

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

### *APPLICATION NUMBER:*

**208609Orig1s000**

*Trade Name:* Ephedrine Sulfate Injection, USP, 50 mg/mL.

*Generic Name:* Ephedrine Sulfate

*Sponsor:* Akorn Inc.

*Approval Date:* March 1, 2017

*Indication:* For the treatment of clinically important hypotension occurring in the setting of anesthesia.

# CENTER FOR DRUG EVALUATION AND RESEARCH

## 208609Orig1s000

### CONTENTS

#### Reviews / Information Included in this NDA Review.

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

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208609Orig1s000**

**APPROVAL LETTER**



NDA 208609

**NDA APPROVAL**

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 acknowledge receipt of your amendment dated December 15, 2016, which constituted a complete response to our July 15, 2016, action letter.

This new drug application provides for the use of ephedrine sulfate injection, USP for the treatment of clinically important hypotension occurring in the setting of anesthesia.

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.

**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.) 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.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, submitted on June 10, 2016, 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, *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. 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 208609.**” 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.

## **PROPRIETARY NAME**

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

## **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.

Because none of these criteria apply to your application, you are exempt from this requirement.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of genotoxicity or adverse effects on fertility, embryonic development, and pre- and post-natal development.

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 you are required to conduct the following:

- 3104-1 Conduct a fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on February 17, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	04/2018
Final Report Submission:	01/2019

- 3104-2 Conduct an embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.

The timetable you submitted on February 17, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	01/2018
Final Report Submission:	12/2018

- 3104-3 Conduct an embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.

The timetable you submitted on February 17, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	04/2018
Final Report Submission:	02/2019

- 3104-4 Conduct a pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

The timetable you submitted on February 17, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2017
Study Completion:	03/2019

Final Report Submission: 03/2020

3104-5 Conduct an in vivo micronucleus genotoxicity assay with ephedrine sulfate.

The timetable you submitted on February 17, 2017, states that you will conduct this study according to the following schedule:

Study Completion: 08/2017  
Final Report Submission: 02/2018

Submit nonclinical and chemistry, manufacturing, and controls protocols to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

### **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, Medication Guide, and patient PI (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 package insert, 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 of 36 months, when stored at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

### **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 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

Enclosures:

Content of Labeling  
Carton and Container Labeling



-----  
**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  
03/01/2017