CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204300Orig1s000

Trade Name: VAZCULEP (Phenylephrine HCl Injection, USP)

Generic Name: Phenylephrine Hydrochloride

Sponsor: **Eclat Pharmaceuticals**

Approval Date: June 27, 2014

Indications:

- For the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204300Orig1s000

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204300/Original 1

NDA APPROVAL

Éclat Pharmaceuticals
c/o The Weinberg Group, Inc.
1129 Twentieth St., NW, Suite 600
Washington, DC 20036

Attention: Marla E. Scarola, MS
Senior Consultant, The Weinberg Group, Inc.

Dear Ms. Scarola:

Please refer to your New Drug Application (NDA) dated and received February 8, 2013, which was refused to file on April 5, 2013, and resubmitted June 28, 2013, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL.

We acknowledge receipt of your amendments dated February 11, and 26, March 20, June 28, July 1 and 8, September 18, October 25, December 20, and 23, 2013, January 6 and 14, February 11, 12, and 13, March 7, 11, 24, 26, and 31, and April 10, 16, and 21, June 6 and 11, 2014.

The June 6, 2014, submission constituted a complete response to our April 28, 2014, action letter.

This new drug application provides for the use of VAZCULEP (phenylephrine hydrochloride) Injection, 10 mg/mL for the treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs*

and As, available at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, submitted on March 22, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204300**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Kim Compton
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3168
10903 New Hampshire Avenue
Silver Spring, MD
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 12 years because necessary studies are impossible or highly impracticable. Although pediatric patients from birth

to less than12 years receive neuraxial anesthesia, they tend not to develop clinically significant hypotension as a result of anesthetic-induced vasodilatation. In addition, the cardiac output of younger pediatric patients is heart rate-dependent, and administration of an alpha-1-receptor agonist could cause a reflex bradycardia. Consequently, phenylephrine is used in very limited circumstance in children less than 12 years of age.

We are deferring submission of your pediatric study for ages greater than or equal to 12 years of age to less than 17 years for this application because this product is ready for approval for use in adults, and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the FDCA 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 FDCA. This required study is listed below.

2168-1 A study in the greater than or equal to 12- to less than 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.

The timetable you submitted June 11, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	8/2015
Study Completion:	8/2018
Final Report Submission:	2/2019

Submit the protocol to your IND 113044, with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of reproductive and developmental or genotoxic potential.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to identify these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2168-2 Conduct a fertility and early embryonic development toxicology study in the rat model for phenylephrine hydrochloride.

The timetable you submitted on June 11, 2014, states that you will conduct this study according to the following schedule:

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

2168-3 Conduct an embryo-fetal developmental toxicology study using the rat model for phenylephrine hydrochloride.

The timetable you submitted on June 11, 2014, states that you will conduct this study according to the following schedule:

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

2168-4 Conduct an embryo-fetal developmental toxicology study using the rabbit model for phenylephrine hydrochloride.

The timetable you submitted on June 11, 2014, states that you will conduct this study according to the following schedule:

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

2168-5 Conduct a peri- and post-natal developmental toxicology study in the rat model for phenylephrine hydrochloride.

The timetable you submitted on June 11, 2014, states that you will conduct this study according to the following schedule:

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

Submit clinical protocols to your IND 113044 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2168-6 Submission of data and shelf-life acceptance criteria for the content of sodium metabisulfite in drug product.

The timetable you submitted on March 24, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	4/2015
Study Completion:	7/2016
Final Report Submission:	10/2016

2168-7 Submission of data and data-based release acceptance criteria for the content of sodium metabisulfite in drug product.

The timetable you submitted on March 24, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 8/2014
Study Completion: 2/2015
Final Report Submission: 3/2015

2168-8 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.

The timetable you submitted on March 11, 2014, states that you will conduct this study according to the following schedule:

Initial Report Submission: 4/2015
Interim Report Submission: 12/2015
Final Report Submission: 12/ 2016

2168-9 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.

The timetable you submitted on March 11, 2014, states that you will conduct this study according to the following schedule:

Initial Report Submission: 4/2015
Interim Report Submission: 12/2015
Final Report Submission: 12/2016

Submit clinical protocols to your IND 113044 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kimberly Compton, RPh, Sr. Regulatory Project Manager, at (301) 796-1191.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, MD
Deputy Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Carton and Container Labeling

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

/s/

RIGOBERTO A ROCA
06/27/2014