CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Memo

Date	6/22/14
From	Christopher D. Breder, MD PhD Clinical Team Leader, Anesthetic Drugs Division of Anesthesia, Analgesia, and Analgesic Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supp #	204300 / Suppl. 0000
Proprietary / Established (USAN) names	Vazculep / Phenylephrine Hydrochloride
Dosage forms / strength	Solution for Injection, USP, 1%
Proposed Indication(s)	Treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia
Recommended:	Approval

1. Introduction to Review

This review serves as both the CDTL Memo and Clinical Review for the Applicant's Complete Response, a Class 1 resubmission of NDA204300.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

NDA 204300 was originally received February 8, 2013, refused to file on April 5, 2013, and resubmitted June 28, 2013, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) as VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL. NDA 204300 provided for the use of VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL for the following indications which were designated as follows:

- NDA 204300/Original 1 – treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia

(b) (4)

On 4/4/14, a Discipline Review letter was sent to the Applicant based on the Clinical review.

(b) (4)

On 4/28/14, a Complete Response Action was taken based on deficiencies found during an inspection of the (b) (4) manufacturing facility for this application. The

Applicant was notified that satisfactory resolution of these deficiencies were required before this application could be approved.

Éclat submitted their response on 6/6/14. In this submission, they commented that according to a communication from (b) (4) to Éclat dated June 2, 2014, (b) (4) was informed by the FDA on the same day that their facility was classified as acceptable. Éclat considers the deficiencies noted in the Complete Response Letter to be fully resolved.

3. CMC/Microbiology/Device

3.1. General product quality considerations
3.1.1. Facilities review/inspection

The application was recommended for approval from the CMC perspective. Dr. Nashed noted in her review that an acceptable recommendation is provided by the Office of Compliance (OC) regarding the status of the manufacturing and testing facilities for this product, as of June 6, 2014.

4. Nonclinical Pharmacology/Toxicology

The Primary Nonclinical reviewer, Dr. Delatte noted in his review that from a nonclinical pharmacology toxicology perspective, NDA 204300 may be approved with the originally recommended PMRs (see Section 13.4) and pending agreement on labeling since there were neither nonclinical deficiencies to address nor new nonclinical information to review in the complete response submitted.

5. Clinical Pharmacology/Biopharmaceutics

A Clinical Pharmacology review was not submitted since the Resubmission did not contain Clinical Pharmacology deficiencies or new Clinical Pharmacology information to review.

6. Clinical Microbiology

There is no need for data pertaining to clinical microbiology for this application.

7. Clinical/Statistical

(b) (4) The package insert submitted with the resubmission is acceptable after minor copy edits.

The Applicant submitted an updated safety review with this submission covering publications from between 10/11/13 and 6/3/14 that focused on identifying clinical trials and case reports in which phenylephrine was delivered intravenously. The search included any articles using the keyword phenylephrine and was limited to human, English-language publications. The Applicant reported reviewing titles and abstracts of approximately 40 articles for relevance. Eight publications that the Applicant felt had provided adequate safety information were

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summarized in this update. The Applicant commented that no new adverse events, unexpected severity of known events, or unexpected serious or clinically important safety findings associated with the use of phenylephrine have been reported in the literature. I concur with their conclusion.

8. Conclusions and Recommendations

8.1. Recommended regulatory action

I recommend approval of this NDA.

8.2. Postmarketing studies, voluntary or required

Pharmacology / Toxicology Postmarketing Requirement (PMR) list

PMR 1
Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

- Final Protocol Submission: 1/2016
- Study Completion: 12/2016
- Final Report Submission: 9/2017

PMR 2
Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

- Final Protocol Submission: 1/2016
- Study Completion: 7/2016
- Final Report Submission: 5/2017

PMR 3
Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

- Final Protocol Submission: 3/2016
- Study Completion: 10/2016
- Final Report Submission: 8/2017

PMR 4
Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

- Final Protocol Submission: 1/2016
- Study Completion: 9/2017
- Final Report Submission: 9/2018

Clinical Postmarketing Requirement

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A study in the ≥12 - <17 year old age group to evaluate the pharmacokinetics, efficacy, and safety of different doses of phenylephrine hydrochloride injection in patients undergoing general anesthesia and neuraxial anesthesia with the following commitment dates:

- Final Protocol Submission: 8/6/15
- Trial Completion: 8/6/18
- Final Report Submission: 2/6/19

CMC Post-Marketing Commitment (PMC) list

PMC 1

Éclat commits to establish final, data-based (b) (4) acceptance criteria for the content of sodium metabisulfite in the drug product, (b) (4) (b) (4)

PMC 2

Éclat commits to (b) (4) release acceptance criteria (b) (4)) for the content of sodium metabisulfite in the drug product, (b) (4) (b) (4)

Agreement

Éclat agrees to provide annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches, as described in NDA amendment dated March 11, 2014. The analysis will be focused on different instability trends for smaller fill volumes with a large head space (i.e., 1 mL and 5 mL) in comparison to the 10 mL fill volume with a small head space. Also, Éclat agrees to submit an evaluation of trends in sodium metabisulfite content in the context of changes in pH and impurity levels as well as analyze the impact of storage orientation on instability trends. The first report is scheduled to be submitted by April 2015, and it will contain analysis of 6 months stability data collected at the accelerated (40 ± 2 °C/75% ± 5% RH) and at long-term (25 ± 2°C/60% ± 5% RH) storage conditions for commercial manufacturing.

8.3. Comments to be conveyed to the applicant in the regulatory action letter (e.g., deficiencies and information needed to resolve each deficiency)

None

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/s/

CHRISTOPHER D BREDER
06/22/2014