

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208609Orig1s000

SUMMARY REVIEW



Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
 Division of Anesthesia, Analgesia, and Addiction Products
 10903 New Hampshire Ave., Silver Spring, MD 20993-0002

Summary Review for Regulatory Action

Date	March 01, 2017
From	Rigoberto Roca, M.D. Deputy Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Deputy Division Director Summary Review
NDA Number	208609
Applicant Name	Akorn Pharmaceuticals, Inc.
Date of Original Submission	September 15, 2015 Complete Response letter issued July 15, 2016
Date of Complete Response Submission	December 15, 2016
PDUFA Goal Date	June 15, 2017
Proprietary Name / Established (USAN) Name	Ephedrine sulfate injection
Dosage Forms / Strength	50 mg/mL
Proposed Indication	Treatment of clinically important hypotension in the setting of anesthesia
Action	Approval

Material Reviewed/Consulted: OND Action Package, including:	
Clinical Review	Alla Bazini, MD
Pharmacology/Toxicology	Marcus Delatte, PhD; Newton Woo, PhD; Dan Melon, PhD
OPQ/ONDP	Jeffrey Medwid, PhD; Arthur Shaw, PhD; Angella Lu PhD; Albert Chen, PhD; Julia Pinto, PhD
OPQ/OPF	Peter Krommenhoek, PhD; Denise Miller, PhD; Rose Xu, PhD; Rebecca Dombrowski, PhD
OPQ/OPF/DIA/IAB II;	Derek Smith, PhD; Juandria Williams, PhD; Christina Capacci-Daniel, PhD
OPQ/OPRO	Steven Kinsley, PhD
Project Management Staff	Kim Compton, RPh; Matt Sullivan, MS

DCCE = Division of Clinical Compliance Evaluation
 DIA = Division of Inspectional Assessment
 DMEPA = Division of Medication Error Prevention and Analysis
 DPV II = Division of Pharmacovigilance II
 IAB II = Inspectional Assessment Branch II
 OND = Office of New Drugs

ONDP = Office of New Drug Products
 OPF = Office of Process and Facilities
 OPDP = Office of Prescription Drug Promotion
 OPQ = Office of Pharmaceutical Quality
 OPRO = Office of Program and Regulatory Operations
 OSE = Office of Surveillance and Epidemiology

1. Introduction

The Applicant, Akorn Pharmaceuticals, Inc., submitted a new drug application (NDA) under the 505(b)(2) regulations on September 15, 2015. The initial submission contained information from published literature to support the application. However, on May 10, 2016, the Applicant amended the application to rely entirely on the Agency's finding of safety and efficacy of NDA 208289 (Akovaz, ephedrine sulfate) which had been approved on April 29, 2016.

The Applicant was issued a Complete Response letter on July 15, 2016, secondary to deficiencies found during an inspection of the manufacturing facility.

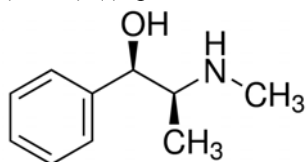
This review will provide an overview of the regulatory and scientific facts of this submission application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and the labeling requested by the Applicant. This review will also serve as the cross-discipline team leader (CDTL) review.

2. Background

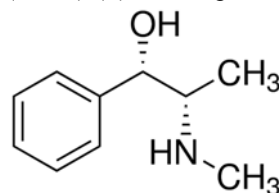
Ephedrine is a sympathomimetic agonist that binds to the α - and β -adrenergic receptors. In addition to direct interaction with the adrenergic receptors, ephedrine can also have indirect effects by causing the release of endogenous catecholamines and/or by preventing their neuronal reuptake. These effects are manifested clinically as an increase in heart rate and cardiac output, and variable increases in peripheral vasculature resistance, resulting in an increase in systemic blood pressure. Ephedrine has been used clinically as a vasopressor for decades; however, it is currently a marketed, unapproved product.

Ephedrine's chemical structure contains two chiral centers, resulting in two stereoisomers of ephedrine (1R,2S and 1S,2R) and two enantiomers (1R,2R and 1S,2S), known as pseudoephedrine. Diagrammatic representations of these structures are depicted below.

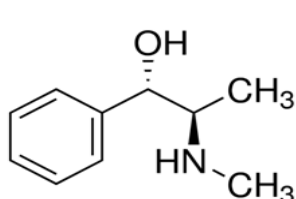
(1R,2S)-(-)Ephedrine



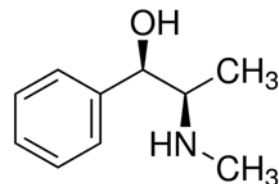
(1S,2S)-(+)-Pseudoephedrine



(1S,2R)-(+)-Ephedrine



(1R,2R)-(-)-Pseudoephedrine



As noted by the team in their reviews, the (-)-(1R,2S)-enantiomer of ephedrine cannot convert to (+)-(1R,2S)- enantiomer of ephedrine due to steric hindrance. However, the stereoisomers differ from each other with respect to their relative efficacy. Therefore, it was important that the Applicant establish with as much certainty as possible, the isomeric structure of the ephedrine used in the clinical trials being reported in the published literature being used to support the NDA. With respect to the salt that was used in the clinical trial (i.e., ephedrine sulfate or ephedrine hydrochloride), the Division concluded that either one would be supportive.

Regulatory History

The regulatory history of this application is well-summarized in Dr. Bazini's review of the first cycle. The following table, adapted from that review, lists the key regulatory milestones and clinical issues identified during the review of this application:

Meeting/Communication/Date	Event/Key clinical issues
PIND Type B/June 6, 2013	1. The Sponsor must expand their search of literature for ephedrine efficacy and safety beyond the indication of Cesarean sections. The indication should be to treat clinically important hypotension in the setting of anesthesia. Additional literature support for ephedrine use in all settings of anesthesia will need to be provided. 2. Sponsor may request a waiver for below a certain age group and request that the pediatric studies that the Sponsor plans to conduct for another age group be deferred until after the initial NDA is approved in adults. 3. The Sponsor must confirm that the enantiomeric composition of the drug product is the same as that in the literature they submit. 4. The safety database should support the safety of ephedrine injection used in the setting of anesthesia in various anesthetic conditions (i.e., general, neuraxial, and regional, as relevant). 5. As the existing data do not appear to contain adequate information regarding the in vivo mutagenic potential and impact on reproductive and developmental toxicity of ephedrine, these studies may be necessary as postmarketing requirements (PMRs).
September 15, 2015	NDA received.
November 11, 2015	NDA filed.
Information Request (IR)/December 23, 2015	Requested information regarding whether ephedrine used in articles supporting efficacy was USP or whether manufacturer of the ephedrine used in each study was identified.

Meeting/Communication/Date	Event/Key clinical issues
Response to IR/January 6, 2016 (S0003)	Sponsor submitted a table identifying each article and stating that the origin of the ephedrine used in the articles was unspecified.
IR/January 13, 2016	Requested information on origin of ephedrine in the safety articles, and clarification on whether the Sponsor reached out to the authors of the articles to obtain this information. Documentation was also requested of the efforts made to obtain this information.
E-mail from Sponsor/January 14, 2016	Sponsor stated in e-mail that they made an effort to contact authors of both efficacy and safety articles but were mostly unsuccessful.
Clinical Safety Update (S0004)/January 15, 2016	The Sponsor submitted additional articles to support safety, however, information on the origin of ephedrine (i.e., enantiomer) was not provided.
IR/January 16, 2016	Requested a detailed description of the efforts made to contact each author and the results, in a tabular format.
Response to IR (S0006)/February 4, 2016	Sponsor submitted a tabulated listing each article and any information on enantiomer and manufacturer, as well as, copies of e-mail communications sent to authors and their replies (if available). The information provided was insufficient to allow review to commence.
Teleconference/March 1, 2016	The Sponsor was notified that the enantiomer information is essential in order to review the submitted literature references, and therefore, the Sponsor should engage in additional efforts to contact the authors of the articles they have, or seek out additional articles, which may contain the pertinent information.
E-mail communication from Sponsor/April 12, 2016	Sponsor submitted an “unofficial” response, containing the results of their efforts.
Teleconference/April 25, 2016	The Sponsor was notified that the information submitted is not sufficient to allow review of their application, and that additional information regarding the enantiomer is necessary.
May 10, 2016	Sponsor submitted a supplement (S0009), including Form 356h, changing their status to a 505(b)(2) with the newly approved product, Akovaz (NDA 208289) as the listed drug.
July 15, 2016	Complete Response letter issued due to deficiencies identified during the routine inspection of the manufacturing facility.

Meeting/Communication/Date	Event/Key clinical issues
December 15, 2016	Applicant submitted responses to the deficiencies identified during the first review cycle.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The Applicant did not submit any new information about the drug substance or the drug product, and none was required.

Facilities Reviews/Inspections

The overall assessment of the facilities inspection was summarized as follows in the OPQ review of the first review cycle:

All facilities were originally found acceptable based on the risk associated with the proposed operations and inspectional history review with a post-approval inspection recommendation for the drug product manufacturer due to identified facility risks.

Further assessment of the drug product manufacturing facility led to the initiation of a pre-approval inspection in June 2016. Based on the expedited review of the inspectional findings and the district's recommendation of withhold due to significant GMP issues, the drug product facility, Akorn, Inc. (FEI 1450114) is found unacceptable for the proposed operations in this NDA.

The Akorn manufacturing facility was re-inspected in December 2016, and found to be satisfactory. The overall assessment of the resubmission was summarized as follows in Dr. Pinto's review:

In the first review cycle, the Office of Compliance had issued a 483 to the Akorn manufacturing site (FEI 1450114). All other facilities involved in the testing and release of the drug substance and drug product were recommended as adequate. In this resubmission all the deficiencies cited have been satisfactorily resolved. The office of compliance has therefore recommended approval for all sites related to the manufacture and testing ephedrine sulfate and ephedrine sulfate injection.

Product Quality Microbiology

The Applicant did not submit any new information about the product quality microbiology, and none was required.

Outstanding or Unresolved Issues

I agree with the review team that there are no product quality issues that preclude approval of this application at this time.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not include any new nonclinical pharmacology or toxicology information in this submission and none was required. Once the Applicant amended their application to use NDA 208289 as the listed drug, they relied on the relevant pharmacology, pharmacokinetics, and toxicology information in the approved label.

The following summary is reproduced from Dr. Delatte's review from the first review cycle:

The Applicant is relying upon the Agency's previous finding of safety and efficacy of Akovaz to support marketing approval of their ephedrine sulfate drug product. There were no original nonclinical pharmacology or toxicology studies submitted in support of this NDA application. The final drug product is ephedrine sulfate in water; therefore, there are no novel excipients in the drug product formulation. All drug substance impurities and drug product degradants are adequately qualified for safety. Also, the safety of the glass ampule used as the container closure system is adequately qualified.

As the referenced product's label and nonclinical literature do not adequately address Sections 8 and 13 of the Applicant's proposed label, several post-marketing requirements (PMRs) will be issued to inform labeling for this product. These PMRs include four reproductive toxicology studies and one in vivo genetic toxicology study.

Outstanding or Unresolved Issues

I agree with the review team that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this application. I also concur that that the additional nonclinical information can be obtained through the following post-marketing study requirements:

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

5. Clinical Pharmacology/Biopharmaceutics

The Applicant did not include any new clinical pharmacology information included in this submission, and none was required.

Outstanding or Unresolved Issues

I agree with the review team that there are no clinical pharmacology issues that would preclude approval of this application.

6. Clinical Microbiology

The drug product is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

7. Clinical/Statistical-Efficacy

The Applicant did not conduct any clinical trials in support of the efficacy of their drug product. Instead, the Applicant is relying on the Agency's finding of efficacy for NDA 208289 (Akovaz, ephedrine sulfate).

Outstanding or Unresolved Issues

I agree with the review team that there are no efficacy issues identified that would preclude approval of this application.

8. Safety

The Applicant did not conduct any clinical trials in support of the safety of their drug product. Instead, the Applicant is relying on the Agency's finding of safety for NDA 208289 (Akovaz, ephedrine sulfate).

The Applicant conducted a review of the published literature to provide a safety update as required by the Complete Response letter. They indicated that they reviewed the published literature from December 12, 2015 (the time of the last update) and identified 24 articles describing clinical exposure to ephedrine. The Applicant also reviewed the FDA's Adverse Events Reporting System database for the newly available quarters from the date of last search (2015Q3 to 2016Q1).

Dr. Bazini reviewed the articles and concluded that no new safety signals were identified, and there were no new safety information that required changes in the package insert.

Outstanding or Unresolved Issues

I agree with the review team that there are no safety issues identified that would preclude approval of this application.

9. Advisory Committee Meeting

An advisory committee meeting was determined to not be necessary during the review of this application as there were no clinically serious new or unexpected safety concerns identified.

10. Pediatrics

Once the Applicant amended their application to reference NDA 208289, the requirements for pediatric studies under the Pediatric Research Equity Act of 2003 (PREA) were no longer applicable, because the application did not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

There were no other relevant regulatory issues.

12. Labeling

Consultations were obtained from the Division of Medication Error Prevention and Analysis, and the Office of Prescription Drug Promotion. When the Applicant amended the application to cite NDA 208289 as the reference drug, the proposed label was amended to reflect the information in the approved NDA's label. The current submission did not propose any changes to the package carton and containers or the package insert.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action
Approval.

Risk:Benefit Assessment

As noted in Dr. Bazini's review, although ephedrine has been associated with a risk of hypertension and tachycardia, its use in the setting of perioperative hypotension has a favorable risk:benefit assessment in view of the increased morbidity and mortality associated with such hypotension in this clinical setting.

I concur with the review team that, due to the findings from the recent facilities inspection, this application can be approved at this time.

Recommendation for Postmarketing Risk Management Activities
None.

Recommendation for other Postmarketing Study Requirements

1. A fertility and early embryonic development toxicology study in the rat model for ephedrine sulfate.
2. An embryo-fetal developmental toxicology study using the rat model for ephedrine sulfate.
3. An embryo-fetal developmental toxicology study using the rabbit model for ephedrine sulfate.
4. A pre- and post-natal developmental toxicology study in the rat model for ephedrine sulfate.
5. An in vivo micronucleus assay (b) (4) ephedrine sulfate.

Recommendation for other Postmarketing Study Commitments
None.

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/s/

RIGOBERTO A ROCA
03/01/2017