CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203826Orig1s000

Trade Name: Phenylephrine Hydrochloride

Generic Name: Phenylephrine Hydrochloride

Sponsor: West-Ward Pharmaceutical Corporation

Approval Date: December 20, 2012

Indications: For increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or anesthesia.

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203826

NDA APPROVAL

West-Ward Pharmaceutical Corp.
Attention: Mr. J. Barton Kalis
Director, Regulatory Affairs
2 Esterbrook Lane
Cherry Hill, NJ 08003

Dear Mr. Kalis:

Please refer to your New Drug Application (NDA) dated December 28, 2011, received January 12, 2012 (user fee receipt date), submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Phenylephrine Hydrochloride Injection, 10 mg/mL.

We acknowledge receipt of your amendments dated March 1, April 24 and 27, May 21, July 18, September 28, October 11,16, 23, 25, 26, November 6 (two) and 29, and December 13 and 19, 2012.

The November 29, 2012 submission constituted a complete response to our November 9, 2012 action letter.

This new drug application provides for the use of Phenylephrine Hydrochloride Injection, 10 mg/mL, for increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation, in such settings as septic shock or 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). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" 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 container labels that are identical to the enclosed carton and immediate container labels submitted on October 23, 2012, 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 titled "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 203826**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product 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:

Quynh Nguyen, Pharm.D., RAC
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4119
10903 New Hampshire Avenue
Silver Spring, Maryland
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)*

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. (See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

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 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 anesthestic-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.

We are deferring submission of your pediatric study for ages ≥12 to 16 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

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

Submit the protocol(s) to your IND, 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1991-2 The package insert provides dosing for intravenous bolus ranging from 40 mcg to 250 mcg. Currently, only a single concentration of 10 mg/mL is approved. In order to achieve doses as small as 40 mcg to 250 mcg, one or more dilutions would need to be performed by a pharmacist or technician, which introduces opportunity for calculation and compounding confusion that can lead to dosing errors. For this reason, we request that you develop an appropriate ready-to-use concentration and packaging configuration to administer the approved intravenous bolus doses. A ready-to-use concentration and packaging configuration will help mitigate the risks of calculation and compounding errors as well as unsafe sterile technique and injection practices. In order to guide the development of an appropriate ready-to-use product for intravenous bolus administration, an appropriate methodology such as a risk assessment, utilizing a recognized risk assessment tool (e.g., Failure Mode and Effects Analysis), should be conducted by a multidisciplinary team. Based on your study results, we request you submit a prior approval supplement to support the approval of a ready-to-use formulation and concentration of phenylephrine hydrochloride appropriate for intravenous bolus administration.

The timetable you submitted on November 6, 2012 states that you will conduct this study according to the following schedule:

Final Report Date:	August 12, 2013
Prior Approval Supplement Submission Date:	June 30, 2014

Submit clinical protocols to your IND for this product and all study 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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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, please contact:

Quynh Nguyen, Pharm.D., RAC
Regulatory Health Project Manager
(301) 796-0510

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
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/

NORMAN L STOCKBRIDGE
12/20/2012