CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208609Orig1s000

MEDICAL REVIEW(S)

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	July 15, 2016
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
PDUFA Goal Date	July 15, 2016
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	Complete Response

Material Reviewed/Consulted: OND Action Package, including:	
Clinical Review	Alla Bazini, MD
Pharmacology/Toxicology	Marcus Delatte, PhD; Newton Woo, PhD; Dan Melon, PhD
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OPQ/OPRO	Steven Kinsley
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Clinical Pharmacology Review	Srikanth Nallani, PhD; Yun Xu, PhD
OPDP	Koung Lee; Jessica Fox
OSE/DMEPA	James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD
OSE/DPV II	Laurelle Cascio, PharmD; Jane L. Gilbert, MD, PhD; Sara Camilli, PharmD, BCPS; Brian Lewis, MD; S. Christopher Jones, PharmD, MS, MPH
Project Management Staff	Kim Compton, RPh; Matt Sullivan, MS

DCCE = Division of Clinical Compliance Evaluation
DMEPA = Division of Medication Error Prevention and Analysis
DPV II = Division of Pharmacovigilance 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

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1. Introduction

The Applicant, Akorn Pharmaceuticals, Inc., has submitted a new drug application (NDA) under the 505(b)(2) regulations. 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.

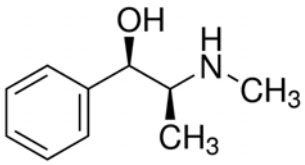
This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and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

2. Background

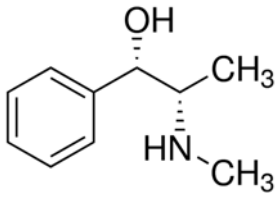
Ephedrine is a sympathomimetic agonist that binds to the α- and ß-adrenergic receptors. In addition to direct interaction with the adrenergic receptors, ephedrine can also have indirect effects by causing the release of endogenous catecholamines and/or by preventing their neuronal reuptake. These effects 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.

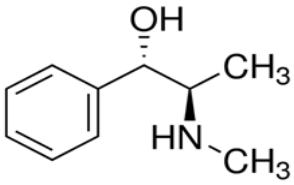
(1R,2S)-(-)Ephedrine



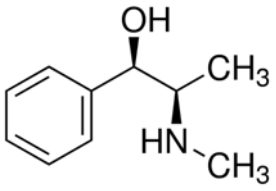
(1S,2S)-(+)Pseudoephedrine



(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. The following table, adapted from Dr. Bazini's 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.
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.

Meeting/Communication/Date	Event/Key clinical issues
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.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Drug Substance

The drug substance, ephedrine sulfate, USP, is supplied by (b) (4), and the manufacture and control is referenced to DMF (b) (4). The DMF was reviewed and found to be supportive for use in the preparation of the drug product.

Drug Product

The following summary description of the drug product is reproduced from the OPQ team's review:

> Ephedrine Sulfate Injection, USP drug product is a clear, colorless solution in water (b) (4) and no other excipients. (b) (4) The product is designed to meet Ephedrine Sulfate Injection USP monograph requirements. The drug product must be diluted with saline or 5% dextrose prior to administration. The product cannot be administered as a bolus injection. The granted expiry is 36 months when stored at 25C.

Facilities Reviews/Inspections

The overall assessment of the facilities inspection is summarized as follows in the OPQ review:

> 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.

Product Quality Microbiology

There were several information requests sent to the Applicant by the OPQ review team during the course of the review. The information in the NDA submission, as well as the Applicant's responses, resulted in an overall favorable assessment and recommendation for approval.

Outstanding or Unresolved Issues

I agree with the review team that the findings from the facilities inspection preclude approval of this application at this time.

4. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any nonclinical pharmacology or toxicology studies in support of this NDA. 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:

> 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 conduct any clinical pharmacology studies. When the Applicant amended their application to rely on the Agency's findings of safety and efficacy for NDA 208289 (Akovaz), they also submitted a biowaiver request. In support of this request, the Applicant cited that their product is an intravenous solution for injection that contains the same active ingredient, in the same concentration and dosage form as the approved listed product. This request was granted by the biopharmaceutics reviewers.

In addition, the Applicant amended their label to reflect the same information as in the Akovaz label. Drs. Lee and Xu concluded that there was no new clinical pharmacology information to review.

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).

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.

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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.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Complete Response.

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 facilities inspection, this application cannot 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 (b) (4) 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
07/15/2016

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	NDA 208609
Priority or Standard	Standard
Submit Date(s)	September 15, 2015
Received Date(s)	September 15, 2015
PDUFA Goal Date	July 15, 2016
Division / Office	Division of Anesthesia, Analgesia, and Addiction Products / Office of Drug Evaluation II
Reviewer Name(s)	Alla Bazini, M.D.
Review Completion Date	July 5, 2016
Established Name	Ephedrine Sulfate Injection
(Proposed) Trade Name	Ephedrine Sulfate USP
Therapeutic Class	α- and β-adrenergic receptor agonist and norepinephrine-releasing agent
Applicant	Akorn Inc.
Formulation(s)	IV Injection; 50 mg/mL
Dosing Regimen	Bolus intravenous injection 5 mg to 10 mg as needed, not to exceed 50 mg
Indication(s)	Treatment of clinically important hypotension in the setting of anesthesia.
Intended Population(s)	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The submitted NDA application is acceptable from a clinical perspective.

1.2 Risk Benefit Assessment

The Sponsor submitted an NDA 208609 for Ephedrine Sulfate Injection (USP, 50 mg/mL) for the indication (b) (4) clinically important hypotension in the setting of anesthesia. Originally, the Sponsor intended to support the safety and efficacy of this product using information available in the published literature, including randomized controlled trials supporting the efficacy and safety of ephedrine in treating hypotension in patients undergoing multiple types of surgical procedures. On May 10th, 2016, the Sponsor changed their approach, requesting to rely on the Agency's previous findings of safety and efficacy of NDA 208289 (Akovaz), which was approved on April 29th, 2016. In addition, the Sponsor submitted an amendment to modify their proposed product label to reflect the language in the approved Akovaz product label.

Dr. Amelia Luckett's overall determination in her NDA 208289 review dated April 28, 2016, was that clinical trials in the publications submitted to support the efficacy of Akovaz demonstrated ephedrine's ability to increase blood pressure. In addition, Akovaz appeared to be safe for the treatment of hypotension in the setting of anesthesia. No deaths and only one serious adverse event was noted in the publications submitted to support the safety of Akovaz. Dr. Luckett states the following in her review:

> "Even though ephedrine has been associated with the risk of hypertension and tachycardia, an episode of perioperative hypotension is associated with increased morbidity and mortality, whereupon the use of ephedrine in this situation results in a favorable risk: benefit assessment."

(Source: NDA 208289 Clinical Review, page 6)

I concur with Dr. Luckett's assessment, which is also applicable to this NDA, as the Sponsor requested and was granted a biowaiver that established that their product contains the same active ingredient, in the same concentration, and dosage form as the reference listed drug, Akovaz (refer to Chemistry, Manufacturing, and Control review, as well as, Biopharmaceutics review).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety issues identified in the review of this application require postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

In a letter dated June 16, 2015, we agreed to the Initial Pediatric Study Plan (iPSP). The revised application is now using Akovaz as the listed drug and since these drugs are very similar (biowaiver granted), pediatric studies as required by PREA are no longer triggered. Flamel Ireland, the holder of the first approved ephedrine NDA (Akovaz), will be required to perform pediatric studies. To ensure that adequate pediatric information is addressed in the label, the Sponsor of this NDA should submit a labeling supplement once adequate data are available to inform a pediatric indication.

From a nonclinical pharmacology toxicology perspective, reproductive and developmental toxicology studies will be required as Postmarketing Requirements. For more information, see the Pharmacology
Toxicology review of this submission.

2 Introduction and Regulatory Background

2.1 Product Information

At the time this NDA was filed, Ephedrine sulfate was a marketed unapproved drug. However, Akovaz (NDA 208289) was approved on April 29th, 2016 for the same indication.

Ephedrine sulfate has the chemical name (1R,2S)-(-)-2-methylamino-1-phenylpropan-1-ol sulfate and functions as both an α-adrenergic and β-adrenergic agonist. The Sponsor intends to make this drug available in a 1 mL ampule that contains 50 mg of ephedrine sulfate. The proposed package insert recommends dilution of Ephedrine sulfate to 5 mg/mL with 9 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection prior to intravenous bolus administration.

The Sponsor proposes the trade name of Ephedrine Sulfate USP and the proposed indication of treatment of clinically important hypotension in the setting of anesthesia. The proposed population is in adults and the dosing regimen is to be bolus intravenous injection 5 mg to 10 mg as needed, not to exceed 50 mg.

2.2 Tables of Currently Available Treatments for Proposed Indications

NDA 208289 Flamel Ireland Ephedrine sulfate (Akovaz) was approved for the indication of "of treatment of clinically important hypotension in the setting of anesthesia." (Flamel Ireland Limited April 2016)

NDA 203826 West-Ward Phenylephrine is approved for the indication of "increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia." (West-Ward Pharmaceuticals December 2012)

NDA 204300 Éclat Vazculep (phenylephrine hydrochloride injection) has the indication of "treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia." (Eclat Pharmaceuticals June 2014)

2.3 Availability of Proposed Active Ingredient in the United States

NDA 208289 (Akovaz) was approved on April 29, 2016.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety of ephedrine is discussed in section 7.0 of this review. Pseudoephedrine is an isomer of the drug product (-)-ephedrine. Pseudoephedrine is marketed as a nasal decongestant and is present in the Final Monograph 21 CFR 341. Product labels of pseudoephedrine contain the following warnings:

> 1. Do not take pseudoephedrine concomitantly with a monoamine oxidase inhibitor or for 2 weeks after discontinuing a monoamine oxidase inhibitor.
>
> 2. If you have heart disease, high blood pressure, thyroid disease, diabetes, or trouble urinating from an enlarged prostate, ask a doctor before taking pseudoephedrine.

Source: Product packaging for:

- CARE ONE® SUPHEDRINE NASAL DECONGESTANT NON DROWSY pseudoephedrine hydrochloride Maximum Strength 30 mg tablets distributed by American Sales Company (American Sales Company July 2009)
- EQUALINE® NASAL DECONGESTANT NON DROWSY MAXIMUM STRENGTH pseudoephedrine hydrochloride tablets, 30 mg distributed by SUPERVALU Inc. (Supervalu Inc. October 2014)

The proposed Ephedrine Sulfate USP package insert states that the pressor effect of ephedrine is increased in patients taking monoamine oxidase inhibitors. The

proposed package insert lists reactive hypertension is an adverse reaction. This is identical to the approved Akovaz package insert.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Submission of this NDA was initially discussed in Pre-IND 118164. Table 1 below lists key dates relating to the PIND and NDA submissions, as well as, key clinical issues discussed in meetings and other communications with the Sponsor.

Table 1 Regulatory Timeline of Key Events

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.

Meeting/Communication/Date	Event/Key clinical issues
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.
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.

Meeting/Communication/Date	Event/Key clinical issues
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 208298) as the listed drug

2.6 Other Relevant Background Information

The Sponsor hired Camargo Pharmaceutical Services, LLC as a consultant.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor has chosen to rely on approved Akovaz labeling for both efficacy and safety. Therefore, no additional information was submitted for clinical review.

3.2 Compliance with Good Clinical Practices

Clinical studies were not performed for this NDA submission. The Sponsor is relying on the Agency's previous finding of safety and efficacy for NDA 208298.

3.3 Financial Disclosures

Financial disclosures were not submitted because no clinical studies were conducted by the Sponsor for this NDA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Sponsor submitted a biowaiver request to the NDA on the basis that the proposed drug ephedrine is an intravenous solution for injection, and the drug contains the same active ingredient, in the same concentration and dosage form, as the approved listed

drug Akovaz. This request was granted by the Agency. Refer to biopharmaceutics review for more information regarding the biowaiver.

4.2 Clinical Microbiology

Clinical microbiology data were not submitted to this NDA because Ephedrine Sulfate USP is not a therapeutic antimicrobial drug.

4.3 Preclinical Pharmacology/Toxicology

No nonclinical studies of ephedrine were conducted for this NDA. The Sponsor relied upon relevant pharmacology, pharmacokinetics, and toxicology information in the approved label of the listed drug, Akovaz. The Pharmacology/ Toxicology team intends to recommend approval of Akovaz with Postmarketing Requirements. For further information, see the Pharmacology Toxicology review of this submission.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Ephedrine is a direct agonist at the α-adrenergic receptor and an indirect agonist at the β-adrenergic receptor.

4.4.2 Pharmacodynamics

Ephedrine increases heart rate and usually blood pressure. The approved Akovaz package insert states:

> "Ephedrine stimulates heart rate and cardiac output and variably increases peripheral resistance; as a result, ephedrine usually increases blood pressure…The overall cardiovascular effect from ephedrine is the result of a balance among α-1 adrenoceptor-mediated vasoconstriction, ß-2 adrenoceptor-mediated vasoconstriction, and ß-2 adrenoceptor-mediated vasodilatation. Stimulation of the ß-1 adrenoceptors results in positive inotrope and chronotrope action."

(Source: Flamel Ireland Limited April 2016)

The package insert proposed for Ephedrine Sulfate USP contains identical information.

4.4.3 Pharmacokinetics

(-)-Ephedrine taken orally is metabolized into norephedrine. Ephedrine and norephedrine are subsequently excreted in urine. A similar pathway for intravenous ephedrine is supported by limited data. Oral ephedrine has a plasma elimination half-life of about 6 hours.

5 Sources of Clinical Data

No clinical trials were performed in support of this NDA submission. The Sponsor is relying entirely on Agency's previous finding of safety and efficacy for NDA 208298 (Akovaz).

5.1 Tables of Studies/Clinical Trials

No clinical trials were submitted in support of this NDA.

5.2 Review Strategy

The Sponsor is fully relying on the Agency's previous finding of safety and efficacy for the Akovaz NDA. No additional data are provided. Subsequently, Section 6 (Review of Efficacy) and Section 7 (Review of Safety) are omitted from this review.

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable.

8 Postmarket Experience

Prior to approval of Akovaz on April 29. 2016, ephedrine was as a marketed unapproved drug. FAERS data was submitted by Flamel and an analysis of FAERS data was conducted for the purpose of NDA 208289 (Akovaz) review and this NDA review by the Division of Pharmacovigilance (DPV). A search of the recent medical literature did not identify any evidence of stroke or cardiac events resulting from ephedrine injection. The medical literature search did identify publications describing fetal acidosis, which is already included in the listed drug's label. Search of FAERS database revealed eleven unique cases describing a fatal outcome with ephedrine injection use, however, analysis of the reports did not find any of the deaths linked to ephedrine injection alone. The most common events reported with ephedrine injection were renal (13 unique cases) and cardiac (28 unique cases). However, since ephedrine is indicated for treatment of hypotension, DPV concluded that adverse events associated with cardiovascular outcomes are to be expected. For further information on

the analysis of FAERS data, see the review of ephedrine FAERS data performed by the DPV.

APPEARS THIS WAY ON ORIGINAL

9 Appendices

9.1 References

American Sales Company. July 2009. "CARE ONE SUPHEDRINE NASAL DECONGESTANT NON DROWSY Product Packaging." In.

Eclat Pharmaceuticals. June 2014. "US Vazculep Package Insert." In.

Flamel Ireland Limited. April 2016. “US Akovaz Package Insert.” In.

Supervalu Inc. October 2014. 'EQUALINE NASAL DECONGESTANT NON DROWSY MAXIMUM STRENGTH Product Packaging '.

West-Ward Pharmaceuticals. December 2012. "US Phenylephrine Hydrochloride Package Insert." In.

9.2 Labeling Recommendations

The package insert for Ephedrine Sulfate USP will have identical clinical sections as the approved package insert for NDA 208289 (Akovaz).

9.3 Advisory Committee Meeting

No advisory committee meeting was conducted for this application.

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

/s/

ALLA T BAZINI
07/05/2016

RIGOBERTO A ROCA
07/05/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208609 **Applicant:** Akorn **Stamp Date:** 9/15/15

Drug Name: Ephedrine **NDA/BLA Type:** Type 7- drug already marketed without approved NDA

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).				eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159 htm	x			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
10.	Has the applicant submitted a benefit-risk analysis for the product?	x			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(2)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			x	All referenced are to published literature
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	x			
14.	Describe the scientific bridge (e.g., BA/BE studies)	x			Applicant proposes the following: Pharmacokinetic (PK) data support that the exposure of ephedrine is insensitive to factors that may

	Content Parameter	Yes	No	NA	Comment
					impact the BA/BE of other drug products. The results of clinical studies in the literature with PK analysis indicate that ephedrine exposure is not significantly different between routes of administration (oral or iv injection) or the concentration of ephedrine used. All clinical PK studies utilized the (-)-ephedrine isomer. No PK info available for other enantiomers. Sponsor proposes the PK for the (-)-ephedrine enantiomer is the only relevant PK because it is the most potent form and believed to be the form used in hospitals. Also, both of the currently marketed unapproved ephedrine products (including sponsor's ephedrine) are USP, meaning they only contain the (-)-ephedrine isomer.
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:	x			The proposed dosage regimen is based on the information in the published literature: 34 RCTs submitted
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	Applicant proposes that efficacy is supported by information from the published literature:

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				42 clinical studies identified (34 RCTs). Applicant states: "Although not formally analyzed in a meta-analysis, despite the differences in the study conduct and patient population, the effect of ephedrine on blood pressure outcomes was similar across these studies and across the various patient populations, including elderly individuals and parturients, as well as under different types of anesthesia (eg, general, neuraxial). Ephedrine has also been shown to be effective at managing clinically significant hypotension across a variety of surgery types, including C section, lower limb surgery, hip or femoral fractures, TURP, TURBT, cataract repair, lobectomy or mastectomy, gynecological, or elective surgeries. The effective dosing is titrated to desired effect but the total dose of ephedrine administered to a patient in these studies was within the range of approximately 5 to 50 mg for all groups under different conditions."
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were			x	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	not previous Agency agreements regarding primary/secondary endpoints.				
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			x	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
25.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?			x	
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Deferral for age 12 to ≤17yo Waiver for age 0-11yo
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?				
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	xYes			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
37.	Are all datasets to support the critical safety analyses available and complete?			x	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			Waiver requested as no clinical studies conducted by sponsor
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer	Date
Clinical Team Leader	Date

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

/s/

ALLA T BAZINI
11/16/2015

RIGOBERTO A ROCA
11/16/2015