CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208943Orig1s000

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	January 27, 2017
From	Rigoberto Roca, M.D. Deputy Director Division of Anesthesia, Analgesia, and Addiction Products
Subject	Deputy Division Director Summary Review
NDA Number	208943
Applicant Name	Par Sterile Products, LLC
Date of Original Submission	March 18, 2016
PDUFA Goal Date	April 18, 2017 (includes a 3-month clock extension)
Proprietary Name / Established (USAN) Name	Corphedra / 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; Valerie Amspacher, PhD; Donna Christner, PhD; Ciby Abraham, PhD; Julia Pinto, PhD
OPQ/OPF	Peter Krommenhoek, PhD; Jessica Cole, PhD; Nallaperum Chidambaram, PhD; Rebecca Dombrowski, PhD; Quallyna Porte, PhD
OPQ/OPRO	Steven Kinsley, PhD
ONDP/Division of Biopharmaceutics	Mei Ou, PhD; Haritha Mandula, PhD
Clinical Pharmacology Review	Deep Kwatra, PhD; Yun Xu, PhD
OPDP	Koung Lee; Sam Skariah, PharmD
OSE/DMEPA	James Schlick, RPh, MBA; Vicky Borders-Hemphill, PharmD
Project Management Staff	Ogochukwu U. Ogoegbunam, PharmD; Parinda Jani

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

1. Introduction

The Applicant, PAR Sterile Products, LLC, 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 December 02, 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.

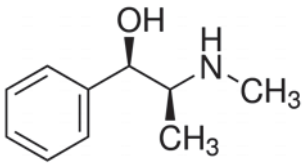
This review will provide an overview of the regulatory and scientific facts of this application and issues that were identified during the course of the review of the submission. Aspects that will be touched upon include the regulatory history, the adequacy of the data to support the application, and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

2. Background

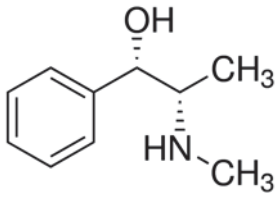
Ephedrine is a sympathomimetic agonist that binds to the α- and ß-adrenergic receptors. In addition to direct interaction with the adrenergic receptors, ephedrine can also have indirect effects by causing the release of endogenous catecholamines and/or by preventing their neuronal reuptake. These effects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

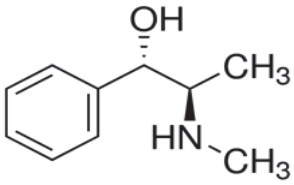
(1R,2S)-(-)Ephedrine



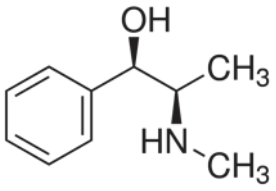
(1S,2S)-(+)Pseudoephedrine



(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:

Date/Meeting or Communication	Event/Key Clinical Issues
July 8, 2015 PIND 126012 WRO	1. Submission of an application for ephedrine under the 505(b)(2) NDA pathway is acceptable. 2. It is unclear whether the ephedrine isomer ratio is the same between the proposed product and the product(s) used in the literature. Therefore, Sponsor must provide adequate justification that the results from the literature can be used to support their proposed product. 3. Any reference to published literature should specifically indicate what stereoisomers were tested and provide justification for why those data are relevant to the proposed drug product. 4. The studies must be individually assessed with discussion of their strength and weakness or deficiency, including comparability of the study drug to the proposed ephedrine injection, such as stereoisomer composition and formulation. If such drug information is unavailable, the Sponsor must provide justification for why data from cited literature is acceptable as a source of information to support their submission. 5. For the efficacy section of the NDA, it is acceptable to include data only from studies in which the stereoisomeric composition of the ephedrine used is known. However, for the safety section of the NDA, the Sponsor may include data from studies in which the stereoisomeric composition of ephedrine is unknown. 6. To the extent possible, the Sponsor should compare the safety findings to determine if there are any differences between ephedrine that may be composed of the (-) stereoisomer versus data that may reflect both the (-) and (+) isomers. The data from literature that does not provide information on the composition and purity of the ephedrine should be clearly identified. 7. Sponsor must provide justification based on robust rationale with supporting information on why pediatric studies should be waived/deferred. 8. Sponsor must address risk of QT-prolongation using adequate published literature.

Date/Meeting or Communication	Event/Key Clinical Issues
October 13, 2015 IND 126012 submission received/	A Phase I, Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of Ephedrine Sulfate in Healthy Volunteers. (Study DCR15239). This study was deemed safe to proceed.
March 18, 2016 NDA Submission	NDA received.
May 17, 2016 NDA Filing	NDA filed.
June 15, 2016 Teleconference	Discussion of review issues identified in the 74-day letter and the recent approval of Akovaz. Sponsor acknowledged the possibility of converting their application to become "b2" to Akovaz.
July 12, 2016 E-mail from Sponsor	Sponsor indicated that they will continue to pursue their own NDA and not rely on approved drug Akovaz.
July 21, 2016 Teleconference	Sponsor confirmed that they will not convert their application to become "b2" to Akovaz. The Division communicated that the Sponsor must work on deficiencies identified in the 74-day letter and submit the responses as soon as possible. Particular emphasis was placed on the importance of identifying the (-) enantiomer in the literature articles and the documentation of the process of identification.
August 18. 2016 Information Request (IR)	Request for a formal biowaiver to be submitted.
August 18, 2016 Response to IR (SD6)	Biowaiver request provided, however, deemed inadequate by review team.
September 7, 2016 IR	Requested Sponsor to provide the most updated list of articles where the proper enantiomer was identified, as well as information on how the information on the enantiomer was identified (i.e., source of information).
September 8, 2016 Response to IR (SD7)	Sponsor provided list of 12 articles in which they were able to make contact with at least one of the authors; however, not all of the authors were able to confirm the proper enantiomer or the manufacturer of the ephedrine used in their study.
September 22, 2016 Response to IR (SD8)	Sponsor provided an updated table of articles where any information about the enantiomer and/or the manufacturer was identified. Table identified 17 articles for treatment of hypotension and 17 articles for prophylaxis of hypotension. Since Sponsor only seeks indication for treatment, the 17 articles for treatment of hypotension were reviewed by CMC and only eight were identified as having adequate proof of the (-) enantiomer.
October 12 and 17, 2016 IR	Requested Sponsor to provide an update on outstanding 74-day letter items.
October 17, 2016 E-mail from Sponsor	Sponsor indicated that they have exhausted their efforts in identifying the enantiomer in the articles and asked the Division as to whether they have an adequate amount of articles for review to occur.
October 18, 2016 Response to IR (SD9)	Sponsor provided response to non-clinical IR items.
November 3, 2016 Teleconference	Sponsor was briefed on which articles are considered acceptable for review for efficacy; however, the Division noted that the Sponsor has not provided the ISS and the ISE, which are essential for review to occur. In addition, the Sponsor was informed that they would need to provide a robust rationale why such low number of subjects (202), particularly low numbers of subjects receiving general anesthesia (12), and low numbers of male subjects (13), are adequate to support approval for their proposed

Date/Meeting or Communication	Event/Key Clinical Issues
	indication. Sponsor indicated they understood the urgency to submit this information as soon as possible and would inform the Division of a timeline in which this information will be provided, in addition to other outstanding 74-day letter issues.
November 7, 2016 Response to IR (SD10)	Sponsor provided partial responses to the non-clinical items identified in the 74-day letter.
November 18, 2016 E-mail from Sponsor	Sponsor indicated they wish to change course and rely on Agency's previous findings of safety and efficacy for the listed drug Akovaz.
November 21, 2016 E-mail from FDA to Sponsor	The Division provided a list of items that would be necessary for Sponsor to submit if they would like to rely on Agency's previous findings of safety and efficacy for the listed drug Akovaz.
November 29, 2016 Teleconference	The Division notified the Sponsor regarding outstanding chemistry, pharmacology/toxicology, and clinical requirements, including supportive documents that are required if they chose to rely on Akovaz.
December 2, 2016 Communication from Sponsor (SD 12)	Sponsor submitted labeling, waiver request for bioequivalence, and new 356h form in order to rely on Agency's previous findings of safety and efficacy for the listed drug Akovaz.
January 18, 2017 Response to IR (SD 14)	Additional information regarding the product quality, which necessitated a review clock extension.

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

The general description and recommendation regarding the approvability of the NDA are summarized as follows in the OPQ review:

> Cophedra (Ephedrine Sulfate Injection, USP) is administered intravenously for the treatment of hypotension associated with anesthesia. It is a (b) (4) sterilized aqueous solution for injection, consisting of ephedrine sulfate as the drug substance. The drug product is in a concentration of 50mg/ml. The only excipient used in the preparation of the drug product is water. It is supplied in a (b) (4) clear glass vial stoppered with a (b) (4) Stopper with a yellow flip-off cap. The product pH is 4.5- 7.0 and nothing is added to adjust pH. The data provided in this NDA satisfactorily supports the drug substance, drug product and the manufacturing process. All manufacturing facilities are recommended as adequate by the Office of Compliance and the Office of Process and Facilities. Sufficient stability data is provided to support an expiry of 24 months, for the product when stored at 25C, in its carton, away from light. Therefore this NDA is recommended for approval.

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 with a (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. (b) (4). Sufficient stability

data is provided to support an expiry of 24 months when stored at 25C in the carton, away from light.

Facilities Reviews/Inspections

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

> Review Summary: ADEQUATE
> Application review under NDA 208943. This facilities review includes evaluation of two sites: a drug substance site and a drug product site. Each of the sites performs all respective operations including testing and packaging. No significant deficiencies are noted in review of either site and an approval recommendation is offered from this discipline for each of the sites.

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 there are no product quality issues that would preclude approval of this application.

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.
>
> A post-marketing requirement (PMR) will be requested to conduct a leachables assessment of Corphedra in its container closure system over the course of stability. This leachables assessment is deemed acceptable as a PMR because the (b) (4) rubber stopper is used in several FDA-approved aqueous injectable drug products and the submitted information regarding the rubber stopper do not raise any significant cause for concern. As the referenced product's label and nonclinical literature do not adequately address Sections 8 and 13 of the Applicant's proposed label, several PMRs that include a full battery of reproductive and toxicology studies and an in vivo genotoxicity study will be issued to inform labeling for this product.
>
> From a nonclinical pharmacology toxicology perspective, NDA 208943 may be approved with the recommended PMRs (see below).

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 (b) (4) and post-natal developmental toxicology study in the rat model for ephedrine sulfate.

5. An in vivo micronucleus assay with ephedrine sulfate.

6. An adequate leachable safety assessment for the (b) (4) rubber stopper (13 mm).

7. An extractable study using model solvents, (b) (4)

5. Clinical Pharmacology/Biopharmaceutics

As noted above, the Applicant's initial intent was to support the NDA with data and information from the published literature. To this end, the Applicant included in the initial submission the results from Study DCR15239, "A Phase I, Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of Ephedrine Sulfate in Healthy Volunteers."

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.

The following summary is reproduced from Dr. Kwatra's review:

> Par Sterile Products, LLC (PAR) submitted a 505 (b) (2) application for Corphedra™ (ephedrine sulfate injection, USP), 50 mg/mL, for intravenous use for the treatment of clinically important hypotension occurring in the setting of anesthesia. As a 505(b) (2) NDA, the applicant intends to rely on the Agency's prior finding of safety and efficacy of ephedrine for the treatment of anesthesia-induced hypotension based on the approval of the Listed Drug (LD) Akovaz™ (Flamel Ireland Ltd. [Flamel]; NDA 208289 approved April 29, 2016). The active ingredient is ephedrine sulfate ([1R,2S]-[-]- methlyamino-1-phenyl-1-propanol sulfate),

a nonspecific α- and β-adrenergic agonist that raises blood pressure mainly by increasing cardiac output via stimulation of cardiac β1 receptors, with a smaller contribution from vasoconstriction. It is provided as a sterile, nonpyrogenic solution for intravenous use in a concentration of 50 mg/mL.

Currently there is only one FDA approved ephedrine sulfate injection which is Akovaz™ from Flamel Ireland Ltd which was approved April 29, 2016 under the NDA 208289. Par initially submitted an 505(b)(2) NDA for Corphedra on March 18, 2016 based on published literature. As a part of that submission PAR conducted Study DCR15239, entitled "A Phase I, Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of Ephedrine Sulfate in Healthy Volunteers" was designed to evaluate the Pharmacokinetics (PK), Pharmacodynamics (PD), and safety of Ephedrine Sulfate Injection at the dose levels of 0.05 mg/kg, 0.1 mg/kg, and 0.2 mg/kg in healthy adult subjects. Par in this study compared their product to another marketed upapproved [sic] product from (b) (4) . Par eventually decided to rely on Akovaz™ as a RLD and on December 2nd submitted a biowaiver requesting a waiver of the need to perform an in vivo bioequivalence study of the drug product, Corphedra™, in comparison to Akovaz™. The sponsor claimed that the criterion for a waiver was that bioequivalence is self-evident. Specifically, the proposed product is a solution intended for intravenous injection. The composition of the proposed product and the RLD are identical, namely active drug in the same concentration and water for injection. Thus, there is no excipient that could alter systemic availability or distribution. Since Par decided to request a biowaiver and rely on the Agency's prior finding of safety and efficacy of Akovaz™ neither the literature submitted nor the study DCR15239 was reviewed. This NDA can be approved solely based on the grant of biowaiver between the new product and the listed drug Akovaz.

Based on email discussion on 12/7/2016, the division of biopharmaceutics indicated that a waiver will be granted for the in vivo bioequivalence study of the drug product, Corphedra™, in comparison to Akovaz™. For more details and final assessment of the biowaiver request, see biopharmaceutics review.

In addition, the Applicant amended their label to reflect the same information as in the Akovaz label. Drs. Kwatra 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).

The Phase 1 clinical pharmacology study in healthy volunteers, Study DCR15239, evaluated three doses of the Applicant's product and a marketed, unapproved formulation of ephedrine, as summarized in the table below (adapted from the Applicant's submission).

Treatment Group	Study Drug Dose	Number of Subjects Receiving Active Treatment	Number of Subjects Receiving Matching Placebo (Saline)
Group A	Par Product, 0.05 mg/kg	4	2
Group B	Par Product, 0.1 mg/kg	4	2
Group C	Par Product, 0.2 mg/kg	4	2
Group D	Reference Product, 0.2 mg/kg	4	2

The design included secondary endpoints that evaluated the pharmacodynamics (PD) response, specifically:

- Changes from baseline in
  - Blood pressure (BP)
    - Systolic, diastolic, and mean arterial blood pressure
  - Heart rate (HR)
- Time to onset of response
- Time to maximal response
- Duration of response

The number of subjects enrolled in the study was too small to permit any type of formal statistical analyses. Dr. Bazini evaluated the results, and the descriptive statistics that were included in the study report, and her conclusions were summarized as follows ("PAR" is the Applicant):

> Subjects receiving ephedrine tended to have higher mean values in all PD variables compared to placebo starting at 2 min post-dose. This was especially evident for BP measurements and less so for HR. PD values generally reverted back to baseline levels at the 24-h follow-up, and most reverted back to baseline levels within approximately 60 minutes post-dosing. The mean maximum % changes from baseline were generally higher in the ephedrine groups compared to placebo. Increasing doses of PAR ephedrine tended to result in greater maximum % changes in SBP, though the small sample size limits these analyses. Across PD parameters, there appeared to be no meaningful differences in the physiological response to PAR ephedrine vs. REF ephedrine at the same dose.

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).

Dr. Bazini evaluated the adverse events reported in Study DCR15239, and did not identify any new safety signal.

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.

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.

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 with ephedrine sulfate.

6. An adequate leachable safety assessment for the (b) (4) rubber stopper (13 mm).

7. An extractable study using model solvents, (b) (4)

Recommendation for other Postmarketing Study Commitments

None.

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
01/27/2017