CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203202Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203202

COMPLETE RESPONSE

Chelsea Therapeutics, Inc.
Attention: Rex Horton
Director of Regulatory Affairs
3530 Toringdon Way, Suite 200
Charlotte, NC 28277

Dear Mr. Horton:

Please refer to your New Drug Application (NDA) dated September 23, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for NORTHERA (droxidopa) 100 mg, 200 mg and 300 mg Capsules.

We acknowledge receipt of your amendments dated October 7, 25, 27, November 4, 7, 8, 10, 16, 22, December 8, 9, 16, 19, 23, 2011 and January 3, 9, 30, 31, February 6, 19, 14, 16, March 2, 6, 8, 12, and 16, 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/ STATISTICAL

You submitted the results of 3 clinical trials (studies 301, 302, and 303) to support the efficacy of droxidopa for the treatment of neurogenic orthostatic hypotension (NOH). Study 302 was conducted first and was a negative study, based on the primary endpoint as originally planned, Item 1 of the Orthostatic Hypotension Symptoms Assessment (OHSA). Exploratory analyses showed positive results on the composite Orthostatic Hypotension Questionnaire (OHQ) endpoint, generating a new hypothesis, i.e., that droxidopa improves the composite OHQ score in patients with NOH. Accordingly, the primary endpoint of study 301 was changed to the composite OHQ score. The results of study 301 were positive. Study 303, a randomized withdrawal study, was not positive. On its face, therefore, the NDA includes one positive study: study 301.

During development, the Division stressed the importance of providing evidence for the durability of droxidopa's effect; however, the study with the best potential to show this, study 303, a randomized withdrawal study, did not succeed. Similarly, study 302, also a randomized withdrawal study, did not support durability of treatment effect. Thus, none of the submitted studies show durability of effect beyond one week.

As noted in FDA guidance,[1] a single, large, multicenter, adequate and well-controlled study can provide evidence of effectiveness under certain circumstances. Generally, reliance on only a single study is limited to situations where a drug prevents mortality or irreversible morbidity, but the Guidance leaves open the possibility of reliance on a single study for treatment effects of lesser importance.

NOH is a rare condition, associated with debilitating symptoms in some individuals. There are few treatment options, and additional therapies are needed. For these reasons, we considered the possibility of approving droxidopa on the basis of study 301, a single adequate and well-controlled study.

Study 301 has many of the characteristics of a single adequate and well-controlled study that could make it adequate to support effectiveness. In the setting of NOH, a rare condition, the study is reasonably sized and it is multi-centered. The finding on the primary endpoint is statistically persuasive. There is reasonable consistency across demographic and disease-specific subgroups, although treatment effects in women, older patients, US patients, and patients with underlying Parkinson's disease were not impressive, despite those subgroups being numerically well-represented in the study. A positive effect on standing systolic BP, a direct drug effect that presumably could lead to symptomatic improvement, increases the weight of evidence.

When considering whether to rely on a single adequate and well-controlled trial, our Guidance[1] tells us to consider critically the possibility of a false positive result, in part by examining all the available data. Here the results of studies 302 and 303 undercut the persuasiveness of study 301. Despite the enrichment strategy used in studies 302 and 303 to select subjects who both respond to and tolerate the drug, neither study succeeded on its primary endpoint. *Inconsistencies in the overall findings, therefore, constitute a reasonable basis for not accepting study 301 alone as adequate evidence of effectiveness.*

Our Guidance[1] also explains that for a single study to support effectiveness, "(1) no single study site…(should provide)…an unusually large fraction of the patients and (2) no single investigator or site…(should be)….disproportionately responsible for the favorable effect seen….If the analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished." In examining the results of study 301, Site 507 was disproportionately responsible for the overall treatment effect: Site 507 contributed only 10% of the subjects, but the results there were strikingly positive and provided much of the overall effect size. Specifically, the p-value for the primary efficacy endpoint of the study as a whole was persuasive (0.003), yet the results are no longer statistically significant when subjects from Site 507 are removed from the analysis. *The disproportionate contribution of Site 507 to the overall results of study 301 diminishes the persuasiveness of the study, providing an even stronger reason for not accepting study 301, the sole positive study, as adequate evidence of effectiveness.*

Prior to submission of the NDA, we advised you that it would be important to provide evidence of durability of droxidopa's treatment effect. This advice has not changed, and the issue has not been addressed adequately in your development program.

[1] Guidance for Industry: "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" May, 1998.

Thus, an additional positive study will be needed to support efficacy. Given the need to provide evidence of durability of effect, we suggest a study designed to demonstrate durability of effect over a 2- to 3-month period. We also recommend that you consult with the Agency on the specific study design elements, including endpoint measures, to be used in future trials.

Finally, we note that true supine hypertension was not assessed in your studies; subjects were advised to keep their head and torso raised by 30 degrees. Lacking data on supine blood pressure, if the drug were to be approved at this time, labeling would likely have to include a boxed warning regarding supine hypertension. If, on the other hand, you were to assess true supine BP, and the results in a reasonable number of subjects did not show severe hypertension, the need for a boxed warning could be reconsidered.

LABELING

We have provided draft recommendations to several sections of the labeling, but reserve comment on the remaining sections until the application is otherwise adequate. Please submit draft labeling that incorporates revisions to the attached labeling.

Your response must include 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.

Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "**ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide.**"

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

We acknowledge receipt of your submission dated September 28, 2011 of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for droxidopa to ensure that its benefits outweigh its risks. Once the complete response (CR) is submitted, we will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PRODUCT QUALITY

Since the primary drug product stability batches did not meet the recommended batch size criteria as per ICH Q1A (R2), include available stability data for batches manufactured at pilot or commercial scale representing the commercial process and container/closure system for all three strengths.

CLINICAL PHARMACOLOGY

The Office of Scientific Investigations (OSI) performed clinical and bioanalytical site inspections for pivotal bioequivalence (BE) study 101 and concluded that the bioanalytical part of the pivotal BE evaluation between 3 x 100 mg capsules (phase III formulation) and

1 x 300 mg capsules (proposed new formulation) is not reliable. Therefore, the BE results from this study are not acceptable. You will need another BE study, preferably comparing 1 x 300 mg capsules (proposed new strength) and 1 x 100 mg + 1 x 200 mg capsules (as used in the phase III program), if you wish to pursue the approval of 300 mg formulation.

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.

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.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Acting Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

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

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

/s/

ELLIS F UNGER
03/28/2012