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RESEARCH**

APPLICATION NUMBER:

208609Orig1s000

OTHER ACTION LETTERS



NDA 208609

COMPLETE RESPONSE

Akorn Inc.
c/o Camargo Pharmaceuticals Services, LLC
2505 Meridian Parkway, Suite 175
Durham, NC 27713

Attention: K. Gary Barnette, PhD
Vice President, Drug Development

Dear Dr. Barnette:

Please refer to your New Drug Application (NDA) dated and received, September 15, 2015, and your amendments, submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ephedrine sulfate injection, USP 50 mg/mL.

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.

PRODUCT QUALITY

During a recent inspection of the Akorn Inc. manufacturing facility (FEI 1450114) for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important

format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit 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>.

Your draft labeling emailed to us on July 6, 2016, is attached. To facilitate review of your submission, provide a highlighted or marked-up copy that shows any changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

You may refer to your June 10, 2016, carton and container labeling in any resubmission.

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.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Based on the above, FDA has determined that if NDA 208609 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess reproductive toxicology, embryonic development toxicology, pre- and post-natal development toxicology, and genotoxic potential in appropriate animal species.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 208609 is approved, you will be required to conduct the following:

- 1 Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.
- 2 Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.
- 3 Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.
- 4 Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.
- 5 Conduct an in vivo micronucleus genotoxicity assay with ephedrine sulfate.

Any additional specific details of these required postmarketing studies, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete these studies prior to re-submitting your application, you may include the final reports and relevant data sets in your Complete Response submission to facilitate review of the information.

OTHER

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. 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 FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

If you have any questions, call Kimberly Compton, RPh, Senior Regulatory Project Manager, Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

RIGOBERTO A ROCA
07/15/2016