CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208943Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208943	Submission Date: March 18, 2016
Relevant IND(s):	126012
Submission Type; Code:	505 (b) (2)
Reference Drug:	Akovaz™ (NDA 208289)
Brand Name:	Corphedra™
Generic Name:	Ephedrine sulfate
Formulation; Strength(s):	injectable solution, 50 mg/mL Ephedrine Sulfate, USP in water for injection
Clinical Pharmacology Reviewer:	Deep Kwatra, Ph.D.
Team Leader:	Yun, Xu, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Anesthesia Analgesia and Addiction Products
Sponsor:	Par Sterile Products, LLC
Proposed Indication:	Treatment of clinically important hypotension occurring in the setting of anesthesia
Proposed Dosage Regimen:	5 to 10 mg IV bolus, (b) (4) (b) (4)

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, NDA 208943 submitted on 03/18/2016 is acceptable.

1.2 Phase 4 Commitments

None

1.3. Summary of Clinical Pharmacology Findings

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 product from (b) (4). Par eventually decided to rely on Akovaz™ as a RLD and on December 2 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,

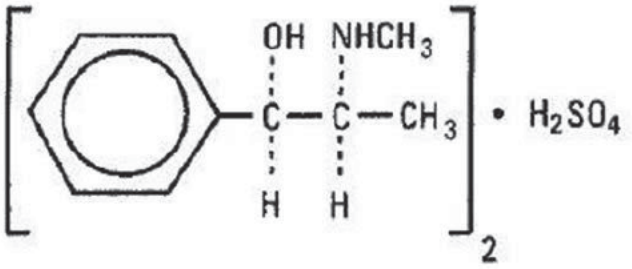
Corphedra™, in comparison to Akovaz™. For more details and final assessment of the biowaiver request, see biopharmaceutics review.

Clinical Pharmacology Studies:
One clinical pharmacology study DCR15239, entitled "A Phase I, Randomized, Double-Blind, Placebo-Controlled, Pharmacokinetic and Pharmacodynamic Study of Ephedrine Sulfate in Healthy Volunteers" was conducted under this NDA. Since this study compared the sponsor's product to another marketed unapproved product and the sponsor decided to apply a biowaiver from clinical studies and instead rely on the Agency's prior finding of safety and efficacy of Akovaz™ and furnish the clinical pharmacology information from the Akovaz™ label, this study was not reviewed.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1: Physical-Chemical Properties of Ephedrine Sulfate	
Drug Name	Ephedrine Sulfate,
Chemical Name	α-[1-(methylamino) ethyl] benzenemethanol sulfate
Structure	
Molecular Formula	428.54
Molecular Weight	(C10H15NO)2·H2SO4 or C20H32N2O6S

Formulation:
Ephedrine Sulfate Injection, USP is a clear, colorless, sterile, solution proposed for intravenous (IV) use. Each 1 mL single use vial contains 50 mg of Ephedrine Sulfate, USP in Water for Injection, USP (50 mg/mL).

2.1.2. What is the regulatory history of Ephedrine Sulfate products?

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. Prior to this approval several pharmaceutical companies marketed the product in the United States as an unapproved medicinal product.

2.1.3 What is the composition of the to-be-marketed formulation of Corphedra™?

The proposed commercial dosage form of contains 50 mg of Ephedrine Sulfate, USP in Water for Injection, USP (50 mg/mL).

Table 2.1.3: Composition of Corphedra™, Function of Ingredients, and References

Ingredients	Quantity[1]	Function	Grade
Ephedrine Sulfate	50 mg	Active Pharmaceutical Ingredient	USP
Water for Injection	QS	(b) (4)	USP/EP
(b) (4)			NF

[1]Quantity in 1 mL

(b) (4)

(b) (4)

2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Ephedrine sulfate is a sympathomimetic amine that directly acts as an agonist at α- and ß-adrenergic receptors and indirectly causes the release of norepinephrine from sympathetic neurons. Pressor effects by direct alpha- and beta-adrenergic receptor activation are mediated by increases in arterial pressures, cardiac output, and peripheral resistance. Indirect adrenergic stimulation is caused by norepinephrine release from sympathetic nerves. Corphedra™ is indicated for the treatment of clinically important hypotension occurring in the setting of anesthesia.

2.1.5 What are the proposed dosage and route of administration?

The route of administration of Corphedra™ is 5 to 10 mg IV bolus, (b) (4)

2.1.6 What are the core studies submitted in this NDA?

The clinical development program includes only one clinical pharmacology study DCR15239 which is a relative bioavailability study with an unapproved product. Due to the sponsors decision to apply a biowaiver from clinical studies and instead rely on the Agency's prior finding of safety and efficacy of Akovaz™ and furnish the clinical pharmacology information from the Akovaz™ label, this study was not reviewed.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Due to the sponsors decision to apply a biowaiver from clinical studies and file this NDA as a 505 (b) (2) to Akovaz™, the dosing for Corphedra™ is identical to that of Akovaz™ and no clinical studies were utilized for support any claims.

2.2.2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contribute to the assessment of clinical pharmacology study data? How was it measured?

No biological biomarker was assessed in this NDA.

2.2.3. What are the general PK characteristics of the drug?

The ADME characteristics of Ephedrine Sulfate as a molecular entity are described in the label for the reference listed drug (Akovaz™ Label).

2.2.4 Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Due to the request and grant of biowaiver, no studies were reviewed or active moieties measured.

2.2.5. What are the characteristics of drug absorption?

Ephedrine Sulfate is an aqueous solution for intravenous use and is by nature 100% bioavailable in the systemic circulation.

2.3. Intrinsic factors

2.3.1. What is the pediatric plan?

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. Since this Akovaz™ has been approved and Corphedra™ is identical to the reference drug Akovaz™, the product does not trigger PREA. No specific pediatric review plan has hence been submitted

2.4. General Biopharmaceutics

2.4.1. What is the relative bioavailability of Corphedra™ compared to the reference drug, Akovaz™?

Corphedra™ is an aqueous solution for intravenous use and is by nature 100% bioavailable in the systemic circulation. Since Corphedra™ and Akovaz™ are identical and both products are solutions of namely active drug and water for injection intended for intravenous injection, bioequivalence is self-evident. Thus the sponsor requested biowaiver from conducting any clinical studies to show relative bioavailability between Corphedra™ and LD which was granted by the division of biopharmaceutics.

2.5 Analytical Section

2.5.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision and selectivity of the method?

N/A

3.0 Labeling Review

No changes have are recommended by this reviewer to the clinical pharmacology section of the proposed label of the sponsor. The sponsor used Akovaz™'s label to address the clinical pharmacology related sections of their product's label and it is identical between the two labels. Since biowaiver is granted between the the sponsor's product and Akovaz™, this is acceptable.

4.0 Appendices

4.1 Sponsor's Proposed Label

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

4.2 OCP Filing/Review Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208943	**SDN**	0000
Applicant	Par Sterile Products	**Submission Date**	03/18/2016
Generic Name	ephedrine sulfate injection, USP	**Brand Name**	CORPHEDRA
Drug Class	Mixed α- and β-adrenoceptor agonist		
Indication	Increasing blood pressure in patients with clinically important hypotension in the setting of anesthesia.		
Dosage Regimen	Treatment of anesthesia-related hypotension: 5 to (b) (4) mg bolus, repeated and adjusted as needed according to blood pressure goal. (b) (4)		
Dosage Form	1 mL (b) (4) containing 50 mg/mL ephedrine sulfate in Water for Injection.	**Route of Administration**	IV
OCP Division	DCP-II	**OND Division**	DAAAP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Deep Kwatra	Yun Xu
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	5/17/2016	**74-Day Letter Date**	5/31/2016
Review Due Date	Click here to enter a date.	**PDUFA Goal Date**	1/18/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☑ No

If yes list comment(s): **We observe that only 4 subjects have been used for each dose level of your PK/PD study. Whether the data can be used for the approval and labeling of your product will be a review issue based on the quality of the data.**

Is there a need for clinical trial(s) inspection?

☐ Yes
☑ No
If yes explain:

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☑ Other (e.g. dose proportionality)		1	Dose proportionality PK/PD study
Intrinsic Factors			
☐ Race			

☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	1
Total Number of Studies to be Reviewed				1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☑No ☐N/A	The Sponsor plans to use literature data only to support this 505(b)(2) application. The Sponsor compared formulation of the new product to that present in literature based on their

		compositions. The Sponsor also submitted a dose proportionality PK/PD study for the proposed product.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		

3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
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9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

Clinical Pharmacology recommendation:
It is acceptable for filing from a clinical pharmacology perspective.

Comments for the 74 day letter:

Only 4 subjects have been used for each dose level of your PK/PD study. Whether the data can be used to support approval and labeling of your product will be a review issue based on quality of the data.

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/s/

DEEP KWATRA
12/14/2016

YUN XU
12/14/2016

CLINICAL PHARMACOLOGY FILING FORM

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Pharmacometrics		
Genomics		

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/s/

DEEP KWATRA
05/16/2016

YUN XU
05/16/2016