# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 209128Orig1s000

| | |
|---|---|
| ***Trade Name:*** | DSUVIA sublingual tablet |
| ***Generic or Proper Name:*** | sufentanil |
| ***Sponsor:*** | ACELRX PHARMS |
| ***Approval Date:*** | November 02, 2018 |
| ***Indication:*** | DSUVIA contains sufentanil, an opioid agonist, and is indicated for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. |

# CENTER FOR DRUG EVALUATION AND RESEARCH

# 209128Orig1s000

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209128Orig1s000

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 209128

**NDA APPROVAL**

AcelRx Pharmaceuticals, Inc.
351 Galveston Drive
Redwood City, CA 94063

Attention: Kimberly Gaumer
Vice President, Regulatory Affairs and Quality Assurance

Dear Ms. Gaumer:

Please refer to your New Drug Application (NDA) dated and received December 12, 2016, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for DSUVIA (sufentanil sublingual tablet).

We acknowledge receipt of your amendment dated May 3, 2018, which constituted a complete response to our October 11, 2017, action letter.

This new drug application provides for the use of DSUVIA (sufentanil sublingual tablet) for use in adults in certified medically supervised healthcare settings, such as hospitals, surgical centers, and emergency departments, for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

## APPROVAL & LABELING

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

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

## 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. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2017, Revision 4)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 209128**." Approval of this submission by FDA is not required before the labeling is used.

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 6 years of age because there is evidence strongly suggesting that the drug product would be ineffective and unsafe in this pediatric group. Specifically, children in this age group do not have the cognitive ability to comply with DSUVIA's sublingual dosing instructions.

We are deferring submission of your pediatric study for ages 6 to less than 17 years of age for this application because pediatric studies should be delayed until additional safety data have been collected in adults. Before the initiation of the pediatric study, the Division will review cases of respiratory depression and dropped/misplaced tablets that lead to accidental exposure.

Your deferred pediatric study required by section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. This required study is listed below.

3523-1 A safety and pharmacokinetic study of DSUVIA (sufentanil sublingual tablets) in pediatric patients ages 6 to less than 17 years with acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

| | |
|---|---|
| Draft Protocol Submission: | 05/2020 |
| Final Protocol Submission: | 08/2020 |
| Study Completion: | 12/2022 |
| Final Study Report: | 03/2023 |

Submit the protocol to your IND 113059, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

## RISK EVALUATION AND MITIGATION STRATEGY (REMS) 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.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for DSUVIA (sufentanil sublingual tablets) to ensure the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure.

Your proposed REMS must include the following:

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have determined that DSUVIA (sufentanil sublingual tablets) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of respiratory depression resulting from accidental exposure listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require health care settings that dispense the drug be specially certified and the drug be dispensed to patients only in certain health care settings.

Your proposed REMS, submitted on May 3, 2018, amended and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce DSUVIA (sufentanil sublingual tablets) into interstate commerce.

In order to assure that the REMS is meeting its goal, REMS Assessment reports must be submitted to the FDA at 6 months and 12 months from the initial date of approval of the REMS and yearly thereafter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Assessments will include an evaluation of the effectiveness of the REMS and any areas for program improvements or modifications.

The REMS assessment plan will include, but is not limited to, the following components (to be assessed for the current reporting period and cumulatively):

1. **For the 6-month Assessment only, in addition to the assement requirements listed below (items 2 through 7), provide the following dates:**
    a. DSUVIA REMS program launch
    b. REMS website goes live
    c. REMS Call Center is operational
    d. When healthcare settings are able to initiate the certification in the REMS process
    e. First notification of when a healthcare setting's certification was instated
2. **REMS Program Utilization Data:**
    a. Number and type of certified healthcare settings
        i. Number and type of certified healthcare settings that received at least one shipment of DSUVIA
        ii. Number and type of certified healthcare settings that dispensed DSUVIA
    b. Number of enrolled wholesalers/distributors

i. Number of wholesalers/distributors that shipped at least one shipment of DSUVIA

ii. Number of orders shipped to certified healthcare settings for DSUVIA

iii. Estimated number of patients who have received DSUVIA therapy

c. Number of DSUVIA units shipped to certified healthcare settings

d. For the reporting period, the number of healthcare setting re-enrollments and the expected number of re-enrollments.

**3. REMS Non-Compliance:**

a. The number and type of certified healthcare settings for which non-compliance with the REMS is detected

i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken

b. The number of enrolled wholesalers/distributors for which non-compliance with the REMS is detected

i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken

c. The number and type of **non-certified** healthcare settings that dispensed DSUVIA and the number of incidents (including dispensing for outpatient use) for each

i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken

d. The number of instances where wholesalers/distributors shipped DSUVIA to **non-certified** healthcare settings or other entities (e.g., pharmacies or a patient's home)

i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken

e. The number, type, and summary description of instances where wholesalers/distributors denied shipment to healthcare settings because the setting:

i. was not certified

ii. was de-certified due to non-compliance with the REMS

f. Number of times DSUVIA was distributed, transferred, or loaned from one healthcare setting to another

i. Provide the source of the report, a description of the event, the cause of the event, and corrective actions taken

g. The number of healthcare settings suspended and/or de-certified for non-compliance with REMS Program requirements and reasons for such actions.

h. The number of wholesalers/distributors suspended and/or de-enrolled for non-compliance with REMS Program requirements and reasons for such actions.

i. Refer to the Non-Compliance plan which will be used to determine what are:

   i. Non-compliance events

   ii. Consequences of non-compliance

   iii. What events constitute suspension or de-certification from the REMS

**4. Annual Healthcare Setting and Wholesaler/Distributor audits:**

a. The number and percentage of healthcare settings, by type, that were audited, including:

   i. The number and percentage that lacked training records for relevant staff.

   ii. The number and percentage that lacked immediate-access to equipment, medications, and trained personnel to ensure compliance with the REMS safe use conditions.

   iii. The number and percentage that lacked documented processes and procedures to verify that DSUVIA is not dispensed for use outside of a certified healthcare setting.

   iv. The number of times that the authorized representative on file with the REMS was no longer the authorized representative of an audited healthcare setting.

   v. The number and percentage of healthcare settings identified in 4.4.a.i through iv that successfully completed the required corrective and preventive action (CAPA) plan within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.

b. The number and percentage of wholesalers/distributors that were audited to ensure that DSUVIA is distributed in accordance with the program requirements (meaning, only to certified healthcare settings), including:

   i. The number and percentage that lacked documented processes and procedures to ensure compliance with REMS-defined requirements.

   ii. The number and percentage that lacked records of training of relevant staff.

   iii. The number and percentage of shipments that were shipped to non-enrolled healthcare settings.

   iv. The number and percentage of wholesalers/distributors identified in 4.4.b.i. through iii that successfully completed the required CAPA within one month of audit. For any that did not complete the CAPA within one month of the audit, describe actions taken.

**5. REMS Call Center**

a. Frequently asked questions and problems identified by the REMS Call Center

   i. Provide a summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) by reporter (authorized representative, Healthcare Setting, patient/caregiver, other)

b. Number of contacts

**6. Surveillance for Accidental Exposures and Other Adverse Events**

a. Quantify the following adverse events, and report all available case descriptions:

   i. Abuse

   ii. Misuse

   iii. Accidental exposure

   iv. Overdose

   v. Respiratory depression

   vi. Medication errors associated with DSUVIA

   vii. Other serious complications associated with DSUVIA

   viii. Any adverse events reported from a non-DSUVIA REMS-certified hospital

b. For each of these adverse events, also quantify the occurrences that resulted in:

   i. Death or

   ii. Major medical outcome.

c. Present accidental exposures to DSUVIA stratified by adult (age ≥ 18 years) or pediatric exposures (sub-categories: age ≤ 5 years and 6-17 years) as well as the setting of the exposure.

d. Perform a root cause analysis (RCA) of any accidental exposures. If a RCA cannot be performed, state the reason(s) for this.

e. Obtain information about these events through:

   i. Adverse event reports

   ii. Literature searches

   iii. Systematic monitoring of mentions in social media

   iv. National database(s) that provide data regarding:

      1. Drug diversion,

2. Patients entering opioid addiction treatment programs, and
3. Calls to poison control centers.

v. Depending on results of monitoring use and adverse events, additional data may be requested.

vi. Relevant auxiliary data may be added to the surveillance data.

**7. REMS Assessment of Effectiveness**

Based on the information provided, an assessment and conclusion will be determined regarding whether the REMS is meeting its goals, and whether modifications to the REMS are needed. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the*

*modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 209128 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.

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.

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

**NDA 209128 REMS ASSESSMENT**

**NEW SUPPLEMENT FOR NDA 209128/S-000**
**CHANGES BEING EFFECTED IN 30 DAYS**
**PROPOSED MINOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 209128/S-000**

**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED MAJOR REMS MODIFICATION**

***or***

**NEW SUPPLEMENT FOR NDA 209128/S-000**
**PRIOR APPROVAL SUPPLEMENT**
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)**
**FOR NDA 209128/S-000**
**REMS ASSESSMENT**
**PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISION FOR NDA 209128**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

## SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

## 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 Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf ).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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.

## EXPIRATION DATING

The drug product is granted an expiry dating of 36 months when stored at 25°C (77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

## REPORTING REQUIREMENTS

You must comply with the reporting requirements described in 21 CFR 314.80(c)(1) (e.g., 15-day alert reports) beginning on the date of **this** letter. The due dates for the periodic (including quarterly) adverse drug experience reports described in 21 CFR 314.80(c)(2) should be calculated from the date of this letter. Annual reports described in 21 CFR 314.81(b)(2) are due within 60 days of the anniversary of the date of approval in accordance with 21 U.S.C. 355(x).

If you have any questions, call Allison Meyer, Regulatory Project Manager, at (301) 796-1258.

Sincerely,

*{See appended electronic signature page}*

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Carton and Container Labeling
REMS

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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JOSHUA M LLOYD on behalf of SHARON H HERTZ
11/02/2018