CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209128Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209128

COMPLETE RESPONSE

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 have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

SAFETY

The safety database, while suitable in number of patients, did not contain a sufficient number of patients dosed at the maximum amount described in the proposed labeling to assess the safety of Dsuvia. This is particularly important as there is a nearly 4-fold increase in the exposure and a more than 2-fold increase in the maximum concentration when Dsuvia is dosed at steady state.

To address this deficiency:

Collect additional data in at least 50 patients with postoperative pain sufficient to evaluate the safety of Dsuvia for a period following the maximum dosing proposed.

HUMAN FACTORS

We have determined that the human factors (HF) validation study data did not demonstrate that the user interface supports safe and effective use of the product by intended users for intended uses and environments. Failures that result in dropped sufentanil tablets pose a risk for accidental exposure, improper dosing, and diversion. Overall, we do not find the risk acceptable and note that you did not propose any additional measures to further mitigate the risk.

To address this deficiency:

Develop mitigation strategies to address the risk of dropped sufentanil tablets. Conduct another HF validation study to demonstrate the effectiveness of the recommended mitigation strategies in addressing the use-related errors that were observed in your validation study and to ensure that the changes do not introduce new risks. We recommend incorporating the following changes to the user interface:

A. Directions for Use (DFU)

1. Revise step 6 of the DFU: "Depress the green Pusher to deliver the tablet to the patient's sublingual space and confirm tablet placement" into two separate steps such as the following:

   "Step 6: Depress the green Pusher to deliver the tablet to the patient's sublingual space."

   "Step 7: Visually confirm tablet placement in the sublingual space."

2. Modify the figures that depict the patient's mouth by labeling parts of the mouth so they represent a more accurate representation of human anatomy. Labeling parts of the mouth within the graphics will help guide users in the proper administration technique.

3. Label each figure (e.g., Figure 1, Figure 2) in the DFU and refer to the figures within the written instructions (e.g. "see Figure 1").

B. Pouch Package

1. Replace the simplified graphics on the back of the foil pouch with the complete DFU (written instruction with revised and labeled graphics) such that complete DFU cannot be easily separated from the foil packet prior to use or discarded along with the carton.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL)

format as described at
http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, March 30, 2017, which addresses the proposed proprietary name, DSUVIA. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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)].

We acknowledge receipt of your proposed REMS, included in your submission dated December 12, 2016, which contains elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for DSUVIA (sufentanil sublingual tablet), if it is approved, to ensure that the benefits of the drug outweigh the risk of respiratory depression resulting from accidental exposure.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

CONTAINER LABEL AND CARTON LABELING COMMENTS

We reserve final comment on the proposed container label and carton labeling until the application is otherwise adequate. The following comments are being shared at this time for your consideration:

A. Single Dose Applicator Container Label

In accordance with the requirements of 21 CFR 201.10(i), the label must include the following information, at a minimum:

1. Proprietary name
2. Established name
3. Lot or control number
4. Name of manufacturer, packer or distributer of the drug

Include all of the above information on this container label. In addition, we recommend including the expiration date[1].

B. Pouch Labeling- Front

[1] United States Pharmacopoeia (USP) General Chapter <7> Labeling

1. To improve readability, consider an alternative presentation for the proprietary name. We recommend the proprietary name "DSUVIA" is presented in all the same color without any intervening matter.

2. (b) (4)

3. If room permits, consider adding the statements, "Instruct the patient to not chew or swallow the tablet. Instruct the patient to not eat or drink and minimize talking for 10 minutes after receiving the tablet."

C. Pouch Labeling - Back

1. Revise the statement, (b) (4) to read, "Administration Information" so that it more accurately reflects the information that follows.

2. Modify the figures that depict the patient's mouth by labeling parts of the mouth so they represent a more accurate illustration of human anatomy. Labeling parts of the mouth within the graphics may help guide users in the proper administration technique.

D. Carton Labeling

To improve readability, consider an alternative presentation of the proprietary name on the carton labeling. We recommend the proprietary name "DSUVIA" is presented in all the same color without any intervening matter.

OTHER

Three citizen petitions (FDA-2017-P-1359, FDA-2017-P-4352, and FDA-2017-P-5396) relevant to the class of drugs to which this application belongs are currently undergoing review with the Agency. Our ongoing review of these citizen petitions does not change DAAAP's decision to issue a complete response for the application that is the subject of this letter. This letter should not be construed to grant, deny, or otherwise comment on any of the citizen petitions identified above.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter

of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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

/s/

SHARON H HERTZ
10/11/2017