

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202788Orig1s000

Trade Name: Subsys

Generic Name: Fentanyl sublingual spray

Sponsor: Insys Therapeutics, Inc.

Approval Date: January 2, 2012

Indications: For the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
REMS	X
Summary Review	X
Officer/Employee List	X
Office Director Memo	
Cross Discipline Team Leader Review	X
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	X
Statistical Review(s)	X
Microbiology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202788Orig1s000

APPROVAL LETTER



NDA 202788

NDA APPROVAL

Insys Therapeutics, Inc.
(c/o) The Weinberg Group, Inc.
1129 Twentieth Street, NW
Suite 600
Washington, DC 20036

Attention: Lauren H. Wind, MPH
Senior Consultant
The Weinberg Group, Inc.

Dear Ms. Wind:

Please refer to your New Drug Application (NDA) dated and received March 4, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Subsys (fentanyl sublingual spray).

We acknowledge receipt of your amendments dated March 14, April 5, 15, 21, and 29, May 18, 20, and 27, June 29, July 7 and 11, August 5 and 25, September 21, 26 (2), and 29, October 3 and 21, November 18, 23, and 28, and December 6, 19, 21, 22, and 28, 2011.

This new drug application provides for the use of Subsys (fentanyl sublingual spray) for the management of breakthrough pain in adult cancer patients who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).”

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 202788.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. There are too few children who would be appropriate for this product for studies to be feasible.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Subsys (fentanyl sublingual spray) to ensure the benefits of the drug outweigh the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, 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). Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Subsys (fentanyl sublingual spray).

Pursuant to 505-1(f)(1), we have also determined that Subsys (fentanyl sublingual spray) can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors that are listed in the labeling. The elements to assure safe use will help assure proper patient selection and dispensing of Subsys (fentanyl sublingual spray).

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Your proposed REMS, submitted on December 28, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

This REMS will use a single shared system for the elements to assure safe use and implementation system in the approved REMS. The individual sponsors who are part of the single shared system are collectively referred to as TIRF sponsors. This single shared system, the TIRF REMS Access program, includes the following products:

NDA 020747	Actiq (fentanyl citrate) oral transmucosal lozenge
NDA 021947	Fentora (fentanyl buccal tablets)
NDA 022266	Onsolis (fentanyl buccal soluble film)
NDA 022510	Abstral (fentanyl) sublingual tablets
NDA 022569	Lazanda (fentanyl) nasal spray
NDA 202788	Subsys (fentanyl sublingual spray)
ANDA 077312	Fentanyl Citrate Oral Transmucosal Lozenge

Other products may be added in the future if additional NDAs or ANDAs are approved.

Your REMS must be fully operational before you introduce Subsys (fentanyl sublingual spray) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. The TIRF REMS Access Program Outreach

The following metrics will be tabulated for every reporting period to assess program outreach efforts:

- a. Number of Dear HCP letters mailed to prescribers (by date)
- b. Number of returned mailings of Dear HCP letters to prescribers
- c. Number of Pharmacist letters mailed to pharmacies (by date)
- d. Number of returned mailings of Pharmacist letters to pharmacies

2. The TIRF REMS Access Program Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and distributors, the following data will be tabulated for each reporting period and cumulatively:

- a. Number of new patients enrolled by state
- b. Number of patients inactivated
- c. Number of new prescribers enrolled by state. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
- d. Number of attempts needed for prescribers to successfully complete Knowledge Assessments, along with the method of completion utilized
- e. Number of prescribers who are inactivated
- f. Number of new pharmacies enrolled by type (inpatient or outpatient), by state. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields
- g. Number of attempts needed for pharmacies to successfully complete Knowledge Assessments
- h. Number of pharmacies that are inactivated by type (inpatient or outpatient)
- i. Dispensing activity for enrolled outpatient pharmacies. Including,
 - (1) Total number of prescriptions authorized
 - (2) Total number of prescriptions denied and reasons for denial
 - i. Number of prescriptions rejected for safety issues (include description of safety issues and any interventions or corrective actions taken)
 - ii. Number of prescriptions rejected for other reasons (include description of other reasons, e.g., prescriber not being enrolled)
- j. Summary of cases identified where a patient received prescriptions for a TIRF medicine from multiple prescribers within an overlapping time frame (description of any investigations and the outcome)
- k. Number of new distributors enrolled. Include the method of enrollment and number of incomplete forms and, to extent possible, a brief description of the reason for incomplete data fields

- l. Number of distributors inactivated, total
- m. A histogram of the number of days between passive enrollment and receipt of a Patient-Prescriber Agreement Form stratified by the method of PPAF submission
- n. A histogram of the number of prescriptions dispensed per patient during the first 10 days after patient passive enrollment stratified by whether there is a PPAF in place.

3. Program Infrastructure and Performance

The following metrics on program infrastructure performance will be tabulated for each reporting period and cumulatively:

- a. Assessment of process for pharmacies to upgrade their pharmacy management systems (mean, maximum, and minimum time needed, number of pharmacies that attempted and failed to upgrade their systems)
- b. Number of times a backup system was used to validate a prescription, with reason for each instance (pharmacy level problem, switch problem, or REMS database problem)
- c. Call center report with
 - (1) Summary of frequently asked questions
 - (2) Problems reported
- d. Description of corrective actions taken to address program/system problems.
- e. Number of reports of lack of enrolled prescribers in a patient's area
- f. Number of reports of lack of enrolled pharmacies in a patient's area
- g. Delays after original prescriptions are denied by pharmacy and brief summary to include characterization of delays

The following reports for unintended system interruptions will be provided for each reporting period:

- h. Reports identified of inadvertent enrollment deactivations
- i. Reports of false positives (e.g., all entities not enrolled but system generated a prescription authorization code)
- j. Reports of failure of re-enrollment notifications to reach stakeholders
- k. Reports of false negatives (e.g., all entities enrolled but the system generated a prescription rejection notice), including brief summary of reason for rejection.

4. Safety Surveillance

- a. TIRF Sponsors will process adverse event reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective Standard Operating Procedures.
- b. Surveillance data from the following sources will be included in the REMS Assessment Reports:

- (1) FDA AERS database using signal detection methods for TIRF medicines with outcomes of death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion
- (2) Other external databases.

5. Periodic Surveys of Patients, Healthcare Providers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements will be evaluated through knowledge, attitude, and behavior (KAB) surveys. The surveys will be administered to randomly selected prescribers, pharmacies, and patients. Survey results will be reported at 12 months and 24 months after the TIRF REMS Access program approval. The TIRF REMS Industry Working Group (TRIG) will discuss with the FDA if additional surveys are needed after 24 months. The results from the surveys will be analyzed together with other REMS assessment data, and a report on any corrective actions taken and the outcome of those actions will be provided.

6. TIRF REMS Access Non-Compliance Plan

The TIRF Sponsors will implement a process for addressing stakeholder non-compliance in the program. The TRIG should provide the following in the first assessment:

- a. A description of personnel that constitute the Non-Compliance Review Team
- b. Describe how non-compliance information is collected and tracked to determine when the plan should be modified

If changes occur in any of the above information, it should be provided in subsequent assessments.

The TIRF sponsors should provide the following data regarding non-compliance in each assessment report:

- a. Identify the number of non-compliant events.
 - b. Describe the non-compliant event and the corrective action measure taken.
 - c. Provide the outcome of the corrective action.
- 7.** The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
- 8.** Information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such

postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

Under section 505-1(g)(2)(C) and (D), FDA may require the submission of a REMS assessment if FDA determines that new safety or effectiveness information indicates that a REMS element should be modified or included in the strategy.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 202788 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission..

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 202788 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 202788
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 202788
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

EXPIRY DATING PERIOD

A 36-month expiration dating period is granted for the drug product when stored at 20-25°C (68 to 77°F) with excursions permitted from 15° to 30°C (59° to 86°F).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matthew Sullivan, Senior Regulatory Project Manager, at (301) 796-1245.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
01/04/2012