CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203202Orig1s000

Trade Name: Northera

Generic Name: Droxidopa

Sponsor: Chelsea Therapeutics Inc.

Approval Date: February 18, 2014

Indications: Treatment of Orthostatic Dizziness, Lightheadedness, or the "Feeling that You are About to Black Out" in Adult Patients with Symptomatic Neurogenic Orthostatic Hypotension Caused by Primary Autonomic Failure (Parkinson's Disease, Multiple System Atrophy, and pure Autonomic Failure), Dopamine Beta-Hydroxylase Deficiency, and Non-Diabetic Autonomic Neuropathy.

Effectiveness Beyond 2 Weeks of Treatment has Not Been Demonstrated. The Continued Effectiveness of Northera Should be Assessed Periodically.

CENTER FOR DRUG EVALUATION AND RESEARCH

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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 203202

ACCELERATED APPROVAL

Chelsea Therapeutics Inc.
Attention: Mr. Joseph Oliveto
President and CEO
3530 Toringdon Way, Suite 200
Charlotte, NC 28277

Dear Mr. Oliveto:

Please refer to your New Drug Application (NDA) originally submitted September 23, 2011, and resubmitted August 13, 2013 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NORTHERA (droxidopa) 100 mg, 200 mg, and 300 mg capsules.

We acknowledge receipt of your amendments dated August 13, 28, September 5, October 15, 17, 29, November 13, December 3, 12, 18, 27, 2013 and January 6, February 4, 5 (two), 6 and 10, 2014. The August 13, 2013, submission constituted a complete response to our March 28, 2012, action letter.

This new drug application provides for the use of NORTHERA (droxidopa) 100 mg, 200 mg, and 300 mg capsules for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of NORTHERA should be assessed periodically.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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, 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 203202**." 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.

PRODUCT QUALITY

A 48 month expiration period is granted for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, packaged in HDPE bottles; a 12 month expiration period is granted for 300 mg capsules packaged in HDPE bottles. An expiration period of 36 months is granted for 100 mg and 200 mg Northera capsules packaged in aluminum foil blister packs.

MARKET PACKAGE

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

Anna Park
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4156
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).*

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your email submission dated February 14, 2014. The timetable you submitted in your email, dated February 14, 2014, states that you will conduct this trial according to the following schedule. This requirement, along with required completion dates, is listed below.

2129-1 A clinical trial of patients with symptomatic neurogenic orthostatic hypotension to assess sustained effects of droxidopa therapy. The trial design consists of a 3 month open-label droxidopa treatment period, followed by a 4-week, randomized, double-blind, placebo-controlled, withdrawal period. The trial will enroll an adequate number of patients to give 80% power to rule out a treatment effect of 0.45 if the true effect is 0. The primary endpoint will be the mean change in ambulatory Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 from randomization to Week 4 of the randomized withdrawal period.

Draft Protocol Submission:	28 March 2014
Final Protocol Submission:	30 May 2014
Total 25% patients First Visit Complete	30 December 2016
Total 50% patients First Visit Complete	29 December 2017
Total 100% of Patients First Visit Complete	28 August 2020
Trial Completion:	31 December 2020
Interim Report Submission (to include topline data of primary and secondary analyses):	26 February 2021
Final Report (as a supplemental application) Submission:	30 April 2021

Submit clinical protocols to your IND 077248 for this product. Submit interim reports to this NDA, and the final report to this NDA as a supplemental application. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of this requirement 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. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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.

Because this drug product for this indication has an orphan designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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.
Director
Office of Drug Evaluation I
Office of New Drugs
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/

ELLIS F UNGER
02/18/2014