CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204300/original 1	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (Vazculep proposed) Established/Proper Name: Phenylephrine Hydrochloride, USP Dosage Form: Injection Strengths: 1%		
Applicant: Eclat Pharmaceuticals, inc.		
Date of Receipt: 6/28/13, cycle 1; 6/6/14 (response to cycle 1 CR)		
PDUFA Goal Date: 8/6/14	Action Goal Date (if different): 6/25/14	
RPM: Kim Compton		
Proposed Indication(s): Treatment of hypotension during anesthesia		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published literature	Nonclinical Pharmacology, ADME, Safety Pharmacology, and Toxicology data; Clinical PK, safety, and efficacy data

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

- **The proposed product bridge to the published literature is a scientific justification that is supported by data from IV studies (100% bioavailable) from published literature and the product is IV (100% bioavailable). The data are relevant without the need for a study (100%= 100%). See 21 CFR 320.24(b)(6).**

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO ☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☒ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐
*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐
*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☒

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): **N 203510, phenylephrine hydrochloride ophthalmic solution, 2.5% and 10%**

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

The applicant didn't rely on any listed drugs.

Listed drug/Patent number(s):

No patents listed ☒ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the

application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

☒ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
06/26/2014

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204300
Product Name:	Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL
PMR/PMC Description:	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/or neuroaxial anesthesia.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	August 2015
	Study/Trial Completion:	August 2018
	Final Report Submission:	February 2018
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☐ Long-term data needed
   - ☐ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☒ Other

   Product is ready for approval

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to describe the pharmacokinetics, efficacy and safety of Vazculep in this age group.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☒ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Administration by both the bolus and infusion methods to be studied for the treatment of hypotension. Dosing of phenylephrine is to be weight-based since weight may be quite variable in this population. Dosing is also to be based on the patient's hemodynamic status.

Evaluation of different dose levels (e.g., mg/kg, in the case of boluses and mcg/kg/min, in the case of infusions) to assess the dose: effect relationship.

The information captured to include, at a minimum, the following:

- **Demographics:** Demographic and medical history information that informs about the subjects' cardiovascular status
- **Efficacy/Pharmacodynamics:** Blood pressure and heart rate, time to onset, maximal response, and duration of response should be defined and captured before and during the treatment
- Concomitant intraoperative and post-operative medications, including their doses and adjustments in inhaled gas concentration or intravenous agent infusion rates
- Interventions used to treat the hypotension, e.g., other pressor agents, intravenous fluid boluses, changes in patient positioning
- Intraoperative events relevant to subjects' physiological status, such as blood loss and fluids administered
- **Pharmacokinetics:** to be characterized at points relative to the phenylephrine administration
- **Safety:** Vital signs (consistent with the American Society of Anesthesiology Monitoring Guidelines), Adverse Events, and Electrocardiograms (ECG) should be collected. Where possible continuous monitoring to be used (e.g., Pulse oximetry, temperature, and ECGs)

Required subjects:
25 subjects in bolus treatment group /dose level
25 subjects in infusion treatment group /dose level

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)
PK, efficacy and safety study

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

NDA 204300

PMR/PMC Description: Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	1/2016
Study Completion:	12/2016
Final Report Submission:	9/2017
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of phenylephrine on fertility and early embryonic development, given the long clinical experience these studies were deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that there are no data to address the effects of phenylephrine on fertility, and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A fertility and early embryonic development study is generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

- **Which regulation?**

  ☐ Accelerated Approval (subpart H/E)
  ☐ Animal Efficacy Rule
  ☐ Pediatric Research Equity Act
  ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

  ☐ Assess a known serious risk related to the use of the drug?
  ☐ Assess signals of serious risk related to the use of the drug?
  ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

  ☐ Analysis of spontaneous postmarketing adverse events?
  Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

  ☐ Analysis using pharmacovigilance system?
  Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

  ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
  Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

  ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo fertility and early embryonic development study in the rat model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

PMR/PMC Development Template

NDA 204300

PMR/PMC Description: Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	1/2016
Study/Trial Completion:	7/2016
Final Report Submission:	5/2017
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of phenylephrine on embryo-fetal development, given the long clinical experience these studies were deemed acceptable as post-marketing requirements. At the time of approval, the drug product label will indicate that there are possible teratogenic effects following subcutaneous administration of phenylephrine based on results of a published study in the literature (see Shabanah, et al., 1969), and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations. Due to these results and the intended use of the product, it is critical to either confirm or refute these findings via modern definitive nonclinical studies.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Two embryo-fetal developmental toxicology studies (rat and rabbit models) are generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rat model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

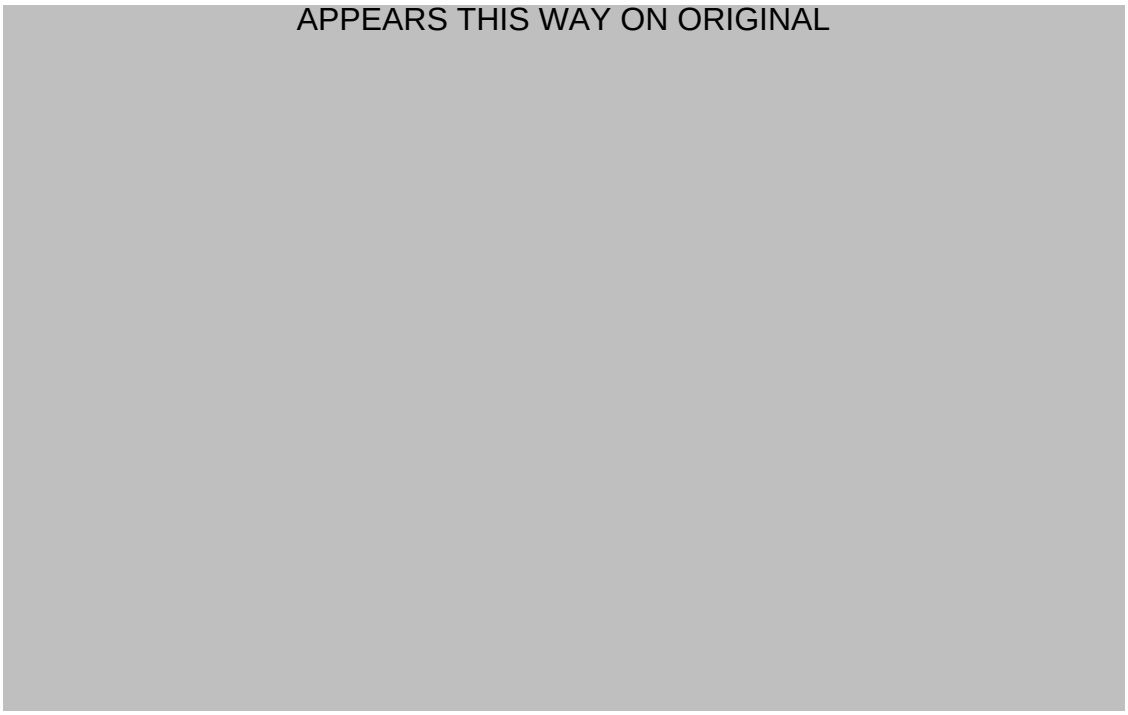
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference List

Shabanah EH, Tricomi V and Suarez JR (1969) Fetal environment and its influence on fetal development. *Surg Gynecol Obstet* **129**:556-564.



PMR/PMC Development Template

NDA 204300

PMR/PMC Description: Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	3/2016
Study/Trial Completion:	10/2016
Final Report Submission:	8/2017
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of phenylephrine on embryo-fetal development, given the long clinical experience this study was deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that there are potential teratogenic effects produced following subcutaneous administration of phenylephrine based on results of a published study in the literature (see Shabanah, et al., 1969), and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations. Due to these results and the intended use of the product, it is critical to either confirm or refute these findings via modern definitive nonclinical studies.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Two embryo-fetal developmental toxicology studies (rat and rabbit models) are generally required to adequately inform the drug product labeling. As this drug product is currently marketed, the drug product labeling will reflect the lack of adequate data until the study is completed. At that time, the labeling will be updated.

If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo embryo-fetal developmental toxicology study using the rabbit model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

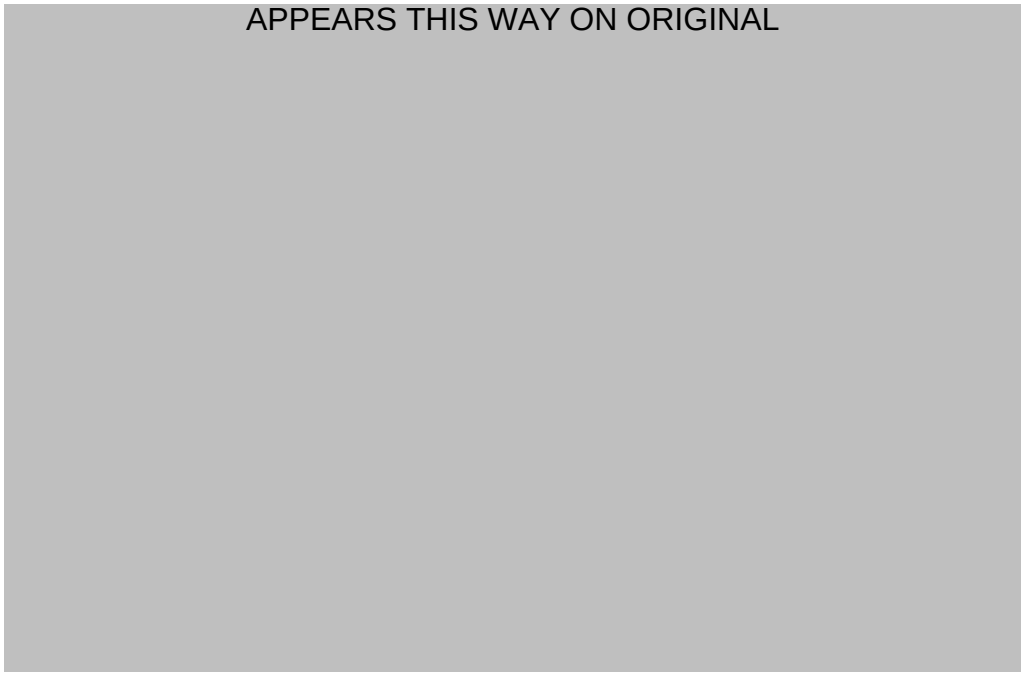
☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

Reference List

Shabanah EH, Tricomi V and Suarez JR (1969) Fetal environment and its influence on fetal development. *Surg Gynecol Obstet* **129**:556-564.



PMR/PMC Development Template

NDA 204300

PMR/PMC Description: Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

PMR/PMC Schedule Milestones:

Final Protocol Submission:	1/2016
Study/Trial Completion:	9/2017
Final Report Submission:	9/2018
Other: N/A	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The drug product is currently a marketed unapproved drug. Although prior clinical experience does not address the effect of phenylephrine on peri- and post-natal development, given the long clinical experience this study was deemed acceptable as a post-marketing requirement. At the time of approval, the drug product label will indicate that (b) (4) , and the drug will be labeled a Pregnancy Category C as per the Code of Federal Regulations.

Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

A peri- and post-natal developmental toxicology study is generally required to adequately inform the drug product labeling. As this drug product is currently marketed, (b) (4) At that time, the labeling will be updated.

If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is an in vivo peri-and post-natal developmental toxicology study using the rat model.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____
(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204300
Product Name: Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL

PMR/PMC Description: Submission of data and shelf-life acceptance criteria for the content of sodium metabisulfite in drug product

PMR/PMC Schedule Milestones:

Final Protocol Submission:	April 2015
Study/Trial Completion:	July 2016
Final Report Submission:	October 2016
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Although the missing controls are needed for the continued assurance and consistent quality of the drug product, the stability of the formulation is further directly controlled by the acceptance criteria which are already in place to control the content of API, pH, individual impurities and total impurities.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to assure consistency and reliability of the drug product quality. The results will establish the minimum level of (b) (4) in drug product formulation to sustain the (b) (4) function and to control this level throughout the shelf-life of the product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Éclat commits to establish shelf-life acceptance criteria for the content of sodium metabisulfite in the drug product, [redacted] (b) (4) (b) (4)

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial

☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 204300
Product Name: Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL

PMR/PMC Description: Submission of data and data-based release acceptance criteria for the content of sodium metabisulfite in drug product

PMR/PMC Schedule Milestones:

Final Protocol Submission:	August 2014
Study/Trial Completion:	February 2015
Final Report Submission:	March 2015
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

Although the missing controls are needed to assure consistent quality of the drug product, the stability of the formulation is further directly controlled by the acceptance criteria which are already in place to control the content of API, pH, individual impurities and total impurities.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the study is to assure consistency and reliability of the drug product quality. The results will establish the initial level of (b) (4) in drug product formulation to sustain the (b) (4) function throughout the shelf-life of the product.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Éclat commits to tighten the currently proposed tentative release acceptance criteria (b) (4) for the content of sodium metabisulfite in the drug product, (b) (4) by March 1, 2015. The (b) (4) submission will include supporting data and justification for the proposed limits.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA #	204300
Product Name:	Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL
PMR/PMC Description:	Submission of 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.

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	December 2016
	Other: Initial Report Submission:	April 2015
	Interim Report Submission:	December 2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The additional studies will require long term data of at least 12 months. Therefore, it is reasonable to conduct these studies post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Data provided in the NDA did not include data for storage of the drug product [redacted] (b) (4) [redacted]. The data also did not include the effect of the [redacted] (b) (4) on stability of the drug product. Because the data that was provided was sufficient to determine the quality of the drug product under conditions [redacted] (b) (4), additional long term studies need to be conducted to support the other storage orientation and addition of [redacted] (b) (4)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Éclat commits to establish shelf-life acceptance criteria for the content of sodium metabisulfite in the drug product. (b) (4) (b) (4) .

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
  The data provided in this study will supplement the stability data provided in the NDA submission, and provide for the continued assurance of the quality of the product over time.
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA	204300
Product Name:	Vazculep (phenylephrine hydrochloride) Injection, 10 mg/mL
PMR/PMC Description:	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. The first report 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	
	Study/Trial Completion:	
	Final Report Submission:	December 2016
	Other: Initial Report Submission:	April 2015
	Interim Report Submission:	December 2015

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   - ☐ Unmet need
   - ☐ Life-threatening condition
   - ☒ Long-term data needed
   - ☒ Only feasible to conduct post-approval
   - ☐ Prior clinical experience indicates safety
   - ☐ Small subpopulation affected
   - ☐ Theoretical concern
   - ☐ Other

   The additional studies will require long term data of at least 12 months. Therefore, it is reasonable to conduct these studies post-approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The Data provided in the NDA did not include data for storage of the drug product, [redacted] (b) (4) [redacted]. The data also did not include the effect of the [redacted] (b) (4) [redacted] on stability of the drug product. Because the data that was provided was sufficient to determine the quality of the drug product under conditions [redacted] (b) (4) [redacted] additional long term studies would need to be conducted, to support the other storage orientation and addition of [redacted] (b) (4) [redacted]

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
   If not a PMR, skip to 4.

   - **Which regulation?**

     ☐ Accelerated Approval (subpart H/E)
     ☐ Animal Efficacy Rule
     ☐ Pediatric Research Equity Act
     ☐ FDAAA required safety study/clinical trial

   - **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

     ☐ Assess a known serious risk related to the use of the drug?
     ☐ Assess signals of serious risk related to the use of the drug?
     ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

   - **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

     ☐ Analysis of spontaneous postmarketing adverse events?
     Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

     ☐ Analysis using pharmacovigilance system?
     Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

     ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
     Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

     ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

Continuation of Question 4

- ☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

  The data provided in this study will supplement the stability data provided in the NDA submission, and provide for the continued assurance of the quality of the product over time.

- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
- ☐ Immunogenicity as a marker of safety
- ☐ Other (provide explanation)

Agreed upon:

- ☒ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)
- ☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?

☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

---

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
06/25/2014

JUDITH A RACOOSIN
06/25/2014

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title[1]	**VAZCULEP (phenylephrine hydrochloride) Injection for intravenous use**
Applicant	Eclat Pharmaceuticals, LLC
Application/Supplement Number	NDA 204300
Type of Application	Original Submission
Indication(s)	FOR THE TREATMENT OF CLINICALLY IMPORTANT HYPOTENSION RESULTING PRIMARILY FROM VASODILATION IN THE SETTING OF ANESTHESIA
Office/Division	ODE II/DAAAP
Division Project Manager	Kimberly Compton
Date FDA Received Application	June 28, 2013
Goal Date	April 28, 2014
Date PI Received by SEALD	April 16, 2014
SEALD Review Date	April 17, 2014
SEALD Labeling Reviewer	Jeanne M. Delasko
Acting SEALD Division Director	Sandra Kweder

1 Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word "must" denotes that the item is a regulatory requirement, while the word "should" denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item **(deficiency)**.
- **YES:** The PI meets the requirement for this item **(not a deficiency)**.
- **N/A**: This item does not apply to the specific PI under review (**not applicable**).

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *Bottom margin < 1/2 inch.*

YES 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period:**
  - *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of-Cycle Period:**
  - Select "**YES"** in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *The horizontal line that separates the TOC from FPI is only a "half" line that goes across the left side (1-column) of the TOC. The horizontal line must be a complete line that goes across the entire bottom (2-columns) of the TOC.*

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *There is "extra" white space before Dosage Forms and Strengths heading. Delete the extra white space.*

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *For HL Dosage Forms and Strengths, numerical identifier "(3)" is missing for first bulleted item. For HL Contraindications, numerical identifier "(4)" is missing after the word "None." For each bulleted item in HL Warnings and Precautions (W&P), the reference (i.e., numerical identifier) should be to the subsection that contains the detailed information, and not to the entire W&P section "(5)". For the first bulleted W&P, "severe bradycardia and decreased cardiac output" references "(5.2)", but this statement is not mentioned under subsection 5.2 in the FPI. Ensure that the correct reference is used for the first bulleted W&P. For the second bulleted W&P, reference "(5.3)" for necrosis, not "(5.4)" bradycardia. For third bulleted W&P, reference "(5.8)", not "(5)." For fourth bulleted W&P, reference "(5.5)", not "(5)." For HL Drug Interactions, first bulleted item, reference "(7.1)", not "(7)"; for second bulleted item, reference "(7.2)", not "(7)".*

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Incorrect section heading is used in HL. "SPECIAL POPULATIONS" must be changed to "USE IN SPECIFIC POPULATIONS". See designated sections listed above.*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.
Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product)**

safely and effectively. See full prescribing information for (insert name of drug product)." The name of drug product should appear in UPPER CASE letters.

Comment: *In the HL Limitation Statement, only insert the name of drug product (i.e., VAZCULEP). Do not include "(phenylephrine hydrochloride) Injection" or "(phenylephrine hydrochloride) Injection, 10 mg/mL" in the HL Limitation Statement.*

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

Selected Requirements of Prescribing Information

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

NO 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Selected Requirements of Prescribing Information

Comment: *Must insert revision date (i.e., April 2014), which is the NDA approval date for this original submission, not "09/2013."*

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

NO 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *For subsection headings 7.1 and 7.2, the headings should be in title case. Subsection heading 7.1 should read "Interactions that Augment Pressor Effect",* (b) (4) *Subsection heading 7.2 should read "Interactions that Antagonize the Pressor Effect",* (b) (4) *Also correct these subsection headings in the FPI.*

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

NO 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment: *Do not bold this statement. See above.*

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

NO 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *There are no periods after the numbers for the section and subsection headings in the FPI. See above.* (b) (4) *. The same applies to the section and subsection headings in the TOC.*

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or "[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment: *This heading is 8 point font. Make this heading the same font size (i.e., 14 point) as the other FPI headings.*

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

    Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

    Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.
- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for:
- [text]
- [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
- [text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEANNE M DELASKO
04/17/2014

ERIC R BRODSKY
04/17/2014
I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, Acting SEALD Director.

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 16, 2014

To: Kim Compton
Senior Regulatory Project Manager
Division Anesthesia, Analgesia, and Addition Products (DAAAP)

From: Eunice Chung-Davies, Pharm.D.
Regulatory Review Officer
Office of Professional Drug Promotion (OPDP)

Subject: NDA 204300
OPDP labeling comments for Vazculep (phenylephrine hydrochloride) Injection for intravenous use

---

In response to DAAAP's August 27, 2013 consult request, OPDP has reviewed the draft Prescribing Information and carton and container labeling for Vazculep (phenylephrine hydrochloride) Injection for intravenous use (Vazculep).

The review of the Prescribing Information is based on the proposed SCPI obtained from Review Division's N:drive \\fdsfs01\ode2\DAAAP\NDA and (b) (4)\NDA 204300 (Phenylephrine Eclat)\Labeling\N 204-300 PI FROM FIRM to FDA 3-19-2014.doc on April 9, 2014 per instructions from the DAAAP RPM. Please see the comments on the marked up version attached below.

The review of the carton and container labeling is based on the carton and container labeling obtained from the EDR (submission dated 3/11/2014). We do not have any comments on the carton and container labeling at this time.

If you have any questions, please contact Eunice Chung-Davies at 301-796-4006 or eunice.chung-davies@fda.hhs.gov .

Enclosure:
Marked up Prescribing Information
Carton and container labeling

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EUNICE H CHUNG-DAVIES
04/16/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date	February 13, 2014
Reviewer	Aleksander Winiarski, PharmD Division of Medication Error Prevention and Analysis
Acting Team Leader	Julie Neshiewat, PharmD, BCPS Division of Medication Error Prevention and Analysis
Drug Name and Strength	Vazculep (Phenylephrine Hydrochloride) Injection, USP 10 mg per mL, 50 mg per 5 mL, 100 mg per 10 mL
Application Type/Number	NDA 204300
Applicant	éclat
OSE RCM	2013-1955

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Vazculep (Phenylephrine Hydrochloride) Injection, NDA 204300, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Phenylephrine Hydrochloride Injection has been available on the US market as an unapproved drug for many years.

On December 20, 2012, West Ward Pharmaceuticals received approval for Phenylephrine Hydrochloride Injection 10 mg/mL, NDA 203826, for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.

The proposed indications for NDA 204300 are slightly different from the approved indication for the West Ward Pharmaceuticals' Phenylephrine product (b) (4)

1.2 PRODUCT INFORMATION

The following product information is provided in the June 28, 2013 insert labeling submission.

- Active Ingredient: Phenylephrine Hydrochloride
- Indication of Use: Treatment (b) (4) of hypotension during anesthesia
- Route of Administration: Intravenous
- Dosage Form: Injection
- Strength: 10 mg per mL, 50 mg per 5 mL, 100 mg per 10 mL
- Dose and Frequency:
    - For treatment of hypotension during anesthesia: Initial intravenous bolus dose of 40 mcg to 100 mcg (not to exceed 200 mcg) with additional doses every 1 to 2 minutes as needed. Intravenous infusions should be started at a rate of 10 mcg/min to 35 mcg/min (not to exceed 200 mcg/min), titrating to effect.
    - (b) (4)
- How Supplied: 1 mL and 5 mL vials in packages of 10 and 10 mL vial packaged as a single unit
- Storage: Room Temperature

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA Adverse Event Reporting System (FAERS) database for Phenylephrine medication error reports. A gap analysis was performed comparing the current search results with the previous Phenylephrine AERS search in OSE review #2012-590, dated October 12, 2012. Any relevant cases identified in OSE review #2012-590 were included in our analysis. We also reviewed the Vazculep labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FAERS database using the strategy listed in Table 1.

Table 1: FAERS Search Strategy

Search Date Range	June 16, 2012 to October 3, 2013
Drug Names	Phenylephrine Hydrochloride (active ingredient)
MedDRA Search Strategy	Medication Errors - HLGT Product Packaging Issues - HLT Product Label Issues - HLT Product Quality Issues (NEC) - HLT

The FAERS database search identified 30 cases. Each case was reviewed for relevancy and duplication. Duplicates were merged into a single case. After individual review, all 30 cases were not included in the final analysis for the following reasons:

- Report related to non-injectable formulations of phenylephrine
- Potential name confusion – concern with the use of the abbreviation "neo" for neosynephrine (phenylephrine) as compared to neostigmine in the Intensive Care Unit setting.

2.2 PREVIOUS REVIEWS

Cases identified in OSE review #2012-590 that were related to overdose or to incorrect techniques in product preparation (compounding errors) were considered relevant. However, most of the errors were attributed to the preparer's knowledge deficits, performance deficits, system errors, or calculation errors and not relevant to the labels and labeling, except for one case that specifically mentioned that the reason for preparing an incorrect concentration was due to lack of clarity.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Vial Labels submitted February 8, 2013 (Appendix B)
- Carton Labeling submitted February 8, 2013 (Appendix C)
- Insert Labeling submitted June 28, 2013 (no image)
- West Ward Pharmaceuticals - Phenylephrine Hydrochloride Injection insert labeling, Dosage and Administration section (Appendix D)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our FAERS search and the risk assessment of Vazculep including the associated labels and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

We note that some of the cases identified in OSE review #2012-590 that were related to overdose or to incorrect techniques in product preparation (compounding errors) may be relevant to the proposed dosage and administration section. One case specifically mentioned that the reason for preparing an incorrect concentration was due to lack of clarity. Therefore, DMEPA concludes that simplifying and clarifying the Dosage and Administration section of the proposed insert labeling, similar to the currently approved injectable Phenylephrine, may be appropriate to minimize these errors (see section 5.1 and Appendix D).

DMEPA provides additional comments to the Applicant to improve readability and increase prominence of important prescribing information on the vial labels and carton labeling (see section 5.2).

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to provide clarity, improve readability, and increase prominence of important prescribing information to promote the safe use of the product.

5 RECOMMENDATIONS

5.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of the supplemental NDA:

A. Full Prescribing Information Dosage and Administration Section

1. The proposed Dosage and Administration section is confusing and requires general reorganization. Consider revising section 2 into subsections that provide general administration instructions, preparation instructions for both bolus and continuous intravenous infusions, and provide dosing for each of the proposed indications, similar to West Ward Pharmaceuticals insert labeling (see Appendix D).
2. The proposed product preparation instructions require multiple dilution steps to achieve the desired doses. We propose eliminating the intermediate step in

the preparation instructions and suggest revising the preparation instructions similar to West Ward Pharmaceuticals insert labeling (see Appendix D, Subsections 2.2 and 2.3).

3. The section uses (b) (4) and (b) (4) symbols, which are listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations[2]. (b) (4) with the abbreviation 'mcg' and the words "greater than" to help prevent misinterpretation of the symbols. Additionally, (b) (4) with the word "to" for clarity.

B. Highlights of Prescribing Information, Dosage and Administration Section

1. See A1 and A3 above.

C. Full Prescribing Information, How Supplied/Storage and Handling Section

1. Consider revising the description of the vial sizes to include the words "single dose vials" for the 1 mL vial, and pharmacy bulk package for the 5 mL and 10 mL vials, similar to the corresponding section in the Highlights of Prescribing Information.

D. General Comment Regarding 1% as a Strength Presentation

1. The Phenylephrine Hydrochloride USP monograph does not require the use of the 1% strength on labels and labeling. To reduce the chance of strength confusion and for consistency with the West Ward Pharmaceuticals insert labeling (b) (4) and replacing it with the standard strength of 10 mg/mL.

5.2 Comments To The Applicant

DMEPA recommends the following revisions prior to the approval of the NDA:

A. Vial Labels

1. The 1 mL vial label uses the abbreviation (b) (4) which is listed on Institute for Safe Medication Practices' (ISMP) list of error-prone abbreviations[3]. (b) (4) with the word "intravenous" for clarity.
2. The 1 mL vial is meant as a single dose configuration; (b) (4) to two statements "For Intravenous Use" and "Single Dose Vial".
3. The éclat logo is the most prominent statement on the 5 mL and 10 mL vial labels. To help ensure that the proprietary name, established name, and strength statements are the most prominent information on the label, (b) (4) as the required manufacturing information is listed on the bottom portion of the Principal Display Panel (PDP).

[2] Available at: www.ismp.org/tools/errorproneabbreviations.pdf . Accessed January 30, 2014.

[3] Available at: www.ismp.org/tools/errorproneabbreviations.pdf . Accessed January 30, 2014.

4. To improve readability, [redacted] (b) (4) to title case "Vazculep".
5. The net quantity statements (1 mL, 5 mL, and 10 mL) appear in close proximity to the strength statements, which create clutter and may be confusing. Relocate the net quantity statements away from the strength statements, such as to the bottom portion of the PDP.
6. The Rx only statement appears in close proximity to the strength statements, which creates clutter. Minimize the size of the Rx only statement and relocate it away from the strength statements, such as to the top right portion of the PDP.
7. To ensure that the proprietary name, established name, and strength statements are the most prominent on the label, decrease the size of the manufacturing information. Additionally, to decrease clutter, [redacted] (b) (4), since the information appears on the carton labeling.
8. As per 21CFR 201.17 and 21CFR 201.18, please indicate where the required lot number and expiration date will appear on the labels.
9. The Phenylephrine Hydrochloride USP monograph[4] does not require the use of the 1% strength on labels and labeling. Additionally, to minimize the chance of a wrong strength error, the total drug content should be provided on all injectable dosage forms where the volume is greater than 1 mL and should appear more prominent than the strength per milliliter. Therefore, revise the presentations of the strength statements to appear as:

Vazculep

(Phenylephrine HCl Injection, USP)

10 mg/mL

Vazculep

(Phenylephrine HCl Injection, USP)

50 mg/5 mL

(10 mg/mL)

Vazculep

(Phenylephrine HCl Injection, USP)

100 mg/10 mL

(10 mg/mL)

[4] USPNF Phenylephrine Hydrochloride Monograph. Accessed January 30, 2014.

10. For the pharmacy bulk 5 mL and 10 mL fill vials, as per FDA Guidance for Industry titled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors,* (b) (4) to a boxed statement to read "Pharmacy Bulk Package – Not for Direct Infusion". Locate the revised boxed statement directly below the strengths.
11. To help ensure appropriate use of the product, add the statement "must be diluted" under the strength statement on the 1 mL fill vial and under the boxed statement "pharmacy bulk package" for the 5 mL and 10 mL fill vials.
12. The help ensure correct storage add the statement "Protect from light" to the bottom potion of the PDP above the manufacturing information.

B. Carton Labeling

1. See A2, A4, A5, A8, A9, A10, and A11 above.
2. To help ensure proper storage of the drug, relocate the statements "Protect from light" and "Store in carton until time of use" from the side panel to the bottom of the PDP, above the manufacturing information.
3. To reduce clutter, the manufacturing information may be relocated to the side panel.

If you have further questions or need clarifications, please contact Lisa Skarupa, OSE Project Manager, at 301-796-2219.

APPENDICES

Appendix A. Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALEKSANDER P WINIARSKI
02/13/2014

JULIE V NESHIEWAT
02/13/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date:	February 6, 2014
From:	Amy M. Taylor, MD, MHS Medical Officer Pediatric and Maternal Health Staff
Through:	Lynne P. Yao, MD OND Associate Director Pediatric and Maternal Health Staff
NDA Number:	204-300
Sponsor:	Éclat Pharmaceuticals, Inc.
Drug:	Phenylephrine HCl Injection, USP 1%
Dosage form and route of administration:	injection, intravenous
Proposed Indications:	For the treatment (b) (4) of hypotension during anesthesia
Consult request:	The Division of Anesthesia, Analgesia, and Addition Products (DAAAP) requests input from PMHS to appropriately label this product.

Background

The sponsor has developed phenylephrine HCl injection for the treatment (b) (4) of hypotension in adults and submitted an NDA for approval. The PDUFA goal date is April 28, 2014.

For decades, phenylephrine HCl injection for intravenous use products were marketed, but unapproved. Phenylephrine HCl Injection developed by West Ward Pharmaceutical Corporation was approved on December 20, 2012. This NDA (203-826) was reviewed by the Division of Cardiology and Renal Products and then transferred to DAAAP after approval.

Proposed pediatric labeling from the sponsor

1 INDICATIONS AND USAGE

PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, 1% is an alpha-1 adrenergic receptor agonist intended for the treatment (b) (4) of hypotension during anesthesia.

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

(b) (4)

Reviewer comment: (b) (4) *the following statement should be included: "Safety and effectiveness in pediatric patients have not been established."* (b) (4)

Sponsor's request for a pediatric waiver

The sponsor is requesting a waiver of required pediatric studies under the Pediatric Research Equity Act (PREA) for pediatric patients ages 0 to (b) (4) years. The sponsor states that for pediatric patients aged 0 to less than 12 years, the studies are impossible or highly impracticable because patients aged 0 to less than 12 years tend not to develop clinically significant hypotension as a result of anesthetic- induced vasodilatation. In addition, the sponsor states that the administration of an alpha-1-receptor agonist would cause reflex bradycardia and that more likely interventions, especially in children under 6 years, would be fluid administration, decreasing anesthetic concentration, or administration of a drug with beta-agonist effects.

(b) (4)

Reviewer comment: The West Ward phenylephrine IV product (NDA 203-826) was granted a waiver under PREA for ages 0 to < 12 years. The approval letter stated:

We are waiving the pediatric study requirement for ages 0 to <12 years because necessary studies are impossible or highly impracticable. This is because:

1. *While pediatric patients aged 0 to <12 years receive neuraxial anesthesia, they tend not to develop clinically significant hypotension as a result of anesthetic-induced vasodilatation.*

2. *In addition, the cardiac output of younger pediatric patients is heart rate-dependent, and administration of an alpha-1-receptor agonist would cause a reflex bradycardia, potentially decreasing the pediatric patient's cardiac output and oxygen delivery. More likely interventions, especially in children under 6 years, would be fluid administration, decreasing anesthetic concentration, or administration of a drug with beta-agonist effects, thereby increasing heart rate.*

[redacted] (b) (4)

[redacted]

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1991-1 Conduct a trial in the ≥12 -16 year old age group to evaluate the dose effect of phenylephrine hydrochloride injection on blood pressure in patients undergoing general anesthesia and neuroaxial anesthesia. Administration by both the bolus and infusion methods must be studied for the treatment of hypotension. Dosing of phenylephrine should be weight-based since weight may be quite variable in this population. The study should include 50 subjects in the bolus treatment group and 50 subjects in the infusion treatment group. The study should capture, at a minimum, the following information:

- *Demographic and medical history information that informs about the subjects' cardiovascular status.*
- *Concomitant intraoperative and post-operative medications, including their doses and adjustments in inhaled gas concentration or intravenous agent infusion rates.*
- *Interventions used to treat the hypotension, e.g., other pressor agents, intravenous fluid boluses, changes in patient positioning.*
- *Intraoperative events relevant to subjects' physiological status, such as blood loss and fluids administered.*

- *Blood pressures and heart rate, time to onset and maximal response and duration of response should be defined and captured before and during the treatment.*
- *Pharmacokinetics of the proposed product need to be characterized at points relative to the phenylephrine administration.*

In your protocol, propose a means of reporting safety data in the ≥12 -16 year old age group that best informs the prescriber about the risk:benefit of different dose levels of phenylephrine.

The timetable you submitted on November 29, 2012 states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 20, 2013
Trial Completion: December 20, 2016
Final Report Submission: May 23, 2017

Reviewer comment: The sponsor's request for a waiver for patients less than 12 years is reasonable. (b) (4) [redacted]

Recommendations

- The labeling language proposed by the sponsor for Subsection 8.4 Pediatric Use should be removed and replaced by the following statement: "Safety and effectiveness in pediatric patients have not been established."

- The sponsor should be required to study pediatric patients 12 to 16 years.

- Studies under PREA for patients less than 12 years should be waived.

All waivers and deferrals under PREA must be reviewed by PeRC. PMHS reminds the review division that PMHS and the PeRC are separate and distinct teams and that PMHS cannot make recommendations on behalf of the PeRC. However, the PeRC often provides recommendations that are consistent with advice provided by PMHS.

Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY M TAYLOR
02/06/2014

LYNNE P YAO
02/10/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: February 6, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Anesthesia, Analgesia, and Addiction Products

Drug: Phenylephrine Hydrochloride Injection, USP, 1%

NDA: 204300

Applicant: Eclat Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Materials Reviewed: Proposed Phenylephrine HCL, USP, (b) (4) labeling, literature provided by sponsor, Lactmed

Consult Question:
"Human/clinical data from the published literature is submitted to inform section 8 Use in Specific Populations. DAAAP needs input from PMHS for appropriately labeling the product, including risk summary for specific populations (maternal, pregnancy category, etc)."

INTRODUCTION

On February 8, 2013, Éclat Pharmaceuticals submitted a 505(b)(2) New Drug Application (NDA 204300) for Phenylephrine Hydrochloride Injection, USP, 1%, for treatment (b) (4) of hypotension during anesthesia. The applicant is relying on published literature for evidence of safety and effectiveness. Phenylephrine Hydrochloride Injection was previously marketed as an unapproved FDA drug product by several manufacturers. On December 20, 2012, West-Ward Pharmaceutical Corp received FDA approval for Phenylephrine Hydrochloride Injection, 10 mg/mL, NDA 203826, for the indication of increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia. NDA 203826 relied on published literature for evidence of safety and effectiveness. NDA 203826 is now listed as the Referenced Listed Phenylephrine Hydrochloride Injection Drug in the Orange Book; however, Eclat Pharmaceuticals chose not to rely on FDA's findings of safety and effectiveness for NDA 203826 for their Phenylephrine Hydrochloride Injection product.

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Pediatric and Maternal Health Staff (PMHS) on October 7, 2013, to review submitted pregnancy data and to provide input on the appropriate pregnancy category classification and to provide appropriate language revisions for the Pregnancy and Nursing Mothers subsections of labeling for Phenylephrine Hydrochloride Injection, USP, 1%. This memorandum contains PMHS-MHT's Phenylephrine HCl injection, USP 1% pregnancy and nursing mothers labeling recommendations. See Appendix A for applicant's proposed pregnancy and nursing mothers labeling and Appendix B for Approved Pregnancy and Nursing Mothers Labeling for West-Ward Pharmaceutical Corp's Phenylephrine Hydrochloride Injection product (NDA 203826).

BACKGROUND

Phenylephrine is a synthetic sympathomimetic amine and a strong post-synaptic α_1-agonist that causes prominent vasoconstriction, resulting in an increase in blood pressure. [1,2,3] Its major action is on the cardiovascular system, with stimulation of vascular α_1 receptors but little action on the heart itself.[4] Phenylephrine also has been shown to significantly raise blood pressure when administered either as a bolus IV injection or by continuous infusion following either spinal/neuraxial or general anesthesia-induced hypotension.

REVIEW OF DATA

The following is a summary of published data on phenylephrine hydrochloride use during pregnancy and lactation. Some of the published literature was submitted by the applicant for review; however, PMHS-MHT also conducted a literature review of the existing reproductive risk and lactation databases for current evidence-based pregnancy and lactation information. MicroMedex Reproductive Risk Information was used to search for available pregnancy use

[1] Thiele RH et al. The physiologic implications of isolated alpha 1 adrenergic stimulation. *Anesthesia Analog*. 2011a 113 (2): 284-296.
[2] Thiele RH et al. The physiologic implications of isolated alpha 1 adrenergic stimulation. *Anesthesia Analog*. 2011ab113 (2): 297-304.
[3] Hardman JG. *Goodman & Gilman's the pharmacological basis of therapeutics. 10th ed*. New York, NY; McGraw-Hill, 1994.
[4] Meyer SM, Fraunfelder FT. Phenylephrine hydrochloride. *Ophthalmology*. 1980. 87:1177-1180.

data and the Drugs and Lactation Database (LactMed)[5] was searched for available lactation data. LactMed is a National Library of Medicine (NLM) searchable database with information on drugs and lactation. LactMed provides information, when available, on maternal levels of drug in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, alternative drugs that can be considered, and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Relevant pregnancy and lactation data from available published studies will be recommended for inclusion in the phenylephrine hydrochloride Pregnancy and Nursing Mothers subsections of labeling.

1. Published data regarding Phenylephrine Hydrochloride during pregnancy:
Prophylactic use of phenylephrine infusions has been documented extensively in the setting of neuraxial anesthesia, in particular, for pressure control during Cesarean section. In a study done by das Neves, et al., which was included in the NDA submission, 120 women undergoing elective cesarean section under spinal block, were randomly divided into three groups. Group 1 received continuous infusion of phenylephrine after the spinal block using an infusion pump (0.15 μg/kg/min). Group 2 received a single dose of phenylephrine (50μg) after the spinal block. Group 3 received a single dose of phenylephrine (50μg) only if hypotension (drop in systolic blood pressure and/or diastolic blood pressure of 20% of baseline level for that patient) occurred. The incidence of hypotension was evaluated. The incidence of hypotension was higher in group 3 with 85% of women affected. In groups 1 and 2 hypotension was seen in 17.5% and 32.5% of the cases respectively.[6]

Hypotension during spinal anesthesia for cesarean section is a common event and seen in up to 69% of patients if prophylaxis is not used. This is due to blocking sympathetic efferent nerves resulting in decreased systemic vascular resistance and a decrease in systemic blood pressure. If short-lived, hypotension is not associated with adverse fetal effects. If spinal induced hypotension is not managed, it leads to placental hypoperfusion, which can result in fetal hypoxia, acidosis and neurologic injury.[7] In another study submitted by the sponsor, Alahuhta, et al., looked at the effects of IV vasopressors on Doppler velocimetry of the maternal uterine and placental arcuate arteries and fetal umbilical, renal and middle cerebral arteries during spinal anesthesia in 19 healthy patients undergoing elective cesarean section. The patients were randomized into 2 groups and either given ephedrine or phenylephrine as a prophylactic infusion. The treatments were diluted with normal saline so that 1 ml of the solution contained 5 mg of ephedrine or 100 μg of phenylephrine, respectively. Both vasopressors restored maternal arterial pressure effectively. The ephedrine group showed no significant differences in any of the Doppler velocimetry recordings relative to baseline values. However, the phenylephrine group showed increase blood flow velocity waveform indices in the uterine and placental arcuate arteries and decreased vascular resistance in the fetal renal arteries. Phenylephrine is a more potent arterial vasoconstrictor than ephedrine,

[5] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT
[6] Das Neves JFNP et al. Phenylephrine for blood pressure control in elective Cesarean section: therapeutic versus prophylactic doses. *Rev Bras Anestesiol*. 2010. 60 (4): 391-398.
[7] Cooper, D. et al. Prospective evaluation of systolic arterial pressure control with a phenylephrine infusion regimen during spinal anaesthesia for caesarean section. *International Journal of Obstetric Anesthesia*. 2012. 21: 245–252.

which explains the difference in effects on uteroplacental vascular resistance. The healthy fetuses tolerated these changes to uteroplacental circulation well and Apgar scores and acid-base values in the umbilical cord were normal. [8]

There is limited information regarding the reproductive toxicology of phenylephrine. The sponsor submitted a publication by Shabanah, et al., in New Zealand rabbits during the second half of pregnancy. This study has shown a small number of phenylephrine-related premature births and decreases in fetal weight. Since phenylephrine is a known vasoconstrictor and not a teratogenic agent, the above effects were attributed to vasoconstriction of blood vessels in the placenta.[9] In an animal study conducted by Cottle, et al., an adverse effect of phenylephrine on blood flow in pregnant ewes was identified. Pregnant ewes (gestational age 118 to 144 days) were infused with phenylephrine (4 μg/kg/min for 30 minutes) and uterine and fetal blood pressure and blood gases, maternal and fetal heart rate, and uterine blood flow were monitored. Phenylephrine depressed uterine blood flow and maternal heart rate by 40% and increased maternal mean arterial blood pressure by 50%. In the fetus, phenylephrine depressed arterial blood PaO2 by 30%, decreased blood pH and increased PaCO but had little effect on fetal blood pressure or heart rate.[10]

Reviewer Comments
Limited data from animal studies provides support for concerns of premature births and decreased fetal weight due to vasoconstriction of blood vessels in the placenta. However, the rapid onset and short duration of effects from intravenous phenylephrine, which will be used during surgery, have allowed this agent to be titrated to effect in individual patients.[11]

2. Published data regarding Phenylephrine Hydrochloride during lactation:
Animal data indicates that phenylephrine may decrease milk production. Oral administration of pseudoephedrine, another vasoconstrictor, decreases milk production in nursing mothers after oral use. This effect was not attributable to changes in blood flow, but depression of prolactin secretion may be a contributing factor. At the maximum recommended pseudoephedrine doses, the calculated infant dose delivered via milk is estimated to be <10% of the maternal dose, and is unlikely to affect a breastfed infant adversely. [12] The bioavailability of phenylephrine when dosed orally is approximately 40%; therefore, if the drug is present in milk, substantial amounts are unlikely to be absorbed by a breastfed infant.[13]

---

[8] Alahuhta, S et al. Ephedrine and phenylephrine for avoiding maternal hypotension due to spinal anaesthesia for caesarean section: Effects on uteroplacental and fetal haemodynamics. *International Journal of Obstetric Anesthesia*. 1992. 1: 129-134.
[9] Shabanah et al. Effect of Epinephrine on fetal growth and the length of gestation. *Surg Gynecol Obstet*. 1969. 129: 341-343.
[10] Cottle et al. Effects of phenylephrine and sodium salicylate on maternal and fetal cardiovascular indices and blood oxygenation in sheep. *American Journal of Obstet.Gynecology*. 1982. 170-176.
[11] Phenylephrine Hydrochloride Injection, USP, 1%, 2.5 Clinical Overview. Eclat Pharmaceuticals NDA 204300: page 18
[12] Aljazaf, K et al. Pseudoephedrine effects on milk production in women and estimation of infant exposure via breastmilk. British Journal of Clinical Pharmacology. 2003. 56 (1): 18-24.
[13] Lactmed: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~2SmclM:1)

DISCUSSION

PREGNANCY AND NURSING MOTHERS LABELING

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential when needed.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

Pregnancy

There are no available animal reproduction data or human pregnancy data for intravenous phenylephrine hydrochloride, with the exception of published studies with use of the drug with anesthesia during cesarean delivery. Due to the lack of developmental data with use during pregnancy, a pregnancy category C[14] is the appropriate pregnancy category classification for intravenous phenylephrine hydrochloride (see 21 CFR 201.57 (c)(9)(i)(A)(3)). In addition, this lack of developmental data must be placed in 8.1 Pregnancy (placement should be under the heading *Risk Summary*). The purpose of the risk summary heading in subsection 8.1 under the proposed PLLR is to provide statements that describe for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug's pharmacology. Information from published studies regarding use of intravenous phenylephrine hydrochloride with anesthesia during cesarean delivery should be placed in 8.1 Pregnancy, *Clinical Considerations*, Labor or Delivery.

[14] Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well controlled studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans."

Lactation
No lactation data are available for intravenous phenylephrine hydrochloride; however, lactation data are available for pseudoephedrine, another vasoconstrictor. Pseudoephedrine is present in human milk in small amounts and clinical lactation studies have demonstrated that a single dose of pseudoephedrine decreases milk production acutely, and that repeat dosing may interfere with lactation.[15] Effects observed in breast fed infants include occasional irritability. Intravenous phenylephrine hydrochloride is intended as single-use; therefore, any impact on lactation should occur acutely and be short lived as the drug's plasma terminal half-life has been reported as 2.62 ± 0.67 hours.[16]

CONCLUSIONS
A pregnancy category C is the appropriate classification for phenylephrine hydrochloride injection, USP, 1% labeling due to the lack of developmental data from studies in pregnant women and/or animal reproduction studies. The pregnancy subsection of phenylephrine hydrochloride injection, USP, 1% labeling was structured in the spirit of the proposed PLLR, while complying with current labeling regulations. The nursing mothers subsection of phenylephrine hydrochloride injection, USP, 1%, labeling was revised to comply with current labeling recommendations, as well as incorporating the breast feeding benefit/risk statement from the proposed PLLR.

PMHS-MHT PHENYLEPHRINE HYDROCHLORIDE INJECTION, USP, 1% LABELING
Based on information from the labeling for the reference drug, phenylephrine hydrochloride injection, USP, 1% PMHS-MHT recommends the following revision to the Pregnancy and Nursing Mothers sections of phenylephrine hydrochloride injection, USP, 1% Labeling. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category C

Risk Summary
There are no adequate or well-controlled studies with PHENYLEPHRINE HYDROCHLORIDE INJECTION, (b) (4) in pregnant women (b) (4) animal reproduction studies (b) (4) been conducted (b) (4), it is not known whether (b) (4) can cause fetal harm when administered to a pregnant woman. (b) (4) should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus.

[15] LactMed: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~5XdmAT:1
[16] See draft labeling submitted February 8, 2013

Clinical Considerations

Labor or Delivery

The most common maternal adverse reactions reported in published studies of phenylephrine use during neuraxial anesthesia during cesarean delivery include nausea and vomiting, (b) (4) bradycardia, reactive hypertension, and transient arrhythmias. Phenylephrine does not appear to (b) (4) alter either neonate Apgar scores or blood-gas status.

Reviewer Comment: This information was moved here (b) (4) .

8.3 Nursing Mothers

It is not known whether phenylephrine is present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition. Exercise caution when (b) (4) is administered to a nursing woman.

Reviewer Comment: The statement "The developmental and health benefits of (b) (4) *should be considered along with the mother's clinical need for* (b) (4) *and any potential adverse effects on the* (b) (4)

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

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIRIAM C DINATALE
02/06/2014

JEANINE A BEST
02/06/2014

LYNNE P YAO
02/10/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	February 5, 2014
Reviewers:	Tara L. Argual, PharmD, Safety Evaluator Division of Pharmacovigilance II
	Jane Gilbert, MD, Medical Officer Division of Pharmacovigilance II
Team Leader:	Sara Camilli, PharmD, BCPS, Safety Evaluator Team Leader Division of Pharmacovigilance II
	Allen Brinker, MD, Medical Officer Team Leader Division of Pharmacovigilance II
Division Director:	Scott Proestel, MD, Division Director Division of Pharmacovigilance II
Product Name:	Phenylephrine HCl 1% Injection
Subject:	All Adverse Events
Application Type/Number:	505(b)(2)NDA/ 204300
Applicant/Sponsor:	Eclat Pharmaceuticals
OSE RCM #:	2013-2826

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) received a literature-based 505(b)(2) NDA from Eclat Pharmaceuticals for phenylephrine hydrochloride 1% injection that proposes to expand the current indication of hypotension treatment [redacted] (b) (4) during anesthesia. DAAAP consulted the Division of Pharmacovigilance (DPV) to review FDA's Adverse Event Reporting System (FAERS) for adverse events that may inform the labeling. This document is an overview of postmarket adverse events and the published medical literature intended to identify new safety signals that can be used to inform the labeling for this product.

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.

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.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) received a literature-based 505(b)(2) NDA from Eclat Pharmaceuticals for phenylephrine hydrochloride 1% injection that proposes to expand the indication to the treatment (b) (4) of hypotension during anesthesia. No new clinical safety or efficacy studies were conducted for this application.

DAAAP consulted the Division of Pharmacovigilance (DPV) to review FDA's Adverse Event Reporting System (FAERS) for adverse events that may inform the draft labeling. In addition, DAAAP requested:

- a breakdown of cases by
  - age (< 18; 18 up to 65; > 65)
  - race
  - gender
- information on location of use (e.g. operating room, ICU, other).

In December 2011, a 505 (b)(2) NDA for phenylephrine HCl 1% injection was submitted by another Sponsor, West-ward Pharmaceuticals, with an indication for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia. In June 2012, the Division of Cardiorenal Products (DCRP) asked DPV to provide FAERS data for phenylephrine HCl for the sole purpose of labeling.[1] No safety signals were identified at that time.

In response to DAAAP's request, and similar to the 2012 data provision, this review is an overview of FAERS and the literature intended to identify new safety signals that can be used to inform the labeling for this product.

1.1 REGULATORY HISTORY

Phenylephrine hydrochloride, USP, 1% injection is an alpha-1 adrenergic receptor agonist, which was marketed as an unapproved product until December 2012. West-ward Pharmaceuticals received FDA approval for phenylephrine injection in December 2012 for the indication of treatment of hypotension. (b) (4)

1.2 PRODUCT LABELING

The sponsor's proposed label is in Appendix 8.1.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 2.1.

Table 2.1. FAERS Search Strategy*	
Date of search	12/30/2013
Time period of search	01/01/1969 - 12/30/2013
Product Terms	phenylephrine; phenylephrine HCl
Route of Administration	IV; INTH; IM; IVBOL; IVDRP
Text string search	searched narrative for “IV”, “intravenous”, or “inject”

* See Appendix 8.2 for description of the FAERS database.

2.2 LITERATURE SEARCH

The medical literature was searched with the strategy described in Table 2.2.

Table 2.2. Literature Search Strategy	
Date of search	01/06/2014
Database	PubMed
Search Terms	phenylephrine, adverse, hypotension
Years included in search	01/01/1991-01/06/2014
limits	Type: Review; Language: English; Subjects: Human

3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 137 reports. These are total counts of FAERS reports and may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse, etc.), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes submitted to FDA.

Appendix 8.3 lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 137 cases in this case series.

Table 3.1 summarizes the demographic characteristics of FAERS reports for phenylephrine HCl1% injection received by FDA from 01/01/1969 to 12/30/2013.

Table 3.1. Demographic Characteristics of FAERS Reports for Phenylephrine HCl 1% Injection Received by FDA from January 1, 1969 to December 30, 2013. (N=137)*		
Sex	Male	56
	Female	59
	Null/Unknown	22

Table 3.1. Demographic Characteristics of FAERS Reports for Phenylephrine HCl 1% Injection Received by FDA from January 1, 1969 to December 30, 2013. (N=137)*		
Age	<18	4
	18-65	52
	>65	37
	Null	44
Country[†]	US	104
	Foreign	33
	Australia	1
	Canada	4
	China	1
	France	9
	Japan	11
	South Africa	1
	United Kingdom	6
Serious Outcomes (n= 117)[§]	Death	13
	Life-threatening	23
	Hospitalized	34
	Disability	11
	Other serious	75
Reported Indication for Use[±]	Hypotension	42
	Anaesthesia	24
	Reversible Ischaemic Neurological	14
	Deficit	8
	Hypertension[**]	6
	General Anaesthesia	5
	Analgesic Therapy	5
	Blood Pressure Management	5
	Induction of Anaesthesia	7
	Unknown	57
Location of Use	Operating room	65
	Intensive Care Unit	11
	Unknown	61
Report type	Expedited	108
	Direct	25
	Periodic	4

Table 3.1. Demographic Characteristics of FAERS Reports for Phenylephrine HCl 1% Injection Received by FDA from January 1, 1969 to December 30, 2013. (N=137)*		
FDA Received Year	1977-1995	15
	1996-2005	15
	2006-2010	70
	2011	17
	2012	9
	2013	11

* Report counts may include duplicate reports, miscoded reports, or unrelated reports.
† Race is rarely reported in FAERS.
§ One case may report more than one outcome
± One case may report more than one indication for use
** 3 unique cases were reported in FAERS. All cases were reported in the literature. 1) a 71-year-old woman who had critical cerebral ischemia secondary to a carotid artery occlusion received high-dose IV phenylephrine for a trial of hypertensive therapy. No other details were provided; 2) a literature report of hemorrhagic conversion and 35% elevation of mean arterial pressure (MAP) coincident with induced hypertension therapy using phenylephrine, no additional details provided; 3) hypertension was not the indication for treatment with phenylephrine (case 7095905- see case summary in Appendix 8.4).

Table 3.2 lists FAERS crude counts of Preferred Terms (PT) reported for phenylephrine HCl 1% injection. Preferred terms with N $\geq$ 4 are sorted by decreasing number. Preferred terms with N $\leq$ 3 were also evaluated; we did not identify any new safety signals among the remaining preferred terms.

Table 3.2. FAERS Crude Counts of Preferred Terms (N$\geq$4) for Phenylephrine HCl 1% Injection as of December 30, 2013. Total Number of reports, N=137; Reports since June 21, 2012, N=16

Preferred Term	Count of PT (N) Total	Count of PT (N) since 6/21/2012	Appears in the Draft Label*^
Maternal Exposure During Pregnancy	21	1	Yes. SP
Bradycardia	19	1	Yes. W/P, AR, OD
Hypertension	16	1	Yes. AR, OD
Hypotension	16	4	IR
Blood Pressure Decreased	9	3	IR
Lung Infiltration	9	0	No
Aphasia	7	0	No
Cardiac Arrest	7	0	No
Drug Ineffective	7	2	U
Encephalopathy	7	0	No
Medication Error	7	0	No
Delirium	6	0	No
Electrocardiogram T Wave Inversion	6	0	No
Metabolic Acidosis	6	0	No
Tachycardia	6	0	Yes. OD
Unresponsive To Stimuli	6	0	No

Table 3.2. FAERS Crude Counts of Preferred Terms (N≥4) for Phenylephrine HCl 1% Injection as of December 30, 2013. Total Number of reports, N=137; Reports since June 21, 2012, N=16			
Preferred Term	**Count of PT (N) Total**	**Count of PT (N) since 6/21/2012**	**Appears in the Draft Label*^**
Ventricular Tachycardia	6	0	Yes. OD
Cardio-Respiratory Arrest	5	0	No
Pulmonary Oedema	5	0	No
Stress Cardiomyopathy	5	0	No
Syncope	5	0	No
Anxiety	4	0	No
Arteriospasm Coronary	4	0	No
Blood Creatine Phosphokinase Increased	4	0	No
Blood Creatine Phosphokinase Mb Increased	4	0	No
Caesarean Section	4	2	PR
Chest Discomfort	4	0	No
Confusional State	4	0	No
Drug Interaction	4	3	Yes. W/P, DI
Headache	4	1	Yes. AR, OD
Mental Status Changes	4	0	No
Oxygen Saturation Decreased	4	2	No
Post Procedural Complication	4	0	PR

* Phenylephrine Hydrochloride Injection, USP, 1% 10 mg/mL, 1 mL single use vial, 5ml pharmacy bulk package vial, and 10ml pharmacy bulk package vial. Draft Package Insert – Content of Labeling. Annotated Draft Phenylephrine Hydrochloride Injection, USP Package Insert in PLR format. Eclat Pharmaceuticals, Chesterfield, MO 63005 USA. Revised September 2013.

^ Definitions: W/P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, OD = Overdosage, SP = Use in Specific Populations: Other Categories: IR = Indication-related, PR = Procedure-related, U = Uninformative

Adverse Event reports since June 21, 2012

There have been 16 reports of adverse events associated with phenylephrine HCl 1% injection reported since the June 21, 2012, DPV Data Provision. The most commonly reported adverse events were hypotension (4), blood pressure decreased (3), drug interaction (3), caesarean section (2), drug ineffective (2), dyspnoea (2), exposure during pregnancy (2), oxygen saturation decreased (2), and therapeutic response decreased (2).

Cases Coded with an Outcome of *Death*

There were 12 unique FAERS cases coded with an outcome of death. Analysis of these reports did not find any reports of death that could be attributed to IV phenylephrine use. Confounding factors including concomitant medications, comorbid medical conditions, or the lack of sufficient clinical information precludes such association. See Appendix 8.4 for individual case summaries.

Cases Age <18

Four cases were reported in patients under the age of 18. Two cases reported medication errors. Case 4671692 reported a 15 year old female appendectomy patient who received phenylephrine instead of the prescribed neostigmine. She was treated and recovered without sequelae. Case 5351081 reported a 9 year old female undergoing an operation for sinus irrigation who **may** have been irrigated with topical vasoconstrictor solution (combination of lidocaine and phenylephrine) and not saline, contributing to a hypertensive crisis, multiple system organ failure, and death.

The remaining reports were of an 11 year old osteosarcoma patient with Enterobacter sepsis who developed QT prolongation and Torsades de Pointes (Case 5568349) and a 12 year old female with familial polyposis undergoing a polypectomy who developed an acute liver disorder (Case 9121591). Case summaries are provided in Appendix 8.4.

Unlabeled Adverse Events

The most common unlabeled AEs reported with phenylephrine HCl 1% injection were *Lung Infiltration* (9), *Aphasia* (7), *Cardiac Arrest* (7), *Drug Ineffective* (7), *Encephalopathy* (7), *Medication Error* (7), *Delirium* (6), *Electrocardiogram T Wave Inversion* (6), *Metabolic Acidosis*(6), *Unresponsive To Stimuli* (6), *Cardio-Respiratory Arrest* (5), *Pulmonary Oedema* (5), *and Stress Cardiomyopathy* (5). Case reports of these adverse events are summarized in Appendix 8.4.

Confounding factors in FAERS cases including concomitant medications, medical history (surgical or procedural complications occurring before phenylephrine administration), comorbid conditions, and/or the lack of sufficient clinical information preclude the association of phenylephrine HCl 1% injection with the aforementioned adverse events.

Designated Medical Events (DME)

Designated Medical Events (DMEs) are events that are inherently serious, severe, and often product-related. The Office of Surveillance and Epidemiology (OSE) created the DME list for working purposes; it has no regulatory significance. DMEs with N < 4 reported with phenylephrine HCL 1% injection include: *Acute Myocardial Infarction (1); Anaphylactic/Anaphylactoid Shock (3); Blindness (3); Convulsion (2); Death (1); Disseminated Intravascular Coagulation (1); Renal Failure (3); Rhabdomyolysis (1); Septic Shock (1); and Torsade De Pointes (2).* Analysis of these cases did not identify any new safety signals; concomitant medications, medical history, comorbid conditions, and/or the lack of sufficient clinical information in the FAERS reports preclude the association of phenylephrine with these adverse events.

3.2 LITERATURE SEARCH

(b) (4)

(b) (4)

The majority of articles retrieved from PubMed focused on the *efficacy* of phenylephrine for use in hypotension associated with spinal anesthesia in obstetrics; others compared the efficacy of phenylephrine with that of ephedrine.

Consistent with the fact that phenylephrine is an older drug used via different routes for different purposes there are a number of published articles describing phenylephrine use in a variety of settings. These include: use in eye drops (to reverse ptosis caused by Botox), use as a decongestant and possible teratogenicity associated with this use in pregnant women, use to reverse a hypothetical drug-induced priapism, and, topical use in nasal/sinus/other surgery and the possible development of hypertension.

4 DISCUSSION

Our review examined all phenylephrine HCL 1% injection adverse events reported in FAERS and the published medical literature in an effort to provide a comprehensive overview of adverse events that could be used to identify new safety signals for labeling of this product.

Our review of all unlabeled adverse events did not find any events that were compelling enough to suggest a new safety signal or to require any addition to the proposed phenylephrine labeling. 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.

5 CONCLUSION

No safety risks were identified from FAERS and published medical literature suggesting the need to modify the proposed phenylephrine label at this time.

6 RECOMMENDATIONS

DPV will continue routine monitoring of all adverse events reported in association with phenylephrine HCl 1% injection.

7 REFERENCES

1. Wu E. Provision of Pharmacovigilance Data; West-ward Pharmaceutical Phenylephrine HCl and All Adverse Events. June 21, 2012

2. Zdanowicz, JA et al., "Broken Heart" after cesarean delivery. Case report and review of literature. Arch Gynecol Obstet. 2011 Apr;283(4):687-94.

(b) (4)

4. Smolinske, SC. Review of parenteral sulfite reactions. J Toxicol Clin Toxicol. 1992;30(4):597-606.
5. Crimi E, Baggish A, Leffert L, Pian-Smith MCM, Januzzi JL, Jiang Y. Acute reversible stress-induced cardiomyopathy associated with cesarean delivery under spinal anesthesia. Circulation 117: 3052-3053, No. 23, 10 Jun 2008
6. Fressard D, Manent P, Gautier M, Thevenot F. Probable injection de neosynephrine a la place de la prostigmine: un evenement indesirable grave. Annales Francaises d'Anesthesie et de Reanimation 2012; 31: 86-87
7. Miller JA, et.al. Safety of Hypertensive Hypervolemic Therapy With Phenylephrine in the Treatment of Delayed Ischemic Deficits After Subarachnoid Hemorrhage. Stroke. 1995; 26:2260-2266.

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

8.2 FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

8.3 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

Case#	Vrsn	MFR Ctrl #
6338688	1	US-BAXTER-2007BH005487
6481276	1	US-BAXTER-2007BH009448
6850418	1	US-ASTRAZENECA-2008AC03133
6986562	1	2009-1
6996277	1	
7101952	1	20090370
7370444	2	JHP201000126
8030032	1	953540
8040375	1	950649
9639777	1	GB-JNJFOC-20131010861
4035815	1	M1301-2003
4056552	1	2003-109738-NL
5757608	1	141435USA
6014069	1	
6061510	1	2006BH010040
6132015	2	2006-147270-NL
6342030	2	US-BAXTER-2007BH005675
6777921	3	2008-183378-NL
6783918	2	GXKR2008CA08958
6948967	1	JP-ROXANE LABORATORIES, INC.-2009-RO-00244RO
7103080	1	US-TEVA-207744USA
7110729	1	2009EK003929
7147069	1	
7293313	1	355738
7874068	1	821044
7966775	3	FR-BAXTER-2011BH017150
7975279	2	2011SP021439
7989667	3	2011SP023020
8197090	2	FR-ASTRAZENECA-2011SE62766
8710577	1	US-JNJFOC-20120707253
8906146	1	US-RANBAXY-2012US-61792
9121591	3	JP-009507513-1302JPN011098
9334528	2	JP-BAXTER-2013BAX014718
9459145	2	US-JHP PHARMACEUTICALS, LLC-JHP201300506
6476763	1	
6675025	1	US-TEVA-173008USA
7106275	1	2009TJ0184
7223756	1	443138
7360978	1	20100127
7757714	1	US-BAXTER-2011BH000236

Case#	Vrsn	MFR Ctrl #
8107202	1	US-BAXTER-2011BH026926
8107213	1	US-BAXTER-2011BH026991
8107413	1	US-BAXTER-2011BH027009
8428991	1	DE-ASTRAZENECA-2012SE11912
8895294	1	US-TEVA-369037USA
8902717	1	US-MYLANLABS-2012S1022666
9306205	2	FR-GLAXOSMITHKLINE-B0892343A
9666330	2	JP-ASTRAZENECA-2013SE80221
7764342	1	-VALEANT-2011VX000002
7766076	1	GB-VALEANT-2010VX002223
8381432	3	JP-ABBOTT-11P-087-0874640-00
6550738	2	US-BAXTER-2008BH001154
8447930	1	FR-VALEANT-2012VX000777
8012831	1	FR-VALEANT-2011VX000050
7095905	1	US-PURDUE-USA-2009-0039693
7097667	1	US-BAXTER-2009BH013016
8605749	3	GB-TEVA-340755ISR
7101949	1	20090379
8092943	1	US-BAUSCH-2011BL005358
9519708	1	
7743409	1	US-BAXTER-2010BH030922
7743411	1	US-BAXTER-2010BH030923
7743412	1	US-BAXTER-2010BH030924
7743413	1	US-BAXTER-2010BH030995
7743415	1	US-BAXTER-2010BH030996
7743418	1	US-BAXTER-2010BH030997
7743419	1	US-BAXTER-2010BH030998
9393811	3	FR-BAXTER-2013BAX025564
9063272	1	FR-JNJFOC-20130117047
7743355	1	US-BAXTER-2010BH030910
7743376	1	US-BAXTER-2010BH030990
7743383	1	US-BAXTER-2010BH030991
7197685	1	GB-BAUSCH-2009BL006226
7743384	1	US-BAXTER-2010BH030993
7743408	1	US-BAXTER-2010BH030921
7518824	3	US-BAXTER-2010BH019785
3191497	1	
3417806	1	
3680813	1	
3813949	1	

Case#	Vrsn	MFR Ctrl #
3865462	1	02H-143-0203035-00
3910247	1	03H-153-0210305-00
4144640	1	
4651248	1	
4916008	1	8901449
4951429	1	
5081813	1	
5351081	1	95080226
5568349	1	
5929436	1	200513809GDS
6035360	1	06H-163-0307243-00
6466771	1	
6704150	1	
6783965	2	GXKR2008CA08957
6783969	2	GXKR2008CA08956
6844430	1	US-ASTRAZENECA-2008AC03135
7125182	1	US-BAXTER-2009BH014159
7193422	5	US-BAYER-200940878NA
7971524	1	
6833736	1	
7101953	1	20090381
6901514	1	CA-GLAXOSMITHKLINE-B0446335A
9008955	1	US-BAXTER-2013BAX000725
5183136	1	
7368870	1	US-BAXTER-2010BH010529
7368871	1	US-BAXTER-2010BH010580
7368872	1	US-BAXTER-2010BH010582
7368873	1	US-BAXTER-2010BH010583

Case#	Vrsn	MFR Ctrl #
7368874	1	US-BAXTER-2010BH010584
7368875	1	US-BAXTER-2010BH010585
7368876	1	US-BAXTER-2010BH010587
7368877	1	US-BAXTER-2010BH010588
7368878	1	US-BAXTER-2010BH010589
7368879	1	US-BAXTER-2010BH010590
7368880	1	US-BAXTER-2010BH010591
7368881	1	US-BAXTER-2010BH010592
7368882	1	US-BAXTER-2010BH010594
7368883	1	US-BAXTER-2010BH010595
9161897	1	2013P1002451
4312858	1	
5383724	1	
5399682	1	96001621
6750884	1	US-BAXTER-2008BH009197
4638326	1	
4671692	1	13573
7339865	1	US-BAXTER-2010BH008108
7880696	1	US-BAXTER-2011BH007398
4920625	1	16828
5148663	1	
4734302	1	14325
8988489	1	
6427773	1	US-BAXTER-2007BH006999
4510521	1	191686784
4832837	1	
7743357	1	US-BAXTER-2010BH030920
7576524	1	US-BAXTER-2010BH022568
4947778	1	9201371

8.4 SELECT CASE SUMMARIES

Cases Coded with an Outcome of *Death*

4920625- a 74 year old male suffered cardiac arrest after IV injection of sodium pentothal 75ml, Neo-synephrine 1mg, and Phenergan 8mg, as well as IM morphine (dose not reported) and subsequent intrathecal administration of tetracaine 12mg and Neo-synephrine 1mg. At autopsy, cause of death was determined to be “pulmonary emboli due to fracture of left femur due to fall.”

4947778- a 46 year old male suffered a subarachnoid hemorrhage. He experienced brain edema, hypoxemia leading to pneumonia, and coagulopathy was noted. The patient then developed hypernatremia, renal failure, and a junctional arrhythmia. Patient died 6 days after subarachnoid hemorrhage occurred. Cause of death was reported as cerebral edema due to initial subarachnoid hemorrhage.

4951429- a 62 year old male patient died from “multiple medical problems” per reporter. Indication for use was reported as hypotensive episodes/ rule out sepsis. No additional clinical details were reported.

5351081- a 9 year old girl underwent an operation for sinus irrigation. Following the needle puncture, a hypertensive crisis of 195/110 occurred and Normodyne (labetalol) injection 5mg was administered. Her blood pressure returned to baseline (110/70). Within 15-20 minutes, hypotension, cyanosis, and shock occurred. Asystole was noted followed by pulmonary edema. The patient was kept alive for several days, but eventually expired due to multiple system organ failure. The reporter stated that, in their opinion, there may have been an embolism of naso-mucopurulent material resulting in septic shock. He reported that he also felt that there was a possibility the patient was irrigated with topical vasoconstrictor solution (phenylephrine and lidocaine) and not saline which could have contributed to the hypertensive crisis. The reporting physician also felt that it is possible that they combination of beta blockade along with the venodilatory properties of Diprivan may have contributed to the pulmonary edema and shock. An autopsy was not performed. The patient was kept alive for several days but eventually died due to multiple system organ failure.

6061510- a patient (age and gender not reported) experienced death coincident with the administration of Dopamine. The patient's medical history and concomitant medications were not provided, however it was reported that the patient was critically ill and unstable. The patient was transferred from the operating room (OR) with the triple pump off. The patient was receiving Dopamine (dose and rate not provided) IV and Neo-Synephrine (dose and rate not provided) IV. The anesthesiologist stated the pump was on and must have turned off during transport. The patient expired; it is unknown if an autopsy was performed. Cause of death was not provided. The reporter stated the patient's death was not related to the event of the pump turning off and non-delivery of Dopamine and Neo-Synephrine.

6844430/7101953- a 25 year old male who was admitted comatose after a self-inflicted gunshot wound to the head. His injuries included left fronto-temporal subarachnoid haemorrhage and cerebral contusions with multiple facial and orbital fractures. His past medical history included depression and multiple suicidal attempts, but he was not on antidepressants. Upon admission, a 1% propofol infusion was initiated for elevated intracranial pressure (ICP) management. In order to maintain cerebral perfusion pressure (CPP), phenylephrine was infused for a total of 299 hours. After 2 days of propofol use, additional thiopental boluses (100-200 mg IV) were required for ICP control and propofol was discontinued and replaced with pentobarbital infusion. Despite aggressive barbiturate therapy, ICP's remained elevated. Patient’s family withdrew life sustaining therapy and the patient expired 1 hour later.

7125182- an 83 year old female was receiving multiple medications via a central venous line with a high flow rate utilizing two Colleague Triple Channel Infusion Pumps. The patient underwent emergent colectomy due to toxic megacolon with C. difficile. At the end of surgery, the two Colleague pumps alarmed “occlusion” while the drugs were being administered. After surgery, the patient was transferred back to the intensive care unit where she experienced ventricular tachycardia and cardiac arrest. She was resuscitated. The next day the patient expired, cause of death not reported.

7370444- a 56-year-old male with untreated hypertension and obesity was involved in a motor vehicle accident and sustained multiple injuries. On hospital day 47, the patient experienced severe hypotension and was administered norepinephrine infusion 40 mcg/minute, vasopressin infusion 0.04 U/minute, IV hydrocortisone 100 mg every 8 hours, and a phenylephrine infusion titrated to 200 mcg/minute. The patient developed refractory shock. Methylene blue was subsequently administered as a vasoconstrictor (initial bolus dose of 100 mg over 10 minutes and then a continuous infusion of 100 mg/hour). During the night the patient became asystolic and died. Reporter states Refractory shock in this case was likely caused by the presence of haemodynamic failure secondary to the patient's condition and the evolving sepsis.

7518824- a 54 year old male patient was admitted to the hospital with acute respiratory failure. The patient went into respiratory arrest (code blue) on the medical surgical unit and was transferred to a Special Care Unit (SCU). The patient was started on a phenylephrine drip via Alaris Medsytem 3 Infusion Pump to maintain blood pressure. The patient was receiving phenylephrine infusion to maintain blood pressure when the pump displayed visual and aural alarms and delivery was interrupted for 1 to 2 minutes. During the swap out of the device the patient became hypotensive and coded but resuscitation efforts were unsuccessful. The infusion pump was evaluated by the facility and Biomed and no malfunction was found. Per the reporter, the death of the patient was not a direct result of an equipment malfunction, but possibly related to user error.

7764342- a literature report of a 24-year-old nulliparous female patient with myasthenia gravis diagnosed at 20 weeks of gestation was treated with immunoglobulin, hydrocortisone, lidocaine, betamethasone, prednisolone, pyridostigmine, phenylephrine, insulin, bupivacaine, and diamorphine during pregnancy. On scanning, multiple fetal abnormalities were seen: an absent stomach bubble, abnormal fetal profile, hypoplastic nasal bone, clenched fists, hyperextended toes and reduced limb flexion, suggesting a neuromuscular disorder. Maternal blood was positive for anti-AChR antibodies with a level of >20 mmol/l (normal range < 0.45 nmol/l). Pregnancy continued with fortnightly plasmapheresis sessions. An elective caesarean section under combined spinal-epidural (CSE) anaesthesia was performed at 34 weeks. Blood pressure was maintained with increments of 0.1 mg phenylephrine; intravenous hydrocortisone 100 mg given before surgery. A live 2754 g female baby was delivered, with dysmorphia, an extended fixed neck, and arthrogryposis (contractures) in all limbs. Apgar scores were 2 and 0 at 1 and 5 min, respectively with poor tone and no respiratory effort. Additional details not provided.

8197090- a 78 year old male patient was hospitalized for a mitral valve replacement with a bioprosthesis. The patient received Ephedrine (ephedrine), 12.0 milligrams and Phenylephrine (phenylephrine) for hypotension (20/11 cmHg). Despite treatment, blood pressure continued to decrease until it was impossible to measure. Cardiopulmonary resuscitation was performed and the patient received a treatment with adrenaline and noradrenaline. IT was speculated that the patient had experienced anaphylactic shock. Surgery was cancelled and rescheduled. Two weeks later, the patient again underwent surgery for a mitral valve replacement; phenylephrine, ephedrine, and pseudo-ephedrine were strictly avoided. The patient presented with cardio-respiratory arrest again. It was quickly resolved by injection of adrenaline and

cardiopulmonary resuscitation. Surgery was maintained and hemodynamic balance was temporarily provided by extracorporeal life support. Two weeks later the patient died as a result of vasoplegic and cardiogenic shock, resistant to the treatment with noradrenaline, adrenaline and Glypressine.

9008955- a patient (age and gender not reported) was hospitalized for pneumonia which progressed into sepsis. The reporter stated that the patient was "in the dying process" and was worsening each day prior to the day of passing away. Phenylephrine did not contribute to the patient's death.

Lung Infiltration

All 9 cases of *Lung Infiltration* were the result of a single literature article[7]. The article reported mild to moderate interstitial infiltrates occurred on the chest x-ray films of nine patients at some time during the course of therapy with phenylephrine. The authors state that this was of minimal clinical significance in four patients who had transient increases in oxygen requirements (in all cases, fractional inspired oxygen of $\leq$50%) and required diuretic therapy on one or more occasions. None of these 4 patients required intubation to maintain adequate oxygenation. Three patients had evidence of fulminant pulmonary edema on admission to the hospital, with marked bilateral pulmonary infiltrates and need for mechanical ventilation and/or fractional inspired oxygen of >50%. In all cases the pulmonary edema resolved within 2 to 3days.

Aphasia

There were 3 unique reports of aphasia in FAERS. One case (case 6550739) occurred after an overdose (50mcg ordered, 10mg administered); no additional details were provided. The remaining reports of aphasia fail to provide a temporal relationship to administration of phenylephrine; case 7095905 reported aphasia occurred a day after treatment with phenylephrine and case 8040375 reported aphasia occurred prior to treatment with phenylephrine.

Cardiac Arrest Cases

Case 4920625 reported a 74 year old male suffered cardiac arrest after IV injection of sodium pentothal 75ml, Neo-synephrine 1mg, and Phenergan 8mg, as well as IM morphine (dose not reported) and additional administration of intrathecal tetracaine 12mg and Neo-synephrine 1mg. At autopsy, cause of death was determined to be “pulmonary emboli due to fracture of left femur due to fall.”

Case 5351081 reported a 9 year old girl underwent an operation for sinus irrigation. Following the needle puncture, a hypertensive crisis of 195/110 occurred and Normodyne (labetalol) injection 5mg was administered. Her blood pressure returned to baseline (110/70). Within 15-20 minutes, hypotension, cyanosis, and shock occurred. Asystole was noted followed by pulmonary edema. The patient was kept alive for several days, but eventually expired due to multiple system organ failure. The report further stated that there was a possibility that the patient was irrigated with topical vasoconstrictor solution (combination of lidocaine and phenylephrine) and not saline, which could have contributed to the hypertensive crisis.

Case 5757608 reported a male patient (age not reported) was inadvertently administered a 10 mg dose of intravenous (IV) phenylephrine in place of the 10 mg dose of IV metoclopramide. The patient coded, suffering cardiac arrest and pulmonary edema. Cardiopulmonary resuscitation (CPR), cardioversion, and mechanical ventilation were required. The patient survived the code, his surgery was completed and he was discharged three days later without any known sequelae.

Case 6338688 reported a 69 year old female admitted to the hospital for pulmonary edema and respiratory distress with a possible myocardial infarct. The patient was taken to the cardiac cath lab for a possible cardiac intervention (procedure and findings not reported). Upon transfer to the coronary care unit (CCU), a Neo-synephrine infusion (dose and rate not reported) was started via a Baxter Colleague Triple Channel CXE Volumetric Infusion Pump. The blood pressure at the time was 70/40. An hour later, a dopamine infusion (dose and rate not reported) was started via the same pump, 2nd channel. Another hour later, a norepinephrine infusion (dose and rate not reported) was started via the same pump, different channel. Shortly thereafter the patient experienced ventricular tachycardia and no blood pressure could be obtained. The patient coded and was subsequently resuscitated and intubated. The patient was shocked and the blood pressure returned to the 70's. One medication's (medication not reported) rate was being increased on the pump when the pump failed on all 3 channels. The patient's blood pressure dropped into the 30's/10-12. Another pump was obtained and the infusions were transferred to the new pump with the medication being increased as originally intended. Baxter Product Surveillance initiated an investigation of the pump.

Case 6948967 reported a 60-year-old woman underwent neck clipping of an unruptured cerebral aneurysm. Multiple episodes of hypotension with systolic blood pressure occurred during dural and cranial closure; these were treated with intravenous ephedrine and phenylephrine. Thirty minutes after the third hypotensive event (systolic blood pressure below 60 mmHg), clinical cardiac arrest occurred and was successfully treated with 1.5 min of chest compression and repeated epinephrine administration.

Case 7125182 reported an 83 year old female patient underwent emergent colectomy due to toxic megacolon with C. difficile. At the end of surgery, the two Colleague pumps alarmed “occlusion” while the drugs were being administered. The facility believed the line (unspecified tubing) may have been occluded. The central venous line was being used as a large volume resuscitation line in one port and the vasoactive agents were in the other port. After surgery, the patient was transferred back to the intensive care unit where she experienced ventricular tachycardia and cardiac arrest and later expired. No autopsy was performed; the cause of death was unknown.

Case 7370444 reported a 56-year-old with untreated hypertension and obesity was involved in a motor vehicle accident and sustained multiple injuries. On hospital day 47, the patient experienced severe hypotension and was administered norepinephrine infusion 40 mcg/minute, vasopressin infusion 0.04 U/minute, IV hydrocortisone 100 mg every 8 hours, and a phenylephrine infusion titrated to 200 mcg/minute. The patient developed refractory shock. Methylene blue was subsequently administered as a vasoconstrictor (initial bolus dose of 100 mg over 10 minutes and then a continuous infusion of 100 mg/hour). During the night the patient

became asystolic and died. Reporter states Refractory shock in this case was likely caused by the presence of haemodynamic failure secondary to the patient's condition and the evolving sepsis.

Cardio-Respiratory Arrest Cases

5757608- see summary in Cardiac Arrest section

6476763- a 31 year old female patient was given Neo-synephrine 20mg IV push instead of 10mg Reglan that was ordered. Patient coded and was revived.

7147069- a 71 year old male experienced unintended administration at close of AAA surgery resulting in cardiovascular collapse and possible anoxic brain injury. No other details were provided.

7518824- a 54 year old male patient was admitted to the hospital with acute respiratory failure. The patient went into respiratory arrest (code blue) on the medical surgical unit and was transferred to a Special Care Unit (SCU). The patient was started on a phenylephrine drip via Alaris Medsytem 3 Infusion Pump to maintain blood pressure. The patient was receiving phenylephrine infusion to maintain blood pressure when the pump displayed visual and aural alarms and delivery was interrupted for 1 to 2 minutes. During the swap out of the device the patient became hypotensive and coded but resuscitation efforts were unsuccessful. The infusion pump was evaluated by the facility and Biomed and no malfunction was found. Per the reporter, the death of the patient was not a direct result of an equipment malfunction, but possibly related to user error.

8197090- a 78 year old male patient was hospitalized for a mitral valve replacement with a bioprosthesis. The patient received Ephedrine (ephedrine), 12.0 milligrams and Phenylephrine (phenylephrine) for hypotension (20/11 cmHg). Despite treatment, blood pressure continued to decrease until it was impossible to measure. Cardiopulmonary resuscitation was performed and the patient received a treatment with adrenaline and noradrenaline. IT was speculated that the patient had experienced anaphylactic shock. Surgery was cancelled and rescheduled. Two weeks later, the patient again underwent surgery for a mitral valve replacement; phenylephrine, ephedrine, and pseudo-ephedrine were strictly avoided. The patient presented with cardio-respiratory arrest again. It was quickly resolved by injection of adrenaline and cardiopulmonary resuscitation. Surgery was maintained and hemodynamic balance was temporarily provided by extracorporeal life support. Two weeks later the patient died as a result of vasoplegic and cardiogenic shock, resistant to the treatment with noradrenaline, adrenaline and Glypressine.

Encephalopathy

Two unique cases of encephalopathy were reported. Case 6901514 reported encephalopathy in a pregnant bipolar patient after electroconvulsive therapy (ECT) induced continuous grand mal seizures, clonus, and increased EEG activity. She received thiopental 100 mg, midazolam 3 mg, and diazepam 10 mg, with no effect. The patient received a total of 1450 mg thiopental, 55 mg diazepam, and 200 mg propofol, over 2 and a half hours. She then received continuous infusion of thiopental 300 mg/h and propofol 200 mg/h. The patient was mechanically ventilated and transferred to ICU. Thiopental and propofol were tapered and discontinued over the next 2 hours and the patient experienced subsequent hypotension (systolic pressure 70-90 mmHg). She was

treated with phenylephrine 0.7-1.5 mcg/kg/min and dopamine 4-10 mcg/kg/min. The patient regained consciousness on day 7.

7095905- A 69 year old male patient was admitted to the hospital for an elective coronary artery bypass grafting (CABG) and aortic valve replacement. He received midazolam IV, Clevidipine IV, nicardipine IV (bolus followed by a 2mg/hr, continuous infusion), fentanyl IV, phenylephrine, 50mcg/min, IV, continuous (over one hour) epinephrine, 2mg/min, IV, (continuous over 3 days). The patient had an uncomplicated anesthetic and operative course. He was extubated six hours after arrival in the cardiothoracic surgical intensive care unit in hemodynamically stable condition. He had an episode of alteration in mental status, delirium, and transient unresponsiveness lasting about 30 seconds, while he was being assisted with ambulation from bed to a chair. He was given fluid resuscitation (type, dose, route, and frequency not reported) and regained neurological function completely. Later that day he was noted to be having difficulty with speech and confusion. The confusion was attributed to the hydromorphone (PCA was discontinued with subsequent improvement in mental status). The patient was then started on morphine PCA. The patient was again noted to have difficulty with speech. A computerized tomogram (CT) scan of the head showed a prior parietal infarct with no evidence of a new infarct. The neurological diagnosis was postoperative encephalopathy leading to delirium.

Medication Error

There were 6 unique reports of medication errors. Four of the 6 cases reported patients receiving phenylephrine instead of the intended medication (1 Nubain (case 3417806), and 3 Reglan (cases 5757608, 6476763, 6750884)). There was one additional report of accidental administration, however, intended medication was not reported (case 5383724). The final case (case 4144640) reported an error in dose; patient received 10mg phenylephrine in error (physician ordered 100 mcg).

Delirium

There was 1 unique case of delirium reported in FAERS (case 7095905). However, delirium occurred after cardiac bypass surgery, and was transient.

Electrocardiogram T Wave Inversion

6844430- A 25-year-old man received a propofol 30-134 ug/kg/min infusion for 135 hours for elevated intracranial pressure management. To maintain cerebral perfusion pressure, he received a phenylephrine 0.04-7.6 ug/kg/min infusion for 299 hours. He also received thiopental sodium after 2 days of propofol use. Propofol was replaced by pentobarbital on day 7 due to an increased noncardiac creatine kinase level of 1778 U/L, metabolic acidosis and a T wave inversion on ECG. Two days after propofol discontinuation, his creatine kinase level peaked at > 25,300 U/L. He had a creatine kinase MB level of 17.8 ng/ml, a troponin level of 0.7 ng/ml, positive urine myoglobin, and an LDH level of 1098 U/L. His intracranial pressure remained increased and, on hospital day 13, life sustaining therapy was withdrawn and he died after 1 hour. The author commented that "the combination of propofol and vasopressors may increase the odds of developing (propofol infusion syndrome) several-fold".

6850418-28-year-old man underwent emergent evacuation of intracerebral hematoma and an external ventricular drainage was placed. A propofol infusion was started at a dosage of 50-75 ug/kg/min intraoperatively and was continued at 95-125 ug/kg/min in the neurosurgical ICU for sedation and elevated intracranial pressure management, for 85 hours. Phenylephrine 0.8-8.0 ug/kg/min was administered along with propofol for 90 hours for cerebral perfusion pressure management. On hospital day 4, he had developed a new T-wave inversion and a prolonged QTc interval of 617ms. On day 5 his creatine kinase and creatine kinase MB levels had increased to 12,858 U/L and 59.5 ng/ml, respectively.

7360978- is a literature report[5] of a 31-year-old woman who developed hypotension and sinus bradycardia approximately 15 minutes after the start of spinal anaesthesia, and received multiple doses of IV ephedrine (total 50mg) and volume resuscitation over approximately 5 minutes; anaesthesia had been achieved with bupivacaine 12mg, fentanyl 10 mcg and morphine 0.2mg. She then received two doses of IV atropine (total 0.8mg) and developed sinus tachycardia with a HR of 150 beats/min. She experienced chest heaviness and a phenylephrine infusion was started. She then reported blindness, felt anxious, and developed seizure-like activity (likely convulsive syncope), 10 minutes after receiving atropine. Propofol and succinylcholine were immediately administered, and she was intubated. The surgery was completed and she was extubated. Phenylephrine was continued and she received oxygen. An ECG 5 hours after surgery showed T-wave inversions in leads V1, V2 and aVL, and this lasted for 4 days. An echocardiogram revealed moderate left ventricular systolic dysfunction and a left ventricular ejection fraction of 40%. Her serum troponin I level was slightly elevated (peak 0.25 ng/mL). The woman was diagnosed with stress-induced cardiomyopathy and received metoprolol and lisinopril. Her symptoms subsequently resolved and an echocardiogram on postoperative day 4 showed complete normalisation of left ventricular function. She was asymptomatic at 4 weeks' follow-up and her ECG was normal; echocardiography revealed a left ventricular ejection fraction of 75% and no wall motion abnormalities.

7368871- literature case[7] See summary of cases in Lung Infiltration section

Metabolic Acidosis

Four unique cases of metabolic acidosis were reported in FAERS. Cases 6844430, 6850418 and 7101952 all occurred in the setting of propofol infusion syndrome. Case 7370444 is summarized in the Cardiac Arrest section, Appendix 8.4.

Unresponsive to Stimuli

There were 2 unique reports of unresponsive to stimuli. See Case 7095905 summary in Encephalopathy section, Appendix 8.4. Case 7975279 did not provide sufficient clinical details for evaluation.

Pulmonary Oedema

There were 5 unique cases of pulmonary oedema reported in FAERS. Three of 5 (Cases 4638326, 4734302, and5757608) reported a dose error or overdose; one case (Case 5351081) reported a suspected accidental topical irrigation with lidocaine/phenylephrine instead of saline and the remaining case (Case 8447930) did not provide sufficient clinical details for evaluation.

Stress Cardiomyopathy

Case 7360978 –is a literature report[5] of a 31-year-old woman who developed hypotension and sinus bradycardia approximately 15 minutes after the start of spinal anaesthesia, and received multiple doses of IV ephedrine (total 50mg) and volume resuscitation over approximately 5 minutes; anaesthesia had been achieved with bupivacaine 12mg, fentanyl 10 mcg and morphine 0.2mg. She then received two doses of IV atropine (total 0.8mg) and developed sinus tachycardia with a HR of 150 beats/min. She experienced chest heaviness and a phenylephrine infusion was started. She then reported blindness, felt anxious, and developed seizure-like activity (likely convulsive syncope), 10 minutes after receiving atropine. Propofol and succinylcholine were immediately administered, and she was intubated. The surgery was completed and she was extubated. Phenylephrine and oxygen were continued. An ECG 5 hours after surgery showed T-wave inversions in leads V1, V2 and aVL (which lasted for 4 days). An echocardiogram 8 hours after surgery revealed moderate left ventricular systolic dysfunction and a left ventricular ejection fraction of 40%. Her serum troponin I level was slightly elevated (peak 0.25 ng/mL). The woman was diagnosed with stress-induced cardiomyopathy and received metoprolol and lisinopril. Her symptoms subsequently resolved and an echocardiogram on postoperative day 4 showed complete normalisation of left ventricular function. She was asymptomatic at 4 weeks' follow-up and her ECG was normal; echocardiography revealed a left ventricular ejection fraction of 75% and no wall motion abnormalities.

A French literature report[6] (case 8447930) reported a 28 year old woman was hospitalized for pelvic pain associated with early recurrence of a mucinous cyst of the left ovary; an oophorectomy was scheduled (a first total cystectomy of the left ovary was performed eight months prior). After the laparoscopic oophorectomy was preformed, the patient's blood pressure (BP) increased from 100/70 to 190/80 mmHg with a heart rate of 150 beats/min. The patient was extubated and transferred to recovery where she presented with dyspnea and a BP of 100/50 mmHg. Blood pressure continued to decrease to 70/30 mmHg. After a 300 mcg infusion of Neo-Synephrine (phenylephrine) with no effect, treatment with dobutamine , 5 and 10 mcg/kg per minute was administered to restore BP to 100/60 mmHg . Two hours after admission to the recovery room, troponin and D-dimer were elevated and chest radiography showed bilateral edema. Echocardiography revealed a septo -basal anterior akinesia with an ejection fraction of 45%. Two assumptions were posed by the reporter: post- ischemia tachycardia or coronary spasm stating that the clinical picture was consistent with postoperative stress cardiomyopathy or coronary spasm with rapid and complete recovery. After systemic analysis of the causes by the reporter, the reporter hypothesized the stress cardiomyopathy was a result of an accidental injection of 1 mL ampule phenylephrine. The facilities surgical cart housed ampules of prostigmine 1 mL (0.5 mg/mL) and 1 mL phenylephrine (5 mg/mL) together. It was further hypothesized that in the preparation of a 2.5mg dose of prostigmine, one of the ampules used was actually phenylephrine (one empty ampule of phenylephrine found amongst the 5 empty ampules of prostigmine).

Pediatric Cases

4671692- 15 year old female patient underwent appendectomy and inadvertently received 10 mg of neosynephrine 1% instead of neostigmine. She developed severe hypertension, apnea, brain edema, and renal failure. She was treated and recovered within 24 hours without sequelae.

5351081- a 9 year old girl underwent an operation for sinus irrigation. Following the needle puncture, a hypertensive crisis of 195/110 occurred and Normodyne (labetalol) injection 5mg was administered. Her blood pressure returned to baseline (110/70). Within 15-20 minutes, hypotension, cyanosis, and shock occurred. Asystole was noted followed by pulmonary edema. The patient was kept alive for several days, but eventually expired due to multiple system organ failure. The report further stated that there was a possibility that the patient was irrigated with topical vasoconstrictor solution (combination of lidocaine and phenylephrine) and not saline, which could have contributed to the hypertensive crisis.

5568349- an 11 year old male was admitted to the hospital with gram negative sepsis, septic shock, fevers, positive blood culture with Enterobacter. He was treated with antibiotics, fluids, red blood cell transfusion, dopamine, epinephrine, and phenylephrine to maintain urine output and blood pressure. Patient was transferred to the ICU still on pressors, and developed prolonged QT interval and Torsades de Pointes. Patient was prescribed magnesium and Dilantin with slow improvement in QT. PMH significant for osteosarcoma, multiple chemotherapeutic drugs including adriamycin and ifosfamide.

9121591- a 12 year old female patient with familial polyposis underwent a polypectomy under general anesthesia. During the operation, the patient was treated with rocuronium bromide, sevoflurane, thiamylal sodium, fentanyl citrate, phenylephrine hydrochloride, lidocaine, and at the end of the operation, sugammadex sodium was injected. After the operation, the patient complained she suffered malaise. Blood tests revealed AST was over 6000 and ALT was over 5000 (bilirubin level was normal), and acute liver disorder was suspected and a transfusion was performed. At the time of the report, the patient was recovering from the acute liver disorder; all liver test values returned to normal.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TARA L ARGUAL
02/05/2014

JANE L GILBERT
02/06/2014

SARA L CAMILLI
02/06/2014

ALLEN D BRINKER
02/06/2014

SCOTT E PROESTEL
02/06/2014

Consultative Review

To: **Kimberly Compton, Regulatory Project Manager**
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: **Barbara Wesley, MD, MPH, Clinical Reviewer**
Christina Chang, MD, MPH, Clinical Team Leader
Audrey Gassman, MD, Deputy Division Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subjects: **Use of phenylephrine and ephedrine in women who undergo neuraxial anesthesia (epidural and intrathecal) for either cesarean section or vaginal delivery**

Date of Request: **October 28, 2013**
Date of Review: **January 30, 2014**

1. Introduction

This consultative review provides DBRUP's assessment regarding maternal and fetal/neonatal safety of two pressor agents used to treat hypotension associated with neuraxial anesthesia. DAAAP is currently reviewing a 505(b)(2) new drug application (NDA) for phenylephrine and anticipates additional NDAs to be submitted for both phenylephrine and ephedrine. All these applications reference published literature to support the indications of peri-operative management (i.e., the treatment (b) (4)) of hypotension associated with neuraxial (predominantly spinal) anesthesia. Because such literature-based data are primarily from use in obstetrical settings where phenylephrine and ephedrine are administered to parturients during labor and delivery, DAAAP asks that DBRUP specifically comment on 1) maternal, fetal, or neonatal safety for either pressor agent used in this setting, and 2) clinically relevant differences between the two pressor agents.

2. Background

Spinal (intrathecal) anesthesia has become the most commonly used anesthetic technique for both elective and unplanned cesarean section due to its ability to provide a rapid and reliable onset of anesthesia.[1] Because adequate anesthesia for cesarean section requires complete blockade up to the level of T4, the resulting sympathectomy is accompanied by decreased systemic vascular resistance resulting in a decrease in venous return to the heart, and is further exacerbated by aortocaval compression from the gravid uterus. The reduced cardiac output accounts for the common occurrence of hypotension (frequently defined as a decrease to 80% of baseline) after the induction of spinal anesthesia in parturients. Consequently, hypotension occurs frequently following induction of spinal

[1] Roofthooft E, van de Velde M. Low-dose spinal anaesthesia for caesarean section to prevent spinal-induced hypotension. Curr Opin Anaesthesiol 2008;21:259-262.

anesthesia, with an incidence approaching 80%.[2] Symptoms of hypotension in the mother may include decreased consciousness, dizziness, nausea, and vomiting. Intra-operative nausea and vomiting may be dangerous for the mother if the airway is compromised. Because uteroplacental blood flow is pressure-dependent, adverse neonatal outcomes following prolonged maternal hypotension may include impaired fetal oxygenation and fetal acidosis.

If recognized and treated promptly, maternal hypotension may not be associated with maternal or neonatal morbidity.[3] However, the optimal management of maternal hypotension has been under debate.[4,5,6,7] In addition to volume preload and left lateral uterine displacement, vasopressors such as ephedrine and phenylephrine have been the mainstay for treating maternal hypotension. Nevertheless, significant variations in practice regarding the dose and dosing regimen of either vasopressor (i.e., boluses for treatment vs. (b) (4) (b) (4)) remain.

Ephedrine is both an α- and β-adrenergic agonist while phenylephrine is a α1-agonist. Historically, support for ephedrine use was identified from nonclinical data in sheep, showing ephedrine to cause less uteroplacental vasoconstriction. Additionally, there was concern regarding the role of pure α1-agonists such as phenylephrine for increasing arterial pressure at the expense of tissue perfusion. Consequently, ephedrine was established as the vasopressor of choice in obstetric anesthesia for decades. However, studies published in the last decade have suggested that phenylephrine may be associated with higher fetal umbilical artery pH values and may thus be preferable to ephedrine.[8,9]

3. Findings in Literature

3.1 Ephedrine Overview

Ephedrine is a nonspecific adrenergic agonist and increases blood pressure mainly by increasing cardiac output via stimulation of cardiac β-1 receptors. Placebo-controlled or dose-response data on ephedrine bolus for spinal hypotension are limited. Comparing

[2] Klohr S, Roth R, Hofmann T, et al. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand 2010;54:909-921.
[3] Norris MC. Hypotension during spinal anesthesia for caesarean section: Does it affect neonatal outcome? Reg Anaesth 1987;12:191-3.
[4] Birnbach DJ, Soens MA. Hotly debated topics in obstetric anesthesiology 2008: a theory of relativity. Minerva Anestesiol 2008;74:409-24.
[5] Veeser M, Hofmann T, Roth R, et al. Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis. Acta Anaesthesiol Scand 2012;56:810-816.
[6] Habib AS. A review of the impact of phenylephrine administration on maternal hemodynamics and maternal and neonatal outcomes in women undergoing cesarean delivery under spinal anesthesia. Anesth Analg 2012;114:377-390.
[7] Cooper DW. Caesarean delivery vasopressor management. Curr Opin Anesthesiol 2012;25:300-308.
[8] Lee A, Ngan Kee WD, Gin T. A quantitative systematic review of randomized controlled trials of ephedrine compared with phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2002;94:920-926.
[9] Riley ET. Spinal anaesthesia for caesarean delivery: keep the pressure up and don't spare the vasoconstrictors. Br J Anaesth 2004;92:459-461.

ephedrine 0.25 mg/kg bolus (15 mg in a 60 kg woman) and crystalloid preload in a single-blind trial in healthy parturients undergoing elective cesarean section, Chan et al found that severe hypotensive episodes (≥ 30 mmHg reduction in systolic blood pressure) were less frequent in the ephedrine group.[10] Otherwise, no differences were noted between ephedrine and fluid preload with respect to the maternal outcomes (incidences of nausea/vomiting and moderate hypotension, defined as ≥ 20 mmHg reduction in systolic blood pressure) and neonatal outcomes (Apgar scores and umbilical artery pH). In a dose-response, randomized, double-blind trial, Ngan Kee et al. evaluated three intravenous doses (10, 20, and 30 mg vs. saline). [11] Ngan Kee concluded that, compared to saline, maternal blood pressure was better maintained with the 30 mg ephedrine dose. However, the 30 mg dose was also associated with the highest incidence of reactive hypertensive episodes (systolic blood pressure > 120% of baseline). As expected, incidences of reactive hypertension in Ngan Kee were dose-related, occurring in 45%, 25%, and 5% of subjects in the 30 mg, 20 mg, and 10 mg groups respectively. Despite the varied degree of blood pressure control, there were no appreciable differences concerning neonatal outcomes among the three ephedrine doses studied. Other investigations such as those by Hall et al.[12] and Turkoz et al.[13] reported results from too limited a sample size, thereby precluding meaningful assessment. Data concerning continuous infusion of ephedrine used for the prevention of maternal hypotension are also scant, given small sample sizes in published trials. Available trials using ephedrine are presented below in Table 1.

Table 1. Trials comparing ephedrine regimens for the management of maternal hypotension during elective cesarean section

Trial	Treatment	N
Chan[10]	0.25 mg/kg bolus vs. IV fluid	23:23
Ngan Kee[11]	10 mg, 20 mg, 30 mg bolus vs. saline	20:20:20:20
Loughrey[14]	6 mg, 12 mg bolus vs. Saline	24:22:20
Hall[12]	1 mg/min vs. 2 mg/min infusion	10:9
Turkoz[13]	5 mg/min infusion vs. 10 mg bolus	15:15

3.1.1 Effects of ephedrine on the mother

Intra-operative nausea and vomiting

Nausea and vomiting are common maternal complications of spinal anesthesia. Correlation between ephedrine doses and reduction in the incidences of nausea and

[10] Chan WS, Irwin MG, Tong WN, et al. Prevention of hypotension during spinal anesthesia for caesarean section: ephedrine infusion versus fluid preload. Anaesth 1997;52:896-913.
[11] Ngan Kee WD, Khaw KS, Lee BB, et al. A dose–response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2000;90:1390–1395.
[12] Hall PA, Bennett A, Wilkes MP, et al. Spinal anaesthesia for caesarean section: comparison of infusions of phenylephrine and ephedrine. Br J Anaesth 1994;73:471-474.
[13] Turkoz A, Togal T, Gokdeniz R, et al. Effectiveness of intravenous ephedrine infusion during spinal anaesthesia for caesarean section based on maternal hypotension, neonatal acid-base status and lactate levels. Anaesth Intensive Care 2002;30:316-320.
[14] Loughrey JPR, Walsh F, Gardiner J. Prophylactic intravenous bolus ephedrine for elective Caesarean section under spinal anaesthesia. Eur J Anaesthesiol 2002;19(1):63-68.

vomiting has not been established. No difference in the incidences of nausea and vomiting between treatment groups were noted in Chan, Ngan Kee, or Loughrey et al. Neither Hall[12] nor Turkoz[13] commented on maternal nausea/vomiting. None of these trials were adequately powered to evaluate the effect of ephedrine on the incidence of intraoperative nausea and vomiting related to spinal anesthesia.

Heart rate

As an α- and β-adrenergic agonist, ephedrine has both chronotropic and inotropic activities. Ephedrine increases maternal heart rate.

Blood pressure

Ephedrine appears effective in restoring maternal hypotension to baseline, but reactive hypertension can occur, particularly when large doses (>20 mg boluses) of ephedrine are used.

3.1.2 Effects of ephedrine on the fetus/neonate

Ephedrine crosses the placenta[15] and increases fetal catecholamine concentrations.[16] Wright et al. demonstrated that intravenous ephedrine (dosed at 5 to 15 mg) administered to correct maternal hypotension associated with neuraxial anesthesia may increase fetal heart rate.[17]

Clinical trials conducted in uncomplicated pregnancies have shown statistically significant decrease of umbilical artery pH and base excess with ephedrine (when compared to phenylephrine).[8] However, clinical correlates for any potential effects on the neonates from the lower pH values are lacking. Cooper et al. showed that the lower fetal umbilical arterial pH associated with ephedrine (relative to phenylephrine) corresponded to a higher umbilical pCO2 value, likely due to relatively higher fetal metabolic rate with ephedrine. Furthermore, the reported umbilical artery pH values were above 7.0 (almost always above 7.2), far from meeting the criterion designated by the American College of Obstetricians and Gynecologists (ACOG) to define an acute intrapartum hypoxic event.[18]

3.2 Phenylephrine

Phenylephrine is a potent, rapidly acting vasopressor with a short duration of action. Survey data in the early 2000s suggested that phenylephrine was reserved as a second line vasopressor because of its predominant vasoconstrictive action and concerns over decreased uteroplacental perfusion.[6] A larger number of clinical trials have been

---

[15] Ward MG, Hughes SC, Shnider SM, et al. Placental transfer of ephedrine. Anesthesiol 1979;51(S3):S307.

[16] LaPorta RF, Arthur GR, Datta S. Phenylephrine in treating maternal hypotension caused by spinal anaesthesia for caesarean delivery: effects on neonatal catecholamine concentrations, acid base status and Apgar scores. Acta Anaesthesiol Scand 1995;39:901-905.

[17] Wright RG, Shnider SM, Levinson G, et al. The effect of maternal administration of ephedrine on fetal heart rate and variability. Obstet Gynecol 1981;57:734-738

[18] Umbilical cord blood gas and acid base analysis. ACOG Committee Opinion No. 348. American College of obstetricians and Gynecologists. Obstet Gynecol 2006;108:1319-22.

conducted to assess the use of phenylephrine in healthy parturients undergoing spinal anesthesia as a treatment for hypotension. These trials have used doses ranging from 40 to 100 mcg boluses. However, placebo-controlled and dose-response data are lacking.

(b) (4)

(b) (4)

1 Page Has Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

3.2.2 Effects of phenylephrine on the fetus/neonate

With the use of four different phenylephrine infusion rates in low-risk parturients (25, 50, 75, and 100 mcg/min), Allen et al. did not observe any differences among the groups with respect to: Apgar scores at 1 and 5 minutes, umbilical cord blood gases, incidence of fetal acidosis (umbilical artery pH < 7.2), and umbilical artery base excess.[20] These findings were consistent with those reported by Stewart et al., who compared phenylephrine infusion rates at 25, 50, and 100 mcg/min.[21]

3.3 Ephedrine vs. phenylephrine

A number of randomized, double-blind, controlled trials evaluated ephedrine and phenylephrine boluses in treating spinal anesthesia-induced maternal hypotension in healthy parturients. These trials are summarized below in Table 3. Phenylephrine was shown to be associated more frequently with maternal bradycardia (and decreased cardiac output in Dyer et al.[27]), but the overall maternal hemodynamic parameters were not appreciably different. With respect to neonatal outcomes, none of the trials suggested clinically significant differences with the two vasopressors, leading the authors to conclude that both ephedrine and phenylephrine boluses are suitable treatment for hypotension associated with spinal anesthesia. However, it should be noted that none of these trials appeared adequately powered for the detection of clinically meaningful outcomes.

Data regarding any comparison between continuous infusions of ephedrine and phenylephrine are not discussed because continuous infusion of ephedrine does not appear to be a common practice at the present time.

Table 3. Trials comparing ephedrine and phenylephrine boluses for the treatment of maternal hypotension

Trial	Treatment	N	Subjects
Pierce 1994[26]	E 5 mg vs. P 40 mcg	13:13	Elective cesarean section
LaPorta 1995[16]	E 5 mg vs. P 40 mcg	20:20	Elective cesarean section
Thomas 1996[23]	E 5 mg vs. P 100 mcg	19:19	Elective cesarean section
Ngan Kee 2008[11]	E 10 mg vs. P 100 mcg	102:102	Elective and non-elective (low risk) cesarean section
Dyer 2009[27]	E 10 mg vs. P 80 mcg	20:20	Elective cesarean section
Prakash 2010[28]	E 6 mg vs. P 100 mcg	30:30	Elective cesarean section

P: phenylephrine; E: ephedrine

Much attention was paid to a 2002 meta-analysis by Lee et al., which challenged the status of ephedrine as the preferred vasopressor for spinal anesthesia-induced hypotension.[88] This systemic review (including a total of 264 patients from seven randomized, controlled trials) comparing ephedrine and phenylephrine suggested that the two vasopressors have similar efficacy for management of spinal anesthesia-induced hypotension in low-risk parturients undergoing elective cesarean sections. The review also noted that maternal bradycardia was more likely to occur with phenylephrine than with ephedrine (relative risk, RR, of 4.79; 95% confidence interval, CI, 1.47-15.60), although the authors stated these bradycardic episodes had responded to atropine without adverse consequences. With respect to neonatal outcomes, the authors noted that women given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine (mean difference of 0.03; 95% CI, 0.16-3.92). Nevertheless, no difference in the incidence of fetal/neonatal adverse effects (umbilical arterial pH < 7.20 or Apgar score < 7) was noted between the two vasopressor groups.

In 2012, a larger meta-analysis, including 18 trials with a total of 1069 patients by Veeser et al.,[5] substantiated findings from the Lee review. However, it is important to note that the clinical trials included in these two meta-analyses are quite heterogeneous. Neither review differentiated among doses of anesthetics used or vasopressor doses and modes of administration by indication (treatment vs. prophylaxis of maternal hypotension). Duration of intra-operative assessment also varied (end of study described as the times of uterine incision, delivery, or 90 minutes after spinal anesthesia). The lack of such stratification may have confounded the findings. To date, there is no robust clinical trial evidence directly comparing the safety of ephedrine and phenylephrine in low-risk

[26] Pierce ET, Carr DB, Datta S. Effects of ephedrine and phenylephrine on maternal and fetal atrial natriuretic peptide levels during elective cesarean section. Acta Anaesthesiol Scand 1994;38:48-51.
[27] Dyer RA, Reed AR, van Dyk D, et al. Hemodynamic effects of ephedrine, phenhylephrine, and the coadministration of phenylephrine with oxitocina Turing spinal anesthesia for elective cesarean delivery. Anesthesiol 2009;111:753-65.
[28] Prakash S, Pramanik V, Chellani H, et al. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anaesthesia for caesarean delivery: a randomized study. Int J Obstet Anesth 2010;19:24-30.

parturients (i.e., healthy women with uncomplicated pregnancies and presenting for delivery at term).

For high-risk pregnancies (i.e., in women who are not low-risk parturients), a prospective study of pregnancies at term[29] and a retrospective study[30] (which included both term and preterm deliveries) found no differences in fetal umbilical artery pH or Apgar scores between ephedrine and phenylephrine.

4. Questions from DAAAP and DBRUP Responses

1. **Is there a maternal, fetal, or neonatal safety concern for either pressor agent when used in the treatment of maternal hypotension during C-sections or vaginal deliveries?**

DBRUP Response:

- In low-risk parturients, ephedrine may be associated with increased fetal heart rate and increased fetal metabolic rate. While some literature has suggested that the use of ephedrine may be associated with lower fetal umbilical artery pH values (relative to phenylephrine), the reported pH values remain above the threshold indicating neonatal depression (pH of 7.0). In low-risk parturients, identified risks for phenylephrine include decreased maternal heart rate and cardiac output.

  When ephedrine and phenylephrine are used for treatment of maternal hypotension, reactive hypertension may occur, particularly with larger doses (e.g., $\geq$ 20 mg ephedrine bolus infusion). Although these reactive hypertensive episodes are usually manageable, they can result in severe maternal hypertension and tachycardia. The literature also suggests that boluses of ephedrine or phenylephrine are less likely to result in inadvertent over-infusion. Therefore, for low risk parturients, boluses of these pressor agents have an acceptable risk/benefit ratio and may be preferable than continuous intravenous infusions.

- Data on the use of either pressor agent in high-risk pregnancies are limited; therefore, we cannot provide an opinion for this population.

2. **Is there a clinically relevant difference in the maternal, fetal, or neonatal outcomes for either pressor agent when used in the treatment of maternal hypotension during C-sections or vaginal deliveries?**

[29] Ngan Kee WD, Khaw KS, Lau TK, et al. Randomised double-blinded comparison of phenylephrine and vs ephedrine for maintaining blood pressure during spinal anaesthesia for non-elective caesarean section. Anaesthesia 2008;63:1319-1926.
[30] Cooper DW, Sharma S, Orakkan P, et al. Retrospective study of association between choice of vasopressor given during spinal anaesthesia for high-risk caesarean delivery and fetal pH. Int J Obstet Anesth 2010;19:44-49.

DBRUP Response:

In the population of low-risk parturients, available data do not suggest any clinically relevant differences in either maternal or neonatal outcomes for either pressor agent when used to treat maternal hypotension in low-risk parturients. Specifically, none of the trials reviewed for this consult have shown clinically significant differences in short-term (based on either Apgar scores or umbilical artery pH) or long term neonatal outcomes.

In the population of high-risk parturients, there are limited data on the use of either pressor agent to provide an opinion as to whether there is a clinically relevant difference in either maternal or fetal risk between products.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINA Y CHANG
01/30/2014
Signing also for Dr. Barbara Wesley who conducted the primary review

AUDREY L GASSMAN
01/30/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Application: NDA 204300

Application Type: New NDA

Name of Drug: Vazculep (phenylephrine HCl) Injection

Applicant: Eclat Pharmaceuticals, Inc

Submission Date: 6/28/13

Receipt Date: 6/28/13

1.0 Regulatory History and Applicant's Main Proposals

The NDA proposes the indication of treatment (b) (4) of hypotension during anesthesia. This application was refused to file with its original submission, and has now been accepted for filing upon resbumission. The Sponsor seeks approval under 505(b)(2) based on information in the literature. They have not performed any clinical studies with their product. There is another approved phenylephrine HCl injection product (from West Ward Pharmaceuticals) that is indicated for the treatment (only) of hypotension in approved settings.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by September 24, 2013. The resubmitted PI will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

NO 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

N/A 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

N/A 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES

21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION”**

If a product **has** FDA-approved patient labeling:

- **“See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.”**
- **“See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.”**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY** or **Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

NO 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

N/A 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

N/A 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

N/A 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Patient Counseling Information

N/A 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
09/06/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204300 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD (proposed Vazculep) Established/Proper Name: Phenylephrine Hydrochloride Dosage Form: Injection Strengths: 1%		
Applicant: Eclat Pharmaceuticals, Inc. Agent for Applicant (if applicable): The Weinberg Group		
Date of Application: 6/28/13 Date of Receipt: 6/28/13 Date clock started after UN: N/A		
PDUFA Goal Date: 4/28/14	Action Goal Date (if different):	
Filing Date: 8/27/13	Date of Filing Meeting: 8/6/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment (b) (4) of hypotension during anesthesia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☒
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		No, this NDA has 2 additional presentations (larger vial sizes) so ORP specifies this makes it suitable to be a B2 instead of an ANDA.
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-

year exclusivity may block the approval but not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			Form was submitted in original filing and has been referenced in resubmission.
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			Forms were submitted in original filing and have been referenced in resubmission.
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			There were no clinical studies conducted with this product.
Debarment Certification	**YES**	**NO**	**NA**	**Comment**

Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			Form was submitted in original filing and has been referenced in resubmission.
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 9/27/12 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: 8/6/13

NDA #: 204300

PROPRIETARY NAME: Phenylephrine HCL Injection 1%, USP

ESTABLISHED/PROPER NAME: Phenylephrine HCL Injection 1%, USP

DOSAGE FORM/STRENGTH: Injection, 1%

APPLICANT: Eclat Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment (b) (4) of hypotension during anesthesia

BACKGROUND: The firm proposes to rely solely on published literature for this B2 application. They do not intend to rely on the Agency's finding of safety and efficacy for the only approved FDA phenylephrine HCl Injection 1% (West-Ward).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton	Y
	CPMS/TL:	Matt Sullivan (Acting)	N
Cross-Discipline Team Leader (CDTL)	Chris Breder		Y
Clinical	Reviewer:	Tim Jiang	Y
	TL:	Chris Breder	Y
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	No Stats/no rvwr assigned	
	TL:	Janice Derr	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	N
	TL:	Dan Mellon	Y

Statistics (carcinogenicity)	Reviewer:		n/a
	TL:		
Product Quality (CMC)	Reviewer:	Eugenia Nashed	Y
	TL:	Olen Stephens	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	Y
	TL:		
CMC Labeling Review	Reviewer:		n/a
	TL:		
Facility Review/Inspection	Reviewer:	TBD	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Aleksander Winiarski	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	• ONDQA Biopharm: Elsbeth Chikale (Y) • OC/OUDLC/Reg Counsel: Kathleen Joyce (Y) • OSE PM: Vaishali Jarral (N)		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**: **Firm has revised application accordingly from original submission and it is now acceptable to file.**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO

If no, for an NME NDA or original BLA , include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment (b)(4) prevention of a disease***	☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? (The applicant is claiming a categorical exclusion from requirement to prepare an environmental assessment as under 21 CFR 25.31(b)) **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Not discussed since NDA was not filed. Will need to be revisited if application is resubmitted.	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Will likely be Bob, if he is away, Rigo can sign, but will be Division level sign off. **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V):	

21st Century Review Milestones (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at:

	http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
09/06/2013

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 204300 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD (proposed Vazculep) Established/Proper Name: Phenylephrine Hydrochloride Dosage Form: Injection Strengths: 1%		
Applicant: Eclat Pharmaceuticals, Inc. Agent for Applicant (if applicable): The Weinberg Group		
Date of Application: 2/8/13 Date of Receipt: 2/8/13 Date clock started after UN: N/A		
PDUFA Goal Date: 12/8/13 (Sunday)	Action Goal Date (if different): 12/6/13	
Filing Date: 4/8/13	Date of Filing Meeting: 3/26/13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Treatment (b) (4) of hypotension during anesthesia		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***				
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		No, this NDA has 2 additional presentations (larger vial sizes) so ORP specifies this makes it suitable to be a B2 instead of an ANDA.
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-

year exclusivity may block the approval but not the submission of a 505(b)(2) application.				
Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).		**X**		**Per clinical review, the application does**

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

				not contain adequately constructed ISS and ISE, nor does it separate its discussion of the two proposed indications.
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**

Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:			**X**	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2]	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***				
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]				
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?		X		Application not filed
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***			X	Application not filed
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** 9/27/12 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

ATTACHMENT

MEMO OF FILING MEETING

DATE: 3/26/13

NDA #: 204300

PROPRIETARY NAME: Phenylephrine HCL Injection 1%, USP

ESTABLISHED/PROPER NAME: Phenylephrine HCL Injection 1%, USP

DOSAGE FORM/STRENGTH: Injection, 1%

APPLICANT: Eclat Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment (b) (4) of hypotension during anesthesia

BACKGROUND: The firm proposes to rely solely on published literature for this B2 application. They do not intend to rely on the Agency's finding of safety and efficacy for the only approved FDA phenylephrine HCl Injection 1% (West-Ward).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Kim Compton	Y
	CPMS/TL:	Matt Sullivan (Acting)	N
Cross-Discipline Team Leader (CDTL)			
Clinical	Reviewer:	Tim Jiang	Y
	TL:	Chris Breder	Y
Clinical Pharmacology	Reviewer:	David Lee	Y
	TL:	Yun Xu	Y
Biostatistics	Reviewer:	Feng Li	N
	TL:	Dionne Price	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Marcus Delatte	Y
	TL:	Dan Mellon	Y

Statistics (carcinogenicity)	Reviewer:		n/a
	TL:		
Product Quality (CMC)	Reviewer:	Yong Hu	Y
	TL:	Olen Stephens	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Langille	N
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Jung Lee	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	• ONDQA biopharm: Elsbeth Chikale • OC/OUDLC/MO: Charles Lee • OC/OUDLC/Reg Counsel: Kathleen Joyce • ORP: Nisha Shah • OSE PM: Teena Thomas		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**: **the application does not contain adequately constructed ISS and ISE, nor does it separate its discussion of the two proposed indications.**	☐ Not Applicable ☐ FILE ☒ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☒ NO

• Advisory Committee Meeting needed? **Comments**: Since NDA not filed, the need for an AC was not discussed. Will need to be revisited if NDA is resubmitted. ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: Not discussed since NDA was not filed. Will need to be revisited if application is resubmitted.	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
<u>CMC Labeling Review</u> **Comments**:	☐ Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Not discussed since NDA was not filed. Will need to be revisited if application is resubmitted.	

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): Not discussed since NDA was not filed. Will need to be revisited if application is resubmitted

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: N/A since NDA was not filed. Will need to be revisited if application is resubmitted

	REGULATORY CONCLUSIONS/DEFICIENCIES
☒	The application is unsuitable for filing. Explain why: **the application does not contain adequately constructed ISS and ISE, nor does it separate its discussion of the two proposed indications.**
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☐ Priority Review
	ACTIONS ITEMS
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY A COMPTON
04/09/2013