CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

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	June 27, 2014
From	Rigoberto Roca, M.D.
Subject	Deputy Division Director Summary Review
NDA/Supplement No.	204300/S-000
Applicant Name	Éclat Pharmaceuticals, Inc.
Date of Original Submission	February 8, 2013/ Resubmitted after RTF: June 28, 2013 Complete Response letter issued April 28, 2014
Date of Complete Response Submission	June 6, 2014
PDUFA Goal Date	August 6, 2014
Proprietary Name / Established (USAN) Name	Vazculep / (phenylephrine hydrochloride) injection
Dosage Forms / Strength	Solution for injection / 10 mg/mL
Proposed Indication	Treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Timothy Jiang, MD, PhD
CDTL Review	Christopher Breder, MD, PhD
Statistical Review	Janice Derr, PhD / Thomas Permutt, PhD
Pharmacology Toxicology Review	Marcus Delatte, PhD / R Daniel Mellon, PhD
ONDQA Review	Eugenia Nashed, PhD / Prasad Peri, PhD
ONDQA Microbiology Review	Stephen Langille, PhD / John Metcalfe, PhD
Clinical Pharmacology Review	David Lee, PhD / Yun Xu, PhD
Project Management Staff	Kimberly Compton, RPh / Matthew Sullivan / Parinda Jani
Pediatric and Maternal Health Staff	Jeanine Best, MSN, RN / Miriam Dinatale, MD / Amy Taylor, MD / Lynne Yao, MD
SEALD	Jeanne Delasko / Eric Brodsky, MD
OMP/OPDP	Eunice Chung-Davies, PharmD
OMPQ/DGMPA/NDMAB	Juandria Williams / Mahesh Ramanadham, PharmD
OSE/DMEPA	Aleksander Winiarski, PharmD / Julie Neshiewat, PharmD
OSE/DPV II	Tara Argual, PharmD / Jane Gilbert, MD / Sara Camilli, PharmD / Allen Brinker, MD / Scott Proestel, MD
DBRUP	Barbara Wesley, MD / Christina Chang, MD / Audrey Gassman, MD

CDTL = Cross-Discipline Team Leader
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DGMPA = Division of Good Manufacturing Practice Assessment
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DRISK = Division of Risk Management
NDMAB = New Drug Manufacturing Assessment Branch
OMP = Office of Medical Policy
OMPQ = Office of Manufacturing and Product Quality
OND = Office of New Drugs
ONDQA = Office of New Drug Quality Assessment
OPDP = Office of Professional Drug Promotion
OSE = Office of Surveillance and Epidemiology
OSI = Office of Scientific
SEALD = Study Endpoints and Labeling Development

1. Introduction

Éclat Pharmaceuticals, Inc., has submitted a 505(b)(2) new drug application (NDA) for phenylephrine hydrochloride. It is formulated as a 1% solution (10 mg/mL), and is intended to be administered through the intravenous route. The proposed indications are for treatment (b) (4) of hypotension during anesthesia, either as a bolus or as a continuous infusion.

The FDA recently approved another phenylephrine formulation for intravenous administration for similar indications (NDA 203826, WestWard Pharmaceuticals). The company has opted to only reference published literature in support for this application, and has opted not to reference any approved NDA for phenylephrine. Subsequently, the review of this application has relied only the information submitted by the applicant in the context of this application and has not relied on the FDA's findings regarding NDA 203826.

The current submission constitutes a response to the Complete Response action letter that was issued to the Applicant on April 28, 2014. For an overview of the regulatory and scientific facts of this application and issues that were identified during the first review cycle, please refer to my memorandum dated April 28, 2014.

2. Background

Phenylephrine is a synthetic form derived from epinephrine and has been used clinically for more than 50 years. It is an α1-adrenergic receptor agonist, with little or no activity on α-2 receptors or β-receptors. The primary site of action is the vascular smooth muscle cells, resulting vascular smooth muscle contraction and subsequent increases in the systolic and diastolic blood pressures. Phenylephrine has also been noted to cause a reflex bradycardia and a decrease in the cardiac output, presumably due to the increased afterload. Phenylephrine has also been demonstrated to have an effect on renal, pulmonary, and splanchnic arteries, but minimal to no effect on cerebral vessels.

Regulatory History

The regulatory history is well summarized in Dr. Jiang's and Dr. Breder's reviews completed during the first review cycle. As noted in my memo from April 28, 2014, the Applicant originally submitted the application on February 8, 2013; however, the application was not filed due to the absences of an Integrated Summary of Efficacy and Integrated Summary of Safety. The Applicant addressed the deficiencies and resubmitted the application on June 28, 2013. A Complete Response letter was issued on April 28, 2014, due to the recommendation of "withhold" having been entered into the EES for a manufacturing site in (b) (4) after an inspection.

3. Chemistry, Manufacturing, and Controls (CMC)

As noted in my memorandum from April 28, 2014, the review team found that the Applicant had submitted adequate information about the drug substance and drug product to support approval of the application. The results from the site inspection precluded approval during the first review cycle.

Reference ID: 3533442

Since the time of the first action, the issues identified during the inspection have been adequately addressed, and the overall recommendation of "Acceptable" was entered into the EES on June 6, 2014. As noted in Drs. Nashed and Pinto review of June 17, 2014, the recommendation was for approval of the application, with the same post-marketing commitments and agreements that had been reached with the Applicant during the first review cycle.

Outstanding or Unresolved Issues

I concur with Drs. Nashed and Pinto that, with the resolution of the issues identified during the manufacturing site inspection, there are no product quality issues that would preclude approval of this application.

4. Nonclinical Pharmacology/Toxicology

The Applicant was not required to submit any additional nonclinical pharmacology/toxicology data to support this application.

Outstanding or Unresolved Issues

Drs. Delatte and Mellon indicated during the first review cycle that there were no pharmacology/toxicology issues that would preclude approval of this supplement. In a memo dated June 18, 2014, Dr. Delatte and Dr. Mellon reiterated their recommendation for approval and for the completion by the Applicant the Post-marketing Requirements (PMRs) identified during the first review cycle, which are as follows:

1. A fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.
2. An embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.
3. An embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.
5. A peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

I concur with the conclusions reached by Drs. Delatte and Mellon.

6. Clinical Pharmacology/Biopharmaceutics

The Applicant was not required to submit any additional data regarding the clinical pharmacology of phenylephrine.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Dr. Lee and Dr. Yun during the first review cycle that there are no clinical pharmacology issues that would preclude approval of this application.

7. Clinical Microbiology

Vazculep is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

Reference ID: 3533442

8. Clinical/Statistical – Efficacy

The Applicant was not required to submit any additional data to support the efficacy of phenylephrine for the requested indication.

Outstanding or Unresolved Issues

I concur with the overall conclusion reached by the review team that the data submitted by the Applicant are adequate to support the indication of treatment of hypotension.

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9. Safety

As noted by Dr. Breder in is memo, the Applicant updated the safety database in support of this application by reviewing the medical literature published between October 11, 2013 and June 3, 2014. The Applicant's search was limited to articles in English-language publications that were related to humans, and containing the keyword "phenylephrine." The Applicant's search yielded approximately 40 articles, 8 of which were deemed to be relevant to this NDA. The Applicant's conclusion was that no new adverse events, unexpected severity of known adverse events, or unexpected serious or clinically significant important safety findings were identified.

Dr. Breder agreed with the Applicant's conclusions.

Outstanding or Unresolved Issues

I concur with the review team that the safety profile of phenylephrine has been adequately characterized by the extensive history of clinical use, the published literature, and evaluation of the FDA's Adverse Event Report System.

10. Advisory Committee Meeting

An advisory committee meeting was not convened for this application during the first review cycle, as there were no issues in this application that required presentation or discussion at an advisory committee meeting. That assessment remained unchanged.

10. Pediatrics

The Applicant requested a waiver of the studies required under the Pediatric Research Equity Act of 2007 (PREA) (b) (4) The Division concurred with the Applicant with respect to patients less than 12 years of age, but considered the studies for patients older than 12 years as possible and desirable, in that dosing information in this age group would be relevant and useful to obtain.

At the Pediatric Review Committee (PeRC) meeting of March 5, 2014, the committee reviewed the Applicant's proposal and the division's position, and concurred with the division that the study in the older age group would be useful. It was also decided that this study could be deferred.

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These conclusions were conveyed to the Applicant and a timeline for the submission of the final report submission was agreed upon.

11. Other Relevant Regulatory Issues

There were no new regulatory issues identified during this review cycle.

Outstanding or Unresolved Issues
There are no other unresolved relevant regulatory issues.

12. Labeling

The labeling was discussed with the Applicant during the first review cycle, and agreements were reached on the text of the document.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval

Risk:Benefit Assessment

I concur with the review team that the Applicant has submitted substantial evidence to support the effectiveness and safety of phenylephrine for the treatment of hypotension that is primarily associated with vasodilation. As noted in my memorandum of April 28, 2014, even though phenylephrine has been associated with the risk of hypertension and reflex bradycardia, an episode of perioperative hypotension is associated with increased morbidity and mortality, whereupon the use of phenylephrine in this clinical situation results in a favorable risk:benefit assessment.

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

These requirements have been discussed with the Applicant during the course of the first review cycle of the application.

a) Clinical (as part of the PREA requirements)
A clinical study in patients between the ages of 12 and 16 years of age, to evaluate the pharmacokinetics, efficacy, and safety of different doses of phenylephrine hydrochloride injection in patients undergoing general anesthesia and/or neuroaxial anesthesia.

Reference ID: 3533442

b) Non-clinical
   1. A fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.
   2. An embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.
   3. An embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.
   4. A peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

Recommendation for other Postmarketing Study Commitments
These Postmarketing Commitments (PMCs) were discussed with the Applicant during the course of the first review cycle of the application. Agreements noted in the CMC reviews as having been reached during the first review cycle are also listed here as PMCs.

1. Submission of data and shelf-life acceptance criteria for the content of sodium metabisulfite in drug product.

2. Submission of data and data-based release acceptance criteria for the content of sodium metabisulfite in drug product.

3. Submission of annual stability reports with evaluation of instability trends upon analysis of data collected for commercial scale validation batches.

4. Submission of 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.

Reference ID: 3533442

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/s/

RIGOBERTO A ROCA
06/27/2014

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NDA/Supplement No.	204300/S-000
Applicant Name	Éclat Pharmaceuticals, Inc.
Date of Submission	February 8, 2013/ Resubmitted after RTF: June 28, 2013
PDUFA Goal Date	April 28, 2014
Proprietary Name / Established (USAN) Name	Vazculep / (phenylephrine hydrochloride) injection
Dosage Forms / Strength	Solution for injection / 10 mg/mL
Proposed Indications	1. Treatment of hypotension during anesthesia [redacted] (b) (4)
Action	1. Treatment of hypotension during anesthesia: Complete Response [redacted] (b) (4)

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Timothy Jiang, MD, PhD
CDTL Review	Christopher Breder, MD, PhD
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1. Introduction

Éclat Pharmaceuticals, Inc., has submitted a 505(b)(2) new drug application (NDA) for phenylephrine hydrochloride. It is formulated as a 1% solution (10 mg/mL), and is intended to be administered through the intravenous route. The proposed indications are for treatment (b) (4) of hypotension during anesthesia, either as a bolus or as a continuous infusion.

The FDA recently approved another phenylephrine formulation for intravenous administration for similar indications (NDA 203826, WestWard Pharmaceuticals). The company has opted to only reference published literature in support for this application, and has opted not to reference any approved NDA for phenylephrine. Subsequently, the review of this application has relied only the information submitted by the applicant in the context of this application and has not relied on the FDA's findings regarding NDA 203826.

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.

2. Background

Phenylephrine is a synthetic form derived from epinephrine and has been used clinically for more than 50 years. It is an α1-adrenergic receptor agonist, with little or no activity on α-2 receptors or β-receptors. The primary site of action is the vascular smooth muscle cells, resulting vascular smooth muscle contraction and subsequent increases in the systolic and diastolic blood pressures. Phenylephrine has also been noted to cause a reflex bradycardia and a decrease in the cardiac output, presumably due to the increased afterload. Phenylephrine has also been demonstrated to have an effect on renal, pulmonary, and splanchnic arteries, but minimal to no effect on cerebral vessels.

Regulatory History

(b) (4)

The Applicant originally submitted the application on February 8, 2013; however, the application was not filed due to the absences of an Integrated Summary of Efficacy and Integrated Summary of Safety. A meeting was held with the Applicant on June 13, 2013, at which the appropriate format for the submission was discussed.

Reference ID: 3497203

3. Chemistry, Manufacturing, and Controls (CMC)

General Product Considerations

Drug Substance

Phenylephrine chloride is a [redacted], soluble in aqueous media. The Applicant purchases the drug substance from [redacted], and it is manufactured under DMF # [redacted]. The DMF was reviewed and deemed to be adequate.

The manufacturing site is in [redacted], and previous inspection resulted in several GMP issues that needed to be addressed. A re-inspection of the facility was conducted by the Agency on [redacted].

Drug Product

The drug product is a sterile, non-pyrogenic solution. [redacted] Inspection of the manufacturing facility and two contractor sites were deemed acceptable.

As noted in Dr. Nashed's review, the drug product is packaged in Type 1 clear glass vials with [redacted] stoppers and [redacted]. The Applicant proposes three fill volumes for marketing: 1 ml, 5 mL, and 10 mL, with the latter two intended only for pharmacy distribution. Data were submitted to support storage at controlled room temperature, 25 ºC (77ºF), with excursions permitted from 15º to 30ºC (59º to 86ºF). The stability data submitted supports an [redacted] expiry data, however, the Applicant's agreement to monitor the observed instability trends and to provide the evaluation report in the annual report has permitted the review team to grant a 24-month expiry period.

Facilities Reviews/Inspections

The drug product manufacturing site [redacted] and two testing sites were inspected and deemed acceptable. The drug substance manufacturing site in [redacted] had previously been inspected and several issues had been identified that needed to be corrected. That site was re-inspected on [redacted]. An overall recommendation is pending at this time in the Establishment Evaluation System (EES), however, a recommendation of "withhold" was entered into the EES for the site in [redacted] on [redacted]. Regarding the implications on this entry in EES for the action on this application, Dr. Mahesh Ramanadham, the Acting Branch Chief in the New Drug Manufacturing Assessment Branch (NDMAB) responded in an email on April 25, 2014, as follows:

> Regarding action; if we remain in the same situation (i.e. no report), we should still be able to take action as the international team entered their recommendation in EES. In my experience we don't usually miss action when we are waiting for additional information for the site compliance evaluation (as site evaluations are not tied to GRMP dates). We usually take action on the most current information we have available, unless there is a compelling reason to miss the date (ex unapproved new drug initiative, current shortage, etc…). As the recommendations are in EES, we have what we need in order to take action, but that decision is ultimately up to DAAP.

Reference ID: 3497203

Product Quality Microbiology

The evaluation of the [redacted] and process controls, and their validation, was conducted by Dr. Stephen Langille. His conclusions were that the information provided in the submission was adequate to support approval.

Specific Issues Identified in the Course of the Review

The following issues were identified in the course of the review and resolved (reproduced from Dr. Nashed's review:

- Data documenting the absence of [redacted] to be submitted by April 2, 2014, per agreement provided on March 19, 2014.

  The Applicant discussed preliminary results for the content of potential [redacted] leachable in communication dated March 19, 2014, [redacted] pplicant agreed to provide final test results and brief method validation in NDA amendment by April 2, 2014. The preliminary negative results for the potential [redacted] leachable and the provided agreement alleviate the CMC safety concerns regarding this leachable. At this point we do not consider it necessary to include the testing for leachables in the drug product stability protocol.

- Specifications for the content of sodium metabisulfite during shelf-life of the product as described in PMC #1.

- Tightening of the tentative release specifications for the content of sodium metabisulfite as described in PMC #2.

  The proposed PMCs are considered sufficient to address the potential safety and quality aspects associated with the level of sodium metabisulfite [redacted] in the drug product formulation. Although most likely there is a minimum level of the [redacted] required to assure the strength of the drug product, the stability of the formulation is indirectly controlled by the acceptance criteria for pH, individual impurities and total impurities. [redacted] In addition, a report will be provided to the Agency documenting the changes occurring in the level of sodium metabisulfite throughout the life-time of the drug product, along with a study documenting a minimum level of sodium metabisulfite required to sustain the [redacted] function.

- Special stability report to be submitted in each Annual Report. It will include analysis of instability trends, including results for all stability-indicating attributes, including the requested data ([redacted], storage orientation), as described in Agreement #1.

  The stability data submitted to this NDA include results for 9 registration batches [redacted] for samples stored in one orientation ([redacted]) for 18 months. Data do not include content of [redacted] (see PMCs) and indicate different instability trends (pH, impurities) for small fill vials (1 mL and 5 mL) with large head volume in comparison to the 10 mL fill with small head volume, most likely due to the [redacted] As a result, the impurity levels and pH are [redacted] for different product fills after storage, however the results are within specification limits. Also, no report or data documenting the preferred-for-storage orientation for the product is currently available.

  The provided Agreement, to include additional storage orientation for stability samples and to provide analysis of the instability trends for the commercial products in each annual report, is adequate to monitor the quality of the proposed-for-marketing product and sufficiently addresses the CMC concerns.

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It is noted that these issues are being addressed with post-marketing commitments and agreements, and do not impact the approvability of the application.

Outstanding or Unresolved Issues
As noted above, the email communication from NDMAB indicated that, since there is a recommendation in EES, we have what we need to in order to take an action on this application. Due to the withhold recommendation, this application cannot be approved until the issues identified in the inspection are resolved.

4. Nonclinical Pharmacology/Toxicology

General Considerations
The Applicant did not conduct any nonclinical pharmacology or toxicology studies. In previous interactions with the Applicant prior to the submission of the application, the Division had indicated that adequate clinical experience with the product could potentially obviate the need for general toxicology studies to support the application.

Dr. Delatte noted in his review that there are no novel excipients with the drug product formulation, and that all drug substance impurities and drug product degradants have been adequately qualified for safety. It was also noted that the container closure system has been adequately qualified for safety.

All the nonclinical information intended to support the application and inform the label with respect to genotoxicity, carcinogenicity, and reproductive and development toxicity, was derived from the published literature.

Carcinogenicity
The results of a 2-year study in rats and a 2-year study in mice that were treated with phenylephrine via their diet were available in the published literature, and it reported no evidence of carcinogenicity under the conditions of the study. The dose employed in the rat study (50 mg/kg or 300 mg/m^2) is 48-fold the human dose and the dose used in the mice study (270 mg/kg or 810 mg/m^2) is 131-fold the maximum daily dose human dose of 10 mg/60 kg person (0.17 mg/kg or 6.3 mg/m^2), based on body surface area comparisons.

Genotoxicity
The published literature contained the results from phenylephrine studies conducted with the Ames assay, in vitro mouse lymphoma assay, in vitro assay for chromosomal aberrations, and the in vitro alkaline elution assay in rat hepatocytes. Dr. Delatte concludes that, based on overall weight-of-evidence all the genetic toxicology and carcinogenicity data, there was no concern for genotoxicity.

Reproductive Toxicology
Dr. Delatte noted in his review that reports of reproductive toxicology studies conducted in rabbits and sheep were available in the literature. The following is a quotation from his review regarding the results of these studies and their implications.

> Review of the literature identified a few nonclinical studies that begin to characterize the potential impact of phenylephrine on reproductive and developmental endpoints.

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Specifically, reproductive toxicology studies in normotensive rabbits were conducted to evaluate the effect of phenylephrine administration during various stages of gestation. These studies indicate that subcutaneous administration of phenylephrine to pregnant rabbits (0.33 mg/kg, TID) resulted in premature labor onset, decreased litter weights, increased neonate deaths and still births, and histopathology findings in the placenta such as necrosis, thickened vascular walls, and narrowed lumina. Studies in normotensive pregnant sheep demonstrated that phenylephrine increases blood pressure and produces reflex bradycardia in both the ewe and the fetus and decreases uterine blood flow at doses that were slightly greater than the upper dosing range in humans. These findings, in normotensive animals, suggest the potential for risk and should be included in the drug product labeling at this point. However, none of the studies are deemed adequate by current standards, and the results from studies in normotensive animals may not reflect clinical conditions if the drug is used only to treat hypotension and restore blood pressure to normal. (b) (4)

Based on the limited data in the literature, the full reproductive and developmental toxicology study battery of studies are recommended as PMRs. Careful design of these studies to include assessment of clinically relevant conditions, if possible, should be discussed with the Sponsor.

Other Nonclinical Evaluations of Interest

There were no other nonclinical evaluations of interest.

Outstanding or Unresolved Issues

I concur with the conclusions reached by Drs. Delatte and Mellon that there are no pharmacology/toxicology issues that would preclude approval of this supplement. I also concur with their recommendation that the Applicant conduct the following Post-marketing Requirements (PMRs):

1. A fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.
2. An embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.
3. An embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.
5. A peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

6. Clinical Pharmacology/Biopharmaceutics

General Considerations

The Applicant did not conduct any clinical pharmacology studies. All the information regarding the clinical pharmacology of their product was derived from published literature. Dr. Lee noted in his review that the Applicant's submission included studies to address the pharmacokinetic, pharmacodynamic, and drug-drug interaction sections of the label.

Pharmacokinetic Information

Dr. Lee noted the following in his review (note: in his review, phenylephrine is abbreviated as "PE"):

> Following an intravenous infusion (12.5 to 20 minutes) of 1 mg (mean dose of 0.84 ± 0.17 mg) tritiated phenylephrine (3H-PE), the PE concentration-time curve exhibited

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biphasic decline, as observed by an initial rapid distribution followed by relatively slow elimination. The reported average steady state volume of distribution (Vss) and elimination half-life were 340 L (range 184 to 543 L) and 151 minutes (2.51 h based on β-phase), respectively. The observed distribution phase was rapid (less than 5 minutes based on α-phase).

Phenylephrine is metabolized primarily by monoamine oxidase and sulfotransferase. Based on 3H-PE intravenous administration, approximately 86% (approximately 80% of the administered dose was eliminated within first 12 h) of the intravenously administered dose was recovered in the urine within 48 h. The excreted unchanged drug (i.e., parent PE) was 16% of the dose in the urine at 48 h post intravenous administration. There are two major metabolites with approximately 57 and 8% of the administered dose excreted as m-hydroxymandelic acid and sulfate conjugates, respectively. The metabolites are considered not pharmacologically active.

Pharmacodynamic Information

Dr. Lee noted in his review that the literature indicates that phenylephrine's onset of action is within seconds, and lasts minutes after administration, but is also dependent on the subject's sensitivity. The two tables that follow are adapted from Dr. Lee's review, summarize the findings from the literature, and the overall assessment is that the pressor responses were in the 6 to 30 mm Hg range when a bolus dose was given with or without a follow-up infusion.

Blood pressure response to phenylephrine (PE) bolus intravenous injection (SBP: systolic blood pressure; SAP: systolic arterial pressure; MAP: mean arterial pressure)

Reference	Patient population	PE Dose	Blood Pressure Just Prior to PE Application	Blood Pressure After PE Application	Δ BP	Time after PE Dose
Goertz et al. 1993b	Coronary artery disease and valvular aortic stenosis	1 µg/kg (~72 µg[a])	MAP 69-71mm Hg	MAP 94-99 mm Hg	23-30 mm Hg	60 sec
Dyer et al. 2008b	Cesarean delivery with spinal anesthesia	50-100 µg, repeated every minute as needed	MAP 91 mm Hg	MAP 108 mm Hg	17 mm Hg	Within 24 to 40 seconds of dosing
Goertz et al. 1993a	Elective minor abdominal or orthopedic surgery	2 µg/kg (~148 µg[c])	61 mm Hg	83 mm Hg	22 mm Hg	30 sec
Ishiyama et al. 2003	Elective surgery under combined general and epidural anesthesia	2 µg/kg (~112 µg[d])	61 mm Hg	80 mm Hg	~19 mm Hg	2.5 min

Reference	Patient population	PE Dose	Blood Pressure Just Prior to PE Application	Blood Pressure After PE Application	Δ BP	Time after PE Dose
Dyer et al. 2009	Cesarean delivery with spinal anesthesia	80 µg	72.8 mm Hg	98.5 mm Hg	25.7 mm Hg	61.8 sec
Alahuhta et al. 1992	Cesarean delivery with spinal anesthesia	100 µg bolus (followed by 100 µg bolus)	SAP 109 mm Hg	SAP 115 mm Hg	6 mm Hg	-

[a] µg/kg x mean weight 69-75 kg = 69-75 µg

[b] Blood pressure response was measured after multiple PE doses

[c] 2 µg/kg x mean patient weight of 74 kg = 148 µg

[d] 2 µg/kg x mean patient weight of 56 kg = 112 µg

[e] Based on mean MAP values pre and post-vasopressor

Blood pressure response to phenylephrine (PE) intravenous infusion with or without initial bolus injection (SBP: systolic blood pressure; SAP: systolic arterial pressure; MAP: mean arterial pressure)

Reference	Patient population	PE Dose	Baseline MAP	Post-dose MAP	MAP Response	Time of Post- dose Evaluation
Nygren et al. 2006	Coronary artery bypass grafting surgery	0.50 ± 0.22 µg/kg/min (range, 0.21± 0.94 µg/kg/min) ~35 µg/min	68 ± 5 mm Hg	92 ± 4 mm Hg	24 mm Hg	NA
Brooker et al. 1997	Elective surgery with tetracaine spinal	40 µg bolus (followed by infusion with 0.5 µg/kg/mina	MAP 82 mm Hg	MAP 100 mm Hg	18 mm Hg	NA

[a] Calculated from mean weight of population studied in Brooker et al. (1997)

Dr. Lee also noted in his review that, although phenylephrine's pressor activity is dependent on the concentration being infused, increasing the duration of infusion did not significantly increase the mean arterial pressure (the following table is adapted from Dr. Lee's review).

Pressor response to phenylephrine dose

Phenylephrine dose	Duration of Infusion (min)	Baseline MAP* (mm Hg)	Post-dose MAP (mm Hg)	Δ in MAP (mm Hg)
0.15 µg/kg/min (~10 µg/min)	4	83 ± 2	85 ± 2	2
	8		85 ± 2	2
0.30 µg/kg/min (~20 µg/min)	4		88 ± 3	5
	8		89 ± 2	6
0.45 µg/kg/min (~30 µg/min)	4		94 ± 2	11
	8		97 ± 2	14

*MAP = mean arterial blood pressure

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Special Populations
The Applicant submitted literature to address special populations. With regard to age, sex, and race, Dr. Lee concluded that the data in the literature were either inconclusive or inadequate to result in dosing modification recommendations.

With respect to patients with hepatic impairment, the data indicated that the cardiovascular response, i.e., increases in blood pressure, was attenuated in patients with severe hepatic disease, potentially requiring higher doses. Dr. Lee proposed wording to include in the labeling to reflect this finding.

Dr. Lee also noted that, in patients with renal impairment, the data indicated that patients with end-stage renal disease exhibited an increased responsiveness to phenylephrine. Dr. Lee is proposing that the package insert note that patients with renal impairment may be started at a lower than recommended dose, with adjustments being made as necessary.

Thorough QT Study
Dr. Breder noted in his review that the literature and the review of post-marketing adverse event reports by Drs. Argual and Gilbert did not identify a signal. Given the extensive history of clinical use, the team concluded that further assessment was not necessary.

Drug-drug Interactions
Concomitant medications may affect the sensitivity of tissue α-adrenoreceptors, resulting in either an increase or a decrease vasopressor effect of phenylephrine. In addition, certain moieties may act as agonists, or antagonists of phenylephrine, requiring adjustments in the dosage. Examples of the drugs that fall into each category will be included in the package insert.

Outstanding or Unresolved Issues
I concur with the conclusions reached by Dr. Lee and Dr. Yun that there are no clinical pharmacology issues that would preclude approval of this application.

7. Clinical Microbiology

Vazculep is not a therapeutic antimicrobial; therefore, clinical microbiology data were not required or submitted for this application.

8. Clinical/Statistical – Efficacy

The Applicant had proposed the following indication for their application: for the "treatment (b) (4) of hypotension during anesthesia." The clinical review team reviewed them as two separate indications, because the patient populations would be different, the dosage recommendations could potentially be different, the amount and type of published information supporting each was different, and the risk:benefit assessment for each was different.

Treatment of Hypotension
As noted by Drs. Breder and Jiang, the published literature has several examples of the use of phenylephrine to raise blood pressure in a variety of surgical settings, including coronary artery

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bypass grafts, valvular heart surgery, and elective abdominal, orthopedic, urologic, and gynecologic procedures. They also noted that the literature also describes the international experience with using phenylephrine to treat anesthesia-induced hypotension (from the United Kingdom, Canada, European Union, Asia, South America, and Africa).

The clinical team evaluated the data from 15 publications describing the use of phenylephrine to treat hypotension. The evaluated the data based on the type of anesthesia (general vs. neuraxial), method of administration (bolus vs. infusion), and patient population (obstetrical vs. non-obstetrical).

In reviewing the data, the team noted that bolus dosed of 150 µg or 200 µg do not result in significant incremental increases in blood pressure compared to the lower doses. This observation is summarized in the table below (adapted from Dr. Breder's review).

Change in Mean Arterial Pressure by dose of phenylephrine

	Change in Mean Arterial Pressure (mm Hg)								
	Time after bolus Phenylephrine injection (in seconds)								
PE Dose (µg)	10	20	30	40	50	60	70	80	90
50 (n = 24)	-0.5 ± 0.5	2.6 ± 1.0	9.7 ± 1.8	11.6 ± 2.1	10.9 ± 1.9	8.8 ± 2.0	7.0 ± 2.2	7.9 ± 2.0	8.0 ± 1.9
100 (n = 17)	0.9 ± 1.0	5.6 ± 1.7	12.6 ± 1.8	14.6 ± 2.2	15.6 ± 2.6	13.6 ± 2.8	13.7 ± 2.8	13.1 ± 2.8	12.9 ± 3.1
150 (n = 3)	-1.0 ± 0.6	1.0 ± 4.6	8.7 ± 6.0	14.7 ± 2.4	13.7 ± 0.70	12.0 ± 1.5	10.3 ± 2.0	9.3 ± 2.0	8.7 ± 1.8
200 (n = 6)	0.7 ± 1.6	3.7 ± 3.3	9.5 ± 2.8	16.0 ± 1.9	18.0 ± 1.5	13.8 ± 2.2	13.3 ± 2.6	13.6 ± 2.4	14.8 ± 2.4

This observation may be due to the increased vascular resistance seen with the 200 µg dose, which, as an increased afterload, can have the effect of decreasing cardiac output.

The team felt that a dosing recommendation of bolus administrations of 40 to 100 µg, to be repeated if needed after a few minutes, struck the balance between achieving a therapeutic effect and not causing an untoward systemic effect.

With respect to phenylephrine infusion rates reported in the literature, Dr. Breder's review noted that infusion rates of 0.21 µg/kg/min to 0.94 µg/kg/min resulted in increases of as much as 50% from baseline. The studies emphasized the importance of initiating the infusion at a low rate, and titrating to the desired blood pressure.

(b) (4)

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(b) (4)

Outstanding or Unresolved Issues

I concur with the overall conclusion reached by the review team that the data submitted by the Applicant are adequate to support the indication of treatment of hypotension. (b) (4)

(b) (4)

9. Safety

As noted by Dr. Jiang and Dr. Breder in their reviews, the safety database submitted by the Applicant was entirely derived from the published literature. In the studies that were intended to

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support the treatment indications, there were 502 patients exposed, [redacted] (b) (4) It was acknowledged that the reporting of the adverse events was not consistent throughout the studies, but, nevertheless, there was enough information contained in the studies to characterize the overall safety profile.

Deaths
There were no deaths reported in the literature submitted to support the safety of the product.

Non-fatal Serious Adverse Events
As noted by Dr. Jiang, adverse events that could be considered potentially life-threatening were reported, included episodes of hypertension and cardiac arrhythmias. However, the articles did not contain enough information to determine whether these events met the criteria to be classified as a serious adverse event.

The review team identified two cases in the literature of hypertensive emergencies that were not cited by the Applicant. The first was a case of stress-induced cardiomyopathy in a woman undergoing an elective cesarean section who had been dosed with phenylephrine to prevent hypotension. The second was a case was a case of coronary dissection in a woman who was treated with phenylephrine for an episode of hypotension during an elective cesarean section.

Early Discontinuations
An assessment of the typed of adverse events that resulted in early discontinuations is not relevant for this indication due to the acute and temporary use of phenylephrine, particularly in the surgical setting.

Common Adverse Events
The most commonly reported adverse events in the published literature were hypertension, bradycardia, nausea and vomiting.

In addition, the review team obtained a consultation was obtained from the Office of Surveillance and Epidemiology, Division of Pharmacovigilance II, to review the FDA's Adverse Event Report System (FAERS), as well as the published literature to identify any new safety signals about phenylephrine that could inform the labeling. Their findings were summarized as follows:

> The search of the FAERS database retrieved 137 reports. There were 12 unique FAERS cases coded with an outcome of death. Analysis of these reports did not find any report of death causally linked to use of IV phenylephrine; nor were there any unique patterns of adverse events across age groups, gender, country of reporter, or location of use. The published literature search of adverse events associated with phenylephrine retrieved one article describing stress cardiomyopathy in an obstetric patient undergoing spinal anesthesia as well as a number of articles reporting maternal bradycardia (labeled) in obstetric patients. The majority of articles retrieved from a review of the published medical literature focused on the *efficacy* of phenylephrine.

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> Our review of all unlabeled adverse events did not find any events that were sufficiently compelling to suggest a new safety signal or to require any addition to the proposed phenylephrine labeling. DPV will continue routine monitoring of all adverse events reported in association with phenylephrine HCl 1% injection.

Outstanding or Unresolved Issues

I concur with the review team that the safety profile of phenylephrine has been adequately characterized by the extensive history of clinical use, the published literature, and evaluation of the FDA's Adverse Event Report System.

10. Advisory Committee Meeting

An advisory committee meeting was not convened for this application, as there were no issues in this application that required presentation or discussion at an advisory committee meeting.

10. Pediatrics

The Applicant requested a waiver of the studies required under the Pediatric Research Equity Act of 2007 (PREA) (b) (4) The Division concurred with the Applicant with respect to patients less than 12 years of age, but considered the studies for patients older than 12 years as possible and desirable, in that dosing information in this age group would be relevant and useful to obtain.

At the Pediatric Review Committee (PeRC) meeting of March 5, 2014, the committee reviewed the Applicant's proposal and the division's position, and concurred with the division that the study in the older age group would be useful. It was also decided that this study could be deferred.

These conclusions were conveyed to the Applicant and a timeline for the submission of the final report submission was agreed upon.

11. Other Relevant Regulatory Issues

Consultations were obtained from the Office of Professional Drug Promotion, the Division of Medication Error Prevention and Analysis, and the Study Endpoints and Labeling Development team. Their recommendations were reviewed and incorporated in the appropriate places in the label.

Consultation was also obtained from the Division of Bone, Reproductive, and Urologic Products with regard to the safety of the use of phenylephrine during labor and delivery.

OSI / Division of Good Clinical Practice Compliance (DGCPC) Audits

There were no clinical trials conducted by the Applicant, therefore, there was no need for audits to be conducted by the DGCPC.

Financial Disclosure

The Applicant did not conduct any clinical trials in support of this application. Therefore, the Applicant did not need to make any statement regarding financial disclosures for investigators.

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Outstanding or Unresolved Issues
There are no other unresolved relevant regulatory issues.

12. Labeling

In addition to the review disciplines mentioned above, representatives from the Division of Medication Error Prevention and Analysis, the Office of Prescription Drug Promotion, and the Pediatric and Maternal Health Staff were also consulted and their recommendations were incorporated during the discussion of the label.

Since the clinical entity of hypotension can be due to a variety of etiologies, and the decision as to when it should be treated is dependent on the clinical circumstances, the indication statement will be modified to reflect that phenylephrine is indicated for treatment of clinically (b) (4) hypotension resulting primarily from vasodilation in the setting of anesthesia.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

1. Treatment of Hypotension: Complete Response

Although the Applicant submitted sufficient information to support approval of phenylephrine for the indication of "treatment of hypotension during anesthesia," the withhold recommendation entered into the EES precludes approval of this application at this time.

(b) (4)

Risk:Benefit Assessment

I concur with the review team that the Applicant has submitted substantial evidence to support the effectiveness and safety of phenylephrine for the treatment of hypotension that is primarily associated with vasodilation. Even though phenylephrine has been associated with the risk of hypertension and reflex bradycardia, an episode of perioperative hypotension is associated with increased morbidity and mortality, whereupon the use of phenylephrine in this clinical situation results in a favorable risk:benefit assessment.

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(b) (4)

Recommendation for Postmarketing Risk Management Activities

None.

Recommendation for other Postmarketing Study Requirements

These requirements have been discussed with the Applicant during the course of the review of the application, but they will not be officially communicated in the CR letter because the application is not being approved at this time.

Clinical (as part of the PREA requirements)

A clinical study in patients between the ages of 12 and 16 years of age, to evaluate the dose effect of phenylephrine administration on blood pressure in patients undergoing general anesthesia or neuroaxial anesthesia.

Non-clinical

1. A fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.
2. An embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.
3. An embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.
4. A peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

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/s/

RIGOBERTO A ROCA
04/28/2014