DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203202/S-006

SUPPLEMENT APPROVAL

Lundbeck NA Ltd.
Attention: Michael Bouchon
Manager, US Regulatory Strategy
Six Parkway North, Suite 400
Deerfield, IL 60015

Dear Mr. Bouchon:

Please refer to your Supplemental New Drug Application (sNDA) dated and received April 1, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Northera (droxidopa) 100 mg, 200 mg, and 300 mg Capsules.

We also acknowledge your amendments dated May 18, and May 31, 2016.

This supplemental new drug application provides for labeling revised as follows (additions are shown as underlined text and deletions are shown as strikethrough text):

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following text was added:

----------RECENT MAJOR CHANGES----------	
Contraindications (4)	09/2016
Warnings and Precautions, Hyperpyrexia and Confusion (5.2)	09/2016
Warnings and Precautions, Allergic Reactions (5.4)	09/2016

2. In **HIGHLIGHTS/ADVERSE REACTIONS**, the following text was added/deleted:

   The most common adverse reactions (> 5% and > 3% compared to placebo) are headache, dizziness, nausea, and hypertension ~~and fatigue (greater than 5%)~~ (6.1)

3. In **HIGHLIGHTS/USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

   - Lactation: Breastfeeding not recommended (8.2)
   - ~~Nursing Mothers: Choose nursing or NORTHERA (8.3)~~

4. Under **CONTRAINDICATIONS**, the following text was added/deleted:

   NORTHERA is contraindicated in patients who have a history of hypersensitivity to the drug or its ingredients *[see Warnings and Precautions (5.4)]*. ~~None.~~

5. Under **WARNINGS AND PRECAUTIONS/Hyperpyrexia and Confusion**, the following text was deleted from the first sentence in the first paragraph:

~~In Japan~~

6. Under **WARNINGS AND PRECAUTIONS/Allergic Reactions,** the following text was added as the first paragraph:

   Hypersensitivity reactions including anaphylaxis, angioedema, bronchospasm, urticaria and rash have been reported in postmarketing experience. Some of these reactions resulted in emergency treatment. If a hypersensitivity reaction occurs, discontinue the drug and initiate appropriate therapy.

7. Under **ADVERSE REACTIONS**, the following section was added:

   6.2 Post Marketing Experience

   The following adverse reactions have been identified during post-approval use of NORTHERA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

   Cardiac Disorders: Chest pain
   Eye Disorders: Blurred vision

   Gastrointestinal Disorders: Pancreatitis, abdominal pain, vomiting, diarrhea

   General Disorders and Administration Site Conditions: Fatigue

   Psychiatric Disorders: Psychosis, hallucination, delirium, agitation, memory disorder

8. Under **DRUG INTERACTIONS,** a new section was added:

   7.3 Non-selective MAO Inhibitors
   The concomitant use of selective MAO-B inhibitors, such as rasagiline or selegiline, was permitted in the NORTHERA clinical trials. However, based on mechanism of action, the use of non-selective MAO inhibitors and linezolid should be avoided as there is a potential for increased blood pressure when taken with NORTHERA.

9. Under **USE IN SPECIFIC POPULATIONS**, the following text was added/deleted:

   8.1 Pregnancy

   ~~***Pregnancy Category C***~~
   ~~There are no adequate and well-controlled trials in pregnant women.~~

   ~~Following consecutive oral administration at doses of 60, 200, and 600 mg/kg/day to pregnant Sprague-Dawley rats, increased incidences of lower body weight and occurrence of undulant rib were noted in fetuses, but they were slight and spontaneously reversed after birth. Based on dose per unit body surface area, these three doses correspond to approximately 0.3, 1, and 3 times, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient. Shortening of the gestation period was observed in rats at 600 mg/kg/day. Low incidences of renal lesions (cysts, indentations, or renal pelvic dilation) were observed on the surface of the kidneys of female rats treated with~~

~~droxidopa during the period of fetal organogenesis. No other potentially teratogenic effects have been observed in rats or rabbits.~~

Risk Summary
There are no available data on use of NORTHERA in pregnant women and risk of major birth defects or miscarriage. NORTHERA did not produce significant reproductive toxicity in pregnant female rats or rabbits or in their fetuses. However, when pregnant female rats were dosed during days 7-17 of gestation (the period of fetal organogenesis) with doses of NORTHERA corresponding to 0.3, 1 and 3 times the maximum recommended daily dose of 1,800 mg in a 60 kg patient, based on body surface area, and when their male and female offspring (who were exposed only during fetal life) were subsequently bred, the female offspring exhibited a dose-dependent reduction in the number of live fetuses across all three doses and an increased number of embryonic/fetal deaths at the two higher doses (*see Data*).

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data
Animal Data
During a multigenerational reproductive toxicity study in rats, pregnant females were dosed during days 7-17 of gestation (the period of fetal organogenesis) with doses of NORTHERA corresponding to 0.3, 1 and 3 times the maximum recommended daily dose of 1,800 mg in a 60 kg patient. Reduced weight gain, renal lesions, and a small number of deaths were observed in females treated with the two higher doses. When their male and female offspring (who were exposed to NORTHERA only during fetal life) were subsequently bred, the female offspring exhibited a dose-dependent reduction in the number of live fetuses across all three doses and an increased number of embryonic/fetal deaths at the two higher doses.

8.2 Lactation

Risk Summary
There is no information regarding the presence of NORTHERA or its active metabolite(s) in human milk, the effects of NORTHERA on the breastfed child, nor the effects of NORTHERA on milk production/excretion. Droxidopa is present in rat milk with peak concentrations seen 4 hours after oral drug administration and drug excretion into milk still occurring 48 hours after administration (*see Data*). However, due to species-specific differences in lactation physiology, animal lactation data typically do not reliably predict levels in humans. Because of the potential for serious adverse reactions, including reduced weight gain in breastfed infants, advise a woman not to breastfeed during treatment with NORTHERA.

Data
Animal Data
In rats, oral administration of droxidopa resulted in excretion into breast milk with peak concentrations seen 4 hours after administration, and excretion still occurring 48 hours after administration. When the drug was administered to nursing dams during the period

of lactation at a dose corresponding to 3 times the maximum recommended daily dose of 1,800 mg in a 60 kg patient when based on body surface area, reduced weight gain and reduced survival were observed in the offspring. Despite the observed decreased weight gain physical development was normal (with respect to timing and organ morphology).

10. Under **OVERDOSAGE**, the following text was added/deleted:

10.1 Symptoms

There ~~was one~~ have been cases of overdose reported during post-marketing surveillance ~~in Japan~~. A patient ingested 7,700 mg of ~~NORTHERA~~droxidopa and experienced a hypertensive crisis that resolved promptly with treatment. Another patient treated with a total daily dose of 2,700 mg of NORTHERA experienced hypertension and an intra-cranial hemorrhage.

11. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added:

Elimination
The total clearance of droxidopa after oral administration (CL/F) was approximately 400 mL/hr following administration of a single 300 mg dose.

12. Under **CLINICAL PHARMACOLOGY**, the following section was revised:

13.2 Animal Toxicology and/or Pharmacology
In long-term chronic toxicity studies, ~~R~~rats and mice treated for 52 and 80 weeks, respectively, at doses up to 300 mg/kg/day in rats and 1,000 mg/kg/day in mice had increased incidences of renal and cardiac lesions (rats and mice) and deaths (rats only). The doses at which these effects were not seen represented 0.2 and 0.3- times, in rats and mice, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient, when based on body surface area.

~~similar to human doses (100 to 300 mg/kg/day for rats and 300 to 1,000 mg/kg/day for mice) had increased incidences of renal and cardiac lesions (rats and mice) and deaths (rats only)~~. No signs of toxicity were observed in monkeys or dogs given droxidopa for 13 weeks at doses 32 times (3,000 mg/kg/day) and 37 times (2,000 mg/kg/day), respectively, the maximum human dose~~recommended total daily dose of 1,800 mg in a 60 kg patient, when based on body surface area.~~

13. Under **PATIENT COUNSELING INFORMATION**, the following section was added:

Allergic Reactions
Counsel patients to discontinue NORTHERA and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction such as anaphylaxis, angioedema, bronchospasm, urticaria or rash occur *[see Warnings and Precautions (5.4)]*.

Lactation
Advise women not to breastfeed during treatment with NORTHERA *[see Use in Specific Populations (8.2)]*.

14. There are numerous editorial revisions made throughout the label.

15. The manufacturing information, the revision date and version number were updated.

There are no other changes from the last approved package insert.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended, and 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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry

(available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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 call:

Lori Anne Wachter, RN, BSN, RAC
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
10/03/2016