

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products

NDA/BLA #s: 202788
PRODUCTS: Subsys (fentanyl sublingual spray)
APPLICANT: Insys, Inc.
FROM: Bob A. Rappaport, M.D., Director, Division of Anesthesia,
Analgesia, and Addiction Products

DATE: January 2, 2011

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for fentanyl sublingual spray to ensure that the benefits of the drug outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors. In reaching this determination we considered the following:

- A. The estimated number of patients in the United States with breakthrough cancer pain is between 1 to 2 million. This estimate is based upon the number of patients with cancer in the US (American Cancer Society), the proportion of cancer patients with moderate to severe pain¹, and the proportion of cancer patients with breakthrough pain².

¹ Marieke HJ, van den Beuken-van Everdingen MHJ, deRijke JM, Kessels SG, Schouten HC, van Kleef M, Patijn. High prevalence of pain in patients with cancer in a large population-based study in The Netherlands. *Pain* 2007;132:312-320.

B. The patients for this product are cancer patients with pain that cannot be adequately controlled using around-the-clock oral or transdermal opioids alone. Many of these patients have multiple concurrent complications of their underlying disease and therapy.

C. The expected benefit of the drug to patients is that the delivery system is different from the existing oral transmucosal fentanyl products. This product is the first of these products to be formulated as a sublingual spray.

D. The expected duration of treatment with the drug will be from days for the sickest patients who are preterminal, to months for patients with less tumor burden and longer prognoses for survival.

E. The most serious of the known adverse events that are related to the use of fentanyl-containing products include death, respiratory depression, and CNS depression which occur primarily if the product is not used properly. In addition to the aforementioned risks, fentanyl sublingual spray, as other fentanyl-containing products, can have a potential to increase intracranial pressure and induce bradyarrhythmias.

F. Fentanyl sublingual spray is not a new molecular entity

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Subsys (fentanyl sublingual spray). FDA has determined that Subsys (fentanyl sublingual spray) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Subsys (fentanyl sublingual spray). FDA has determined that Subsys (fentanyl sublingual spray) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks relative to benefits of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Subsys (fentanyl sublingual spray).

The elements of the REMS will be a Medication Guide, elements to assure safe use including prescribers training, pharmacies certification, and dispensing Subsys (fentanyl sublingual spray) to patients with evidence or other documentation of safe use conditions, an implementation system, and a timetable for submission of assessments of the REMS.

Bob A. Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Addiction Products

² Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain* 1999;81:129-134.

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/s/

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01/02/2012

BOB A RAPPAPORT
01/03/2012

**Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 29, 2011

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products (DAAP)

Through: Claudia Karwoski, Pharm.D., Director
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From: **Scientific Lead,**
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DRISK Review Team
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Gita A. Toyserkani, Pharm.D., MBA, Senior Risk
Management Analyst

Subject: Final Risk Evaluation and Mitigation Strategy (REMS)
review for Subsys (Fentanyl) sublingual spray

Drug Name (Established Name): Subsys, fentanyl citrate sublingual spray

Dosage and Route: Sublingual spray 100mcg, 200mcg, 400mcg, 600mcg, and 800mcg

Therapeutic Class: Opioid

Application Type/Number: NDA 202-788

Applicant: Insys Therapeutics, Inc

Effective Date: 12/29/2011

1. INTRODUCTION

The purpose of this review is to evaluate the proposed Risk Evaluation and Mitigation Strategy (REMS) for Subsys (Fentanyl) sublingual spray.

1.1 Product Overview

Subsys is a formulation of fentanyl, a potent opioid analgesic, for administration as a spray via the sublingual route, and a member of a group of Schedule II controlled substances that the Agency has collectively termed transmucosal immediate release fentanyl (TIRF) products. Actiq, Fentora, Onsolis, Abstral, and Lazanda are approved TIRF medicines indicated for the management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. These formulations deliver fentanyl rapidly via the oral mucosa in a variety of dosage forms. Drug delivery in this manner eliminates first pass metabolism that occurs with oral formulations and results in increased bioavailability. Subsys is the first of the transmucosal products to be delivered as a spray for sublingual administration.

The time to maximum concentration for Subsys varies with dosage, ranging from 0.67 hours for the 600mcg dose to 1.25 hours for the 100 and 200mcg doses. The proposed indication for Subsys the same as for the approved TIRF medicines.

The rate and maximum plasma concentrations vary considerably between the available TIRF medicines, as well as Subsys, therefore, they are not interchangeable. Life-threatening respiratory depression may occur at any dose in the following situations: in patients who are not opioid tolerant, if accidentally consumed by a child or for anyone for whom they were not prescribed, or if used for the treatment of acute or postoperative pain. It is because of these risks that a REMS is required for the transmucosal immediate-release fentanyl products.

1.2 Regulatory and Review History for Subsys and the TIRF REMS

Subsys has been part of ongoing and interrelated discussions within the Agency that included the review teams for other TIRF products, and often involved Senior Management. Following receipt of the Subsys NDA, Insys Therapeutics, Inc became a member of the TIRF REMS Industry Working Group (TRIG) and began collaborating with the group to align the Single-Shared System (SSS).

Following are highlights of key regulatory actions and communications regarding the REMS for Subsys as well as the TIRF REMS Single Shared System:

17 August 2010: Pre-NDA meeting, fentanyl sublingual spray (FSS), (IND 72-411, meeting minutes memo dated 10/18/10, Author: Compton, K) Insys was instructed to submit a REMS for FSS with their original NDA submission which must include a Medication Guide, Elements to Assure Safe Use, an Implementation System, and a Timetable for Assessments. The development of a Single Shared REMS for all manufacturers of TIRF products was discussed and Insys was encouraged to work with other manufacturers towards this goal.

28 October 2010: Meeting with all TIRF medicine sponsors (innovator and generic), to inform them that, in order to minimize the burden on healthcare providers and patients, a

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single-shared REMS should be implemented for the TIRF medicines (Meeting Minutes: memo dated 01/03/2011; Author: Adeolu, Abolade A).

12 November 2010: REMS Notification letters were issued to all of the sponsors of the pending and approved TIRF products. The letters described the elements of the TIRF single-shared REMS that could be standardized and implemented for each TIRF product individually, and ultimately across all TIRF medicines collectively, as a single-shared REMS.

04 March 2011: Subsys (NDA 202788; Seq No. 000) submitted. The original submission included a proposed REMS similar to the approved individual REMS for Abstral.

09 December 2011: Submission of the TIRF REMS SSS to the NDAs for Actiq, Fentora, Onsolis, Abstral, Lazanda, and to the ANDA for Fentanyl Citrate Oral Transmucosal Lozenge.

28 December 2011: Approval of the TIRF REMS Single Shared System for the above TIRF medicines.

- **28 December 2011: Submission of SUBSYS REMS (NDA 202-788, Sequence 028).**

2. MATERIALS REVIEWED

2.1 Data and Information Sources reviewed

Subsys Proposed REMS, submitted on December 28, 2011

Subsys Prescribing Information, original submitted on 3/4/11, revision December 28, 2011

2.2 Data and Information Sources referenced

DRISK Final REMS Review for the TIRF Products, Reviewer Toyserkani GA, dated December 27, 2011.

3. RESULTS OF REVIEW OF PROPOSED SUBSYS RISK EVALUATION AND MITIGATION STRATEGY

Insys submitted the proposed REMS for Subsys which is identical to the approved TIRF REMS SSS with the following exceptions:

- The Subsys product name was added to the following documents:
 - All Letters (Dear Healthcare Provider, Inpatient and Outpatient Pharmacy, and Distributor)
 - Patient Prescriber Agreement
 - REMS Supporting Document
- Attachment 1 of the REMS (approved TIRF products) was also updated to include Subsys and is appended to the following documents:
 - All Overviews (Prescriber, Outpatient and Inpatient Pharmacy, Patient and Caregiver, Wholesaler)

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- All Enrollment forms (Prescriber, Outpatient, Chain, and Inpatient Pharmacy, and Wholesaler/Distributor)
- Product specific information on Subsys was added to the Educational Program.

Please refer to the December 27, 2011 Final REMS Review which describes the REMS document and REMS appended materials and provides DRISK's concurrence with the single-shared REMS for the TIRF medicines.¹

4. DISCUSSION AND RECOMMENDATIONS

The DRISK Review Team finds the proposed REMS for SUBSYS, as submitted December 28, 2011 (and appended to this review) to be acceptable, and recommends approval. Following approval of Subsys, each sponsor of an approved TIRF product in the SSS, will submit a proposed REMS modification which will be updated to include Subsys.

¹ Toyserkani G. Final REMS Review for Transmucosal Immediate-Release Fentanyl (TIRF) Products (NDAs 22-510, 20-747, 21-947, 22-569, 21-947, and 22-266), dated December 27, 2011.

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/s/

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12/29/2011

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