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APPLICATION NUMBER:

203826Orig1s000

OTHER ACTION LETTERS



NDA 203826

COMPLETE RESPONSE

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, and 26, and November 6 (two), 2012.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

We believe that additional data in pediatric patients are required. These data may be obtained post-approval as part of a Postmarketing Requirement (PMR) in which you commit to conduct a pediatric study. We would need to reach agreement on this PMR before the application is approved.

The following describes the pediatric study that we propose:

Conduct a study 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 information you capture needs to include, at a minimum, the following:

- 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.

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.

Below are our suggested numbers and timelines:

50 subjects in bolus treatment group / 50 subjects in infusion treatment group

Final Protocol Submission: 1 year from approval

Study/Trial Completion: 3.5 years from approval (total duration of study = 2.5 years)

Final Report Submission: 4 years from approval (total duration of report generation = 0.5 years)

Please refer to the *Guidance for Industry: How to Comply with the Pediatric Research Equity (September 2005)*.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

ENCLOSURE:
Draft Labeling

7 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/

NORMAN L STOCKBRIDGE
11/09/2012