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

Risk Evaluation and Mitigation Strategy (REMS) Modification Review

Date:	June 01, 2012
Reviewer(s):	Division of Risk Management (DRISK) Megan Moncur, M.S. Senior Risk Management Gita A. Toyserkani, Pharm.D., MBA, Senior Risk Management Analyst Doris Auth, Pharm.D., Risk Management Analyst
Team Leader:	Megan Moncur, M.S. DRISK
Division Director	Claudia Manzo, Pharm.D. DRISK
Drug Name(s):	See table below
Therapeutic Class:	Opioid Agonist: Transmucosal Immediate-Release Fentanyl (TIRF) Products

Drug Name	Dosage and Route	Application Type/Number	Supplement Number	Applicant/ Sponsor	TSI #
Abstral (fentanyl)	Sublingual tablet	NDA 22-510	S-005	Prostrakan, Inc.	-
Actiq (fentanyl citrate)	Oral transmucosal lozenge	NDA 20-747	S-034	Cephalon, Inc.	-
Fentora (fentanyl citrate)	Buccal tablet	NDA 21-947	S-015	Cephalon, Inc.	290
Lazanda (fentanyl)	Nasal spray	NDA 22-569	S-007	Archimedes Pharma US Inc.	-
Onsolis (fentanyl)	Buccal soluble film	NDA 22-266	S-009	Meda Pharmaceuticals	-
Subsys (fentanyl)	Sublingual spray	NDA 202-788	S-003	Insys Therapy	-

*** This document contains proprietary and confidential information that should not be released to the public. **

1 INTRODUCTION

The purpose of this review is to document the Office of Surveillance and Epidemiology (OSE), Division of Risk Management's (DRISK) acceptance of the proposed Risk Evaluation and Mitigation Strategy (REMS) Modification for the Transmucosal Immediate-Release Fentanyl (TIRF) Single-Shared REMS. This is the first modification that has been proposed for the TIRF REMS.

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

1.2 REGULATORY AND OTHER RELEVANT HISTORY

A single-shared REMS program, the TIRF REMS Access Program, was approved on December 28, 2011. Subsequently, an enforcement discretion letter was issued[1] that detailed conditions and timelines that were to be met during transition to the full operation of the TIRF REMS, including deadlines for launch of the system (March 12, 2012), for implementation of a solution to allow closed system pharmacies[2] to participate in the TIRF REMS (April 30, 2012), and for enrolling closed system pharmacies in the TIRF REMS (June 30, 2012).

[1] There have been two enforcement discretion letters issued for the TIRF REMS. The first letter was issued on January 31, 2012, but was superseded. The second letter was approved in DARRTS on March 20, 2012, but, inadvertently, not provided to TIRF sponsors until May 11, 2012.

[2] For the purpose of the TIRF REMS, a closed system pharmacy is defined as an outpatient pharmacy that uses a pharmacy management system that does not support the process of electronically transmitting the validation and claim information currently required by the TIRF REMS Access program. For example, some pharmacies that are part of integrated healthcare delivery systems may qualify as closed system pharmacies.

At the time of the TIRF REMS approval, an NDA for the TIRF product Subsys was under review. On January 4, 2012, Subsys received agency approval; FDA notified the TIRF sponsors that they would be required to submit a REMS Modification to include the newly approved product. The TIRF sponsors proposed additional, editorial revisions to include in the REMS modification. Consequently, a REMS Modification was also required to be submitted for Subsys. The REMS Modifications were received in February 2012[3].

On February 29, 2012, DAAAP notified DRISK that new packaging configurations for Subsys were under review, and therefore, new NDC numbers would need to be included in the relevant TIRF materials. During a teleconference on March 16, 2012, FDA notified the TIRF sponsors of the need to revise the NDC numbers, and informed them of other required editorial changes (e.g. including the correct version of Attachment 1). The TIRF sponsors provided verbal approval for FDA to incorporate these minor changes on their behalf, thus precluding the need for another submission.

On March 12, 2012, the single-shared system was launched. Shortly thereafter, multiple offices across the agency were contacted by external stakeholders with concerns and questions about the TIRF REMS. Many of the concerns raised referenced operational issues, which the TIRF sponsors were able to effectively manage and address within the context of the approved REMS. However, to address a concern that was raised about the privacy language in the Patient-Provider Agreement Form (PPAF)[4], FDA determined that changes to the REMS would be required. To expedite approval of these changes, they were incorporated in the February 2012 REMS modification that was already under review.

On April 12, 2012, the TIRF sponsors submitted (via e-mail) a proposed closed system pharmacy enrollment form. To ensure that enrollment of closed system pharmacies could be completed prior to the June 30th deadline, as specified in the enforcement discretion letter, FDA revised the REMS document to incorporate information about the closed system pharmacy solution and the new enrollment form. FDA informed the TIRF sponsors that the closed system revisions, and the revisions to the PPAF would be added to the REMS modification already under review; redline versions of the revised documents were e-mailed to the sponsors on May 15, 2012.

The TIRF sponsors documented their acceptance of all revisisions proposed by FDA in a memo that they e-mailed to OSE Project Manager, Mark Liberatore, on May 31, 2012 (see Memorandum to File, dated June 01, 2012). All revisions are discussed further in Section 3.

[3] The REMS Modifications were submitted to each TIRF sponsor's NDA between February 08 and 13, 2012

[4] The stakeholder, who was both a physician and pain patient, expressed concern that language in the PPAF was asking people to relinquish their rights to their protected health information (PHI) in order to have access to TIRF medications.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials were reviewed:

- NDA submissions:

Drug Name	Application Type & Number	Supplement Number	FDA Received Date
Abstral	NDA 22-510	S-005	February 13, 2012
Actiq	NDA 20-747	S-034	February 08, 2012
Fentora	NDA 21-947	S-015	February 09, 2012
Lazanda	NDA 22-569	S-007	February 10, 2012
Onsolis	NDA 22-266	S-009	February 10, 2012
Subsys	NDA 202-788	S-003	February 08, 2012

- Submission(s) sent via e-mail to the OSE Project Management staff
    - April 12, 2012; e-mail to Darrell Jenkins (closed system enrollment form)
    - May 30, 2012; e-mail to Mark Liberatore (additional revisions proposed by TIRF sponsors)

The following materials were referenced:

- May 31, 2012; e-mail to Mark Liberatore (Memo from TIRF sponsors)

2.2 ANALYSIS TECHNIQUES

The REMS modification was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA), and to ensure that only FDA-required changes were made.

3 RESULTS OF REMS MODIFICATION REVIEW

An overview of the documents that have been revised under this REMS Modification is included in the table below. For additional details, refer to Appendix 1 for redline versions of all revised documents.

Document Name	Overview of revision(s)
REMS document	> Added revised PPAF attestation > Added information about closed system pharmacies, and the related enrollment form > Removed the word 'proposed' from the coversheet
Attachment 1	> Added Subsys to the list of products
PPAF	> Revised attestation and privacy language to address stakeholder concerns
Closed System Pharmacy Enrollment Form	> New form
Pharmacy Enrollment Forms (Outpatient and Chain)	> NDC#s for Subsys were added and subsequently revised > Replaced submitted version of Attachment 1 (which includes extraneous information) with version that only lists the names of the TIRF products
Education Program	> Updated product-specific information to include Subsys
Letters (Outpatient Pharmacy, Inpatient Pharmacy, and Distributor)	>Subsys added to the list of products mentioned in the letters

4 DISCUSSION & CONCLUSION

In conclusion, the revisions proposed in the TIRF REMS modification (submitted by individual TIRF sponsors between February 8 through 13, 2012), and described in Section 3 above, are acceptable.

5 RECOMMENDATIONS

DRISK recommends approval of the TIRF REMS modification submitted in February 2012, and appended to this review (see Appendix 2).

APPENDIX 1

Redline Versions of Revised Documents

FOLLOWING THIS PAGE, FDA_6220 TO FDA_6393 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/

MEGAN M MONCUR
06/04/2012

ROBERT B SHIBUYA
06/04/2012
I concur (signing for Claudia Manzo).