CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202788Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	January 4, 2012
From	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Division Director Summary Review
NDA #	202788
Applicant Name	Insys Therapeutics, Inc.
Date of Submission	March 14, 2011
PDUFA Goal Date	January 4, 2012
Proprietary Name / Established (USAN) Name	Subsys Fentanyl Sublingual Spray
Dosage Forms / Strength	Single-dose sublingual spray 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
Proposed Indication	Management of breakthrough pain in patients with cancer, 18 years of age and older, who are already receiving and who are tolerant to regular opioid therapy for their underlying persistent cancer pain
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	
CDTL	Sharon Hertz, M.D.
Clinical Review	Luke Yip, M.D.
Biostatistics Review	Yan Zhou, Ph.D.; Dionne Price, Ph.D.
Pharmacology Toxicology Review	Elizabeth Bolan, Ph.D.; Dan Mellon, Ph.D.
ONDQA-CMC/Quality Review	Julia Pinto, Ph.D.; Prasad Peri, Ph.D.
OPS/NDMS-Microbiology Review	Bryan Riley, Ph.D.
CDRH/ODE/DAGID/GHDB	LCDR Alan Stevens, Jacqueline Ryan, M.D.
Clinical Pharmacology Review	Wei Qiu, Ph.D.; Yun Xu, Ph.D.
OSI	John Lee, M.D.; Susan Thompson, M.D.
Project Management	Kathleen Davies; Sara Stradley, M.S.
OSE/DMEPA	Anne Tobenkin, Pharm.D.; Lubna Merchant, Pharm.D.; Kellie Taylor, Pharm.D., MPH; Carol Holquist, R.Ph.
OSE/DRISK	Doris Auth, Pharm.D.; Megan Moncur, MS; Gita Toyserkani, Pharm.D., M.B.A.; Claudia Karwoski, Pharm.D.
OMP/OMPI/DMPP	Sharon Mills, BSN, RN; Barbara Fuller, RN, MSN; LaShawn Griffiths, MSHS-PH, BSN;
OMP/OPDP/DDTCP	L. Shenee' Toombs, Pharm.D.
Controlled Substances Staff	Chad Reissig, Ph.D.; Silvia Calderon, Ph.D.

OND=Office of New Drugs
OMP: Office of Medical Policy
OMPI=Office of Medical Policy Initiative
OPDP= Office of Prescription Drug Promotion
DMPP = Division of Medical Policy Programs
DDTCP: Division of Direct-to-Consumer Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention
DRISK= Division of Riak ManagementOSI=Office of Scientific Investigations
CDTL=Cross Discipline Team Leader
ONDQA=Office of New Drug Quality Assessment
OPS/NDMS=Office of Pharmaceutical Sciences/New Drug Microbiology Staff
CDRH/ODE/DAGID/GHDB=Center for Devices and Radiological Health/Office of Device Evaluation/Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices/General Hospital Devices Branch

1. Introduction

Insys Therapeutics, Inc. submitted this 505(b)(2) application for their sublingual, transmucosal, immediate-release formulation of fentanyl, packaged in a single-dose spray device. The referenced drug product application is Actiq, NDA 20-747. A single efficacy study was required for this NDA as this is our standard requirement for 505(b)(2) applications for reformulated opioid drug products for which there are no changes to the route of administration or patient population. In addition, several pharmacokinetic studies and two open-label safety studies were submitted in support of this application. Of note, the reviews for this application often refer to the product as fentanyl sublingual spray or FSS.

2. Background

The following summary of the history and development of the transmucosal, immediate-release fentanyl (TIRF) product class has been reproduced from page 2 of Dr. Hertz's review:

> This application represents the sixth NDA for a transmucosal immediate-release fentanyl (TIRF) product 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 regular opioid therapy for their underlying persistent cancer pain. Actiq was the first oral transmucosal fentanyl product approved and is a lozenge on a stick that is moved between the gum and the buccal mucosa. Actiq was approved under Subpart H, in large part because of the risk for accidental pediatric exposure due the similarity in appearance to a lollipop. A RiskMAP was created to attempt to manage the risks associated with this product. In addition to providing some methods to try and minimize the risk for accidental pediatric exposure, other goals described in the RiskMAP included preventing use in opioid non-tolerant patients and other unsafe off-label use. Fentora (NDA 21-947) was the second oral transmucosal fentanyl formulation approved and is a tablet that is placed between the buccal mucosa and gum where it dissolves with an element of effervescence. Fentora was approved with a RiskMAP comparable to Actiq.
>
> Onsolis (NDA 22-266), Abstral (NDA 22-510) and Lazanda (NDA 22-569) followed Actiq and Fentora. Onsolis is formulated as a bioerodible membrane that adheres to the buccal mucosa. Abstral is a sublingual tablet formulation. Lazanda is formulated as a nasal spray. These three products were approved with risk evaluation and mitigation strategies (REMS). The reason for the switch to a REMS is described below.
>
> The indication for this group of products, the management of breakthrough cancer pain in adult patients who are already receiving, and who are tolerant to, opioid therapy for their underlying persistent cancer pain is narrow for two reasons. First, the population identified has a specific need for a treatment to address cancer-associated breakthrough pain, which is characterized by a quick onset, often high severity, and relatively short duration. These formulations of fentanyl are designed to have a relatively rapid rise to Cmax and a relative short duration of effect. Fentanyl is a very potent opioid that can cause respiratory depression in microgram quantities. For this reason, the indication also

reflects the need for patients to be opioid-tolerant, a physiological state in which patients are more tolerant to the CNS depression and respiratory depression associated with opioids.

Based on the postmarketing history of the approved products, it became clear that prescribers have found the TIRFs to be useful in patients without cancer pain, both in the setting of chronic pain with episodes of breakthrough pain and other painful conditions. In the Actiq RiskMAP quarterly reports, the use of Actiq in noncancer pain has exceeded its use in cancer pain, although it is used primarily in opioid-tolerant patients with chronic noncancer pain.

Postmarketing trends have also shown an increasing number of nonopioid-tolerant patients being prescribed TIRFs and reports of deaths in opioid nontolerant patients. The TIRFs are not bioequivalent with one another, and in spite of warnings in the labeling, have been inappropriately substituted in the pharmacy and by prescribers. As a result, the Agency determined the risks associated with these products would be better addressed through a REMS than the original risk management programs. Abstral, Onsolis and Lazanda were approved with REMS. To reduce the burden to the healthcare community, a TIRF class REMS has been developed. All five of the previously approved products are being rolled into this class REMS including Actiq and Fentora which have yet to stand up their own individual REMS. Subsys will be a part of this class REMS as well.

3. CMC

The following summary of the CMC, microbiology and device data and reviews has been reproduced from pages 3 through 6 of Dr. Hertz's review:

The following is from Dr. Pinto's review:

> The drug substance, fentanyl base, is a narcotic analgesic and a Schedule II controlled substance that binds to opioid receptors. The Chemistry, Manufacturing, and Control (CMC) information for Fentanyl base is provided in DMF (b) (4) The API is made by (b) (4) at their (b) (4) facility which is recommend as adequate by OC (report attached in the appendix). The API will be stored and shipped (b) (4) and has a retest period of (b) (4) The DMF has been reviewed and found to be adequate (P. Maturu, Rev #4 June 2009 and J. Pinto, Rev #5, Oct 2011).

The drug product is formulated as a sublingual, single-dose spray in concentrations of 1 mg/ml, 2 mg/ml, 4 mg/ml, 6 mg/ml and 8 mg/ml, with a total fill per vial of (b) (4) The dose is (b) (4) The formulation consists of the active substance, in dehydrated alcohol, propylene glycol, water, xylitol and menthol. The pump consists of an actuator, insert, spray pin, needle, stopper, glass vial and vial holder. (b) (4)

Three packaging configurations are planned containing 6, 14, or 28 devices in a carton. Each carton includes a disposal system to accommodate both used and unused devices.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.