CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208609Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208609	Submission Date(s): 9/15/2015, 5/10/2016, 5/16/2016
Brand Name	Ephedrine Sulfate USP
Generic Name	Ephedrine Sulfate Injection
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Akorn Inc.
Relevant IND(s)	-
Submission Type	505(b)(2)
Formulation; Strength(s)	IV Injection; 50 mg/mL
Indication	Treatment of clinically important hypotension in the setting of anesthesia.
Proposed Dosage Regimen	The recommended dosages for the treatment of clinically important hypotension in the setting of anesthesia are an initial dose of 5 to 10 mg administered by intravenous bolus. May administer additional boluses as needed; not to exceed a total dosage of 50 mg.

Table of Contents

1 Executive Summary

1.1 Recommendation

The submitted application is acceptable from a clinical pharmacology perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Akorn 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. Based on the USP standard, the proposed injectable product is (b) (4) intended for administration by intravenous injection.

Currently, Akorn is marketing unapproved Ephedrine Sulfate Injection unapproved in the United States of America. According to publically available information, there are only two manufacturers of ephedrine sulfate products for injection in the US according: the Sponsor (Akorn) and Sandoz. According to the FDA Drug Shortages website, the Sandoz product is currently unavailable, leaving only the Akorn product to supply the markets.

Originally, the sponsor intended to support the safety and efficacy of this product using extensive information available in the published literature, including randomized controlled trials supporting the efficacy of ephedrine in treating hypotension, as well as safety information from publications describing experience with dosing ephedrine in patients. On May 10th, 2016, the sponsor changed the approach requesting the Agency to rely on the previous findings of safety and efficacy from Akovaz (NDA 208289), which was approved on April 29th, 2016. In addition, the sponsor submitted their product label referring to Akovaz product label.

The sponsor also submitted a biowaiver request to the NDA on the basis that the proposed product is an intravenous solution for injection and the product contains the same active ingredient, in the same concentration and dosage form as the approved listed product Akovaz. Refer to biopharmaceutics review on whether the biowaiver request is granted.

The submitted label relies on the Akovaz product label and hence the submission is acceptable from a clinical pharmacology perspective. Since the Sponsor plans to entirely rely on the previous findings of NDA 208289 to support this product, there is no new clinical pharmacology study to review.

2 Labeling

After filing the 505(b)(2) NDA, the sponsor changed the approach from to rely on literature to rely on label for Akovaz. See attached proposed labeling in Appendix. The Sponsor uses the label of NDA 208289 to support the clinical pharmacology related sections.

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

3.2 Filing memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208609	**SDN**	1
Applicant	Akorn Inc	**Submission Date**	9/15/2015
Generic Name	Ephedrine Sulfate Injection, USP	**Brand Name**	Ephedrine Sulfate Inj
Drug Class			
Indication	(b) (4) clinically important hypotension in the setting of anesthesia		
Dosage Regimen			
Dosage Form	IV Injection	**Route of Administration**	IV
OCP Division	DCP2	**OND Division**	DAAAP

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.
Pharmacometrics		
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	11/16/2015	**74-Day Letter Date**	11/28/2015
Review Due Date	6/10/2016	**PDUFA Goal Date**	7/15/2016

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)

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	1	
☐ Transporter Characterization		
☑ Distribution	1	
☐ Drug-Drug Interaction	1	
In Vivo Studies		
Biopharmaceutics		

☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☑ Mass Balance Study		1	Sponsor submitted one publication to indicate predominant renal elimination of ephedrine. However, a renal impairment study was not conducted.
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☑ Healthy Subjects		1	
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**	2	**In Vivo**	2
Total Number of Studies to be Reviewed				

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	IV Injection
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	
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	At the Filing meeting: CMC reviewer Dr. Julia Pinto confirmed that ephedrine can only exist as a (-) enantiomer. Therefore, inter-conversion to (+) may not be relevant. Bioanalytical methodology related publications are submitted.
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	Only publications documenting clinical experience with ephedrine were submitted.
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	Publications necessary for review of NDA have been submitted.
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	Only publications documenting PK information were submitted.
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	Published clinical experience is submitted.
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	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
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

The clinical pharmacology and clinical database for this NDA is comprised of publications documenting clinical experience with parenteral ephedrine sulfate. Adequacy of these publications supporting the clinical pharmacology information of the product will be a NDA review issue.

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/s/

SRIKANTH C NALLANI
06/08/2016

YUN XU
06/08/2016

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SRIKANTH C NALLANI
11/16/2015

YUN XU
11/16/2015