revision would affect select TIRF REMS material.
- On November 4, 2014, DAAAP approved Abstral prior approval supplement (S-013) including revised TIRF REMS documents, reviewed by DRISK[1] which subsequently prompting additional modifications to the TIRF REMS, currently under review, thereby requiring an amendment to the current proposed TIRF REMS Modification #3.

1.3 MATERIALS INFORMING OUR REVIEW:

- Miller, C. DRISK REMS Modification Review for Abstral (NDA 22510) DARRTS dated July 29, 2014
- Miller, C. DRISK TIRF REMS Modification Interim Comments #1 review of the TIRF REMS dated October 20, 2014.

2 PROPOSED REMS MODIFICATION WITH RATIONALE

On November 4, 2014, Abstral (fentanyl) sublingual tablets (NDA 22510) prior approval supplement/REMS Modification (S-013) was approved[2]. This supplement approval included language to allow direct conversion from Actiq (fentanyl) oral transmucosal lozenge, which is bioequivalent to Abstral, without re-titration. This supplement also included the DRISK review of the TIRF REMS and subsequently required revisions to select TIRF REMS material as discussed in the DRISK Abstral REMS Modification Review[3]. These revisions to TIRF REMS material include the following:

1. **Education Program for Prescribers and Pharmacists**:

[1] DRISK REMS Modification Review for Abstral (NDA 22510) DARRTS July 29, 2014 (C. Miller)

[2] DAAAP Prior Approval Labeling Supplement (S-013) for Abstral (fentanyl) sublingual tablets approval letter dated November 4, 2014.

[3] Miller, C. DRISK REMS Modification Review for Abstral (fentanyl) sublinqual tablets completed July 29, 2014

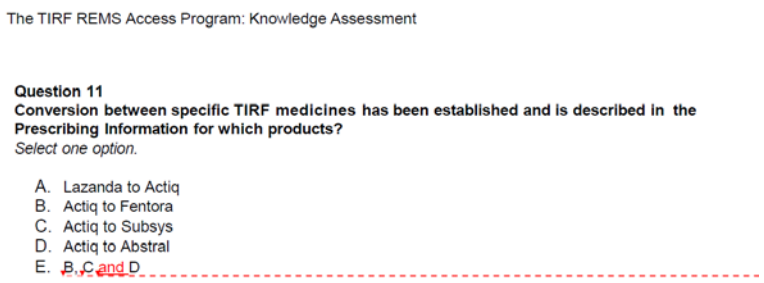
a. Slide 15:

For patients being converted specifically from Actiq to Fentora, Actiq to Subsys **or Actiq to Abstral,** you must refer to the Full Prescribing Information for detailed information

b. Slide 17 Products covered Under this Program for Abstral

Product	Initial dose	Max dose per episode	Frequency	Titration
Abstral® (fentanyl) sublingual tablets	Always 100 mcg. (unless the patient is being converted from □600 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 100 mcg 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.

TIRF REMS Knowledge Assessment Question 11:



The TIRF REMS Access Program: Knowledge Assessment

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

A. Lazanda to Actiq
B. Actiq to Fentora
C. Actiq to Subsys
D. Actiq to Abstral
E. B, C and D

Reviewer comments: Based on the approval of this prior approval supplement, these modifications will need to be incorporated in this TIRF REMS Modification and and are provided in our full recommendations to the TRIG in Section 6 along with accompanying Attachments that include DRISK comments and track change documents.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments below (Section 4 Comments for the Applicant) on the TIRF REMS Access Program proposal. Please request that the TRIG respond to these comments as soon as possible to facilitate further review for this submission.

The comments below are based on DRISK's preliminary review of the REMS modification proposal for TIRF products. Appended to this review is the REMS modification proposal and the REMS materials including comments and track changes

4 COMMENTS FOR THE APPLICANT

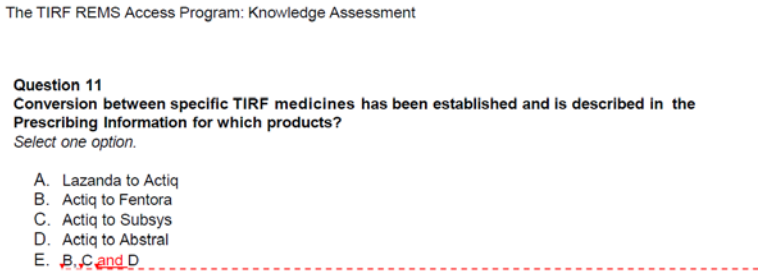
We have the following comments, below, as a result of the approval prior approval supplement (S-013) REMS modification for Abstral (NDA 22510) on November 4, 2014.

EDUCATION PROGRAM FOR PRESCRIBERS AND PHARMACISTS (ATTACHMENT 3)

1. **Slide 15:** Dosage and Administration General, Bullet #3 should be revised as indicated in the redlined document, to reflect the addition new conversion of Actiq to Abstral: For patients being converted specifically from Actiq to Fentora, Actiq to Subsys **or Actiq to Abstral**,you must refer to the Full Prescribing Information for detailed instructions.
2. **Slide 17:** Revise the Products covered Under this Program for Abstral, as indicated in the redlined document, under the 'Initial Dose' column to read **"unless the patient is being converted from 600 mcg ACTIQ. Please see Full Prescribing Information"**.

WEB PAGE PROTOTYPE (ATTACHMENT 17)

1. Page 46: Update the table to reflect updated information on conversion of Actiq to Abstral. Under the 'Initial Dose' column to read **"unless the patient is being converted from 600 mcg ACTIQ. Please see Full Prescribing Information"**
2. Page 62: Knowledge Assessment Question 11: Update to reflect updated information on conversion of Actiq to Abstral. Multiple choice question should be revised as follows:



The TIRF REMS Access Program: Knowledge Assessment

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D. Actiq to Abstral
E. B, C and D

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
11/04/2014

KIMBERLY LEHRFELD
11/05/2014