

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**202788Orig1s000**

**SUMMARY REVIEW**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHESIA, ANALGESIA, AND ADDICTION PRODUCTS**

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Summary Review for Regulatory Action

<b>Date</b>	January 4, 2012
<b>From</b>	Bob A. Rappaport, M.D. Director Division of Anesthesia, Analgesia, and Addiction Products
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	202788
<b>Applicant Name</b>	Insys Therapeutics, Inc.
<b>Date of Submission</b>	March 14, 2011
<b>PDUFA Goal Date</b>	January 4, 2012
<b>Proprietary Name / Established (USAN) Name</b>	Subsys Fentanyl Sublingual Spray
<b>Dosage Forms / Strength</b>	Single-dose sublingual spray 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg
<b>Proposed Indication</b>	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
<b>Action:</b>	Approval

Reference ID: 3066841

<b>Material Reviewed/Consulted</b>	
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 Risk Management  
 OSI=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

NDA 202788

2

Subsys

Division Director's Review and Summary Basis for Approval

January 4, 2012

Reference ID: 3066841

## 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 C<sub>max</sub> 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

NDA 202788

Subsys

Division Director's Review and Summary Basis for Approval

January 4, 2012

3

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.

NDA 202788

Subsys

Division Director's Review and Summary Basis for Approval

January 4, 2012

4

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