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 pain[1], and the proportion of cancer patients with breakthrough pain[2].

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[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 bradyarrythmias.

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

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[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/

SARA E STRADLEY
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 Division of Risk Management (DRISK)
From:	**Scientific Lead,** Doris Auth, Pharm.D., Risk Management Analyst **DRISK Review Team** Megan Moncur, M.S., Team Leader 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

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