GETTING YOUR PATIENT STARTED ON NORTHERA® (droxidopa)

Northera® (droxidopa) capsules 100 mg • 200 mg • 300 mg

Sample Treatment Form instructions

The following pages are designed to help you understand how to properly complete the NORTHERA Treatment Form for your patients—including required fields, titration information, and signature approvals—and how to submit the form to the Northera Support Center (NSC).

- The sample form illustrates the fields that are required (red and underlined) to process NORTHERA prescriptions
- Properly completing these fields will help limit the number of calls made to your office
- Make sure to check your patient's primary diagnosis and all conditions that apply
- Determine the best titration schedule
- The provider must sign the prescription form before faxing the completed form. Prescriber must write "Brand necessary" below signature if choosing "Dispense as written." In addition, the patient or caregiver should sign the HIPAA release to ensure that the NSC can contact him or her directly if more information is needed.

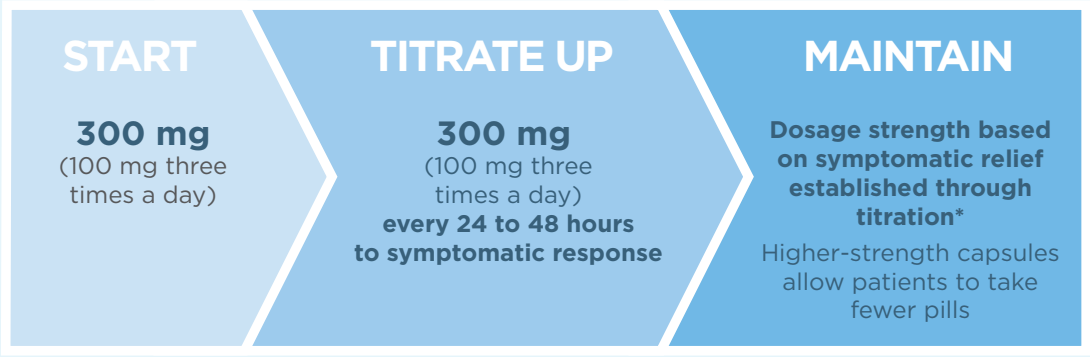
All names and information presented in this sample are for illustrative purposes only and do not reflect real patient information.

For additional guidance on how to complete the titration section of the Treatment Form, please see the information below.

Optimizing titration for symptomatic neurogenic orthostatic hypotension (nOH) relief

- The goal of nOH treatment is to reduce symptoms reported by patients[1-4]

RECOMMENDED NORTHERA TITRATION (total daily dose)[5]



*Recommended maximum dose 1800 mg (600 mg three times a day).[5]

- The image above illustrates the standard 24- to 48-hour titration schedule. Please choose Box A (24-hour) or Box B (48-hour) for this schedule
- NORTHERA is available in 100 mg, 200 mg, and 300 mg strength capsules[5]
- For a custom titration schedule of NORTHERA, please choose Box C
- For a fixed maintenance schedule of NORTHERA, please choose Box D

A patient's maintenance dose may be prescribed through 100 mg, 200 mg, and 300 mg strength capsules once symptomatic relief has been established through titration.[5] Switching patients to higher-strength capsules may help reduce the number of pills taken daily.

Northera Support Center (NSC) information

The NSC will confirm coverage with your patient's insurance carrier, provide coverage information to both you and your patient, and ensure medication delivery.

For any questions about the prescription process, contact the NSC toll-free **Monday–Friday, 8 AM–8 PM, EST**.

NSC Call number: 844-601-0101
NSC Fax number: 844-601-0102

References: 1. Freeman R. *N Engl J Med*. 2008;358(6):615-624. **2.** Gibbons CH, Schmidt P, Biaggioni I, et al. *J Neurol*. 2017;264(8):1567-1582. **3.** Freeman R, Wieling W, Axelrod FB, et al. *Clin Auton Res*. 2011;21(2):69-72. **4.** Isaacson SH. *Am J Manag Care*. 2015;21(suppl 13):s258-s268. **5.** NORTHERA [package insert]. Deerfield, IL: Lundbeck.

Please see Important Safety Information, including Boxed Warning for supine hypertension, at the end of the form. For more information, please see the accompanying NORTHERA full Prescribing Information, or go to NORTHERA.com.

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takes user to northera.com

Northera® (droxidopa) capsules 100 mg • 200 mg • 300 mg

NORTHERA Treatment Form

Red and underlined fields are required

HIPAA RELEASE

Patient Authorization for Use and Disclosure of Personal Health Information

I authorize my healthcare providers (including pharmacy providers) and health plans to disclose my personal health information related to this prescription form or my use or potential use of NORTHERA, including my personal contact information on this form (collectively, my "Information"), to the patient support program called the NORTHERA Support Center (the "Program") so that the Program may use and disclose the Information in order to: (1) establish my benefit eligibility; (2) communicate with my healthcare providers and health plans about my benefit and coverage status and my medical care; (3) provide support services, including facilitating the provision of NORTHERA to me, as well as any information or materials related to such services or Lundbeck products, including promotional or educational communications; (4) evaluate the effectiveness of NORTHERA support programs; (5) report safety information, including in communications with the US Food and Drug Administration and other government authorities; (6) contact me regarding this prescription form or my use or potential use of NORTHERA and provide me with related patient support communications, including through messages left for me that disclose that I take or may take NORTHERA; and (7) allow Lundbeck to analyze the usage patterns and the effectiveness of Lundbeck products, services, and programs and help develop new products, services, and programs, and for other Lundbeck general business and administrative purposes.

I understand that my pharmacy provider(s) may receive remuneration in exchange for the provision of my Information as authorized above, and that once my Information has been disclosed to the Program, federal privacy law may no longer restrict its use or disclosure and that it may be redisclosed to others. I also understand, however, that the Program plans to use and disclose my Information only for the purposes described above or as required by law.

I understand that if I refuse to sign this Authorization, that will not affect my right to treatment or payment benefits for health care. I also understand that if I sign, I may later withdraw this Authorization by sending written notice of my withdrawal from the Program to the NORTHERA Support Center Coordinating Center at PO Box 220267, Charlotte, NC 28222, and that such withdrawal will not affect any uses and disclosures of my Information prior to the Program's receipt of the notice. I am entitled to a copy of this signed Authorization, which expires 10 years from the date it is signed by me or such timeframe as allowed by law.

SAMPLE DO NOT FAX

PATIENT HIPAA

PATIENT/GUARDIAN SIGNATURE:	PATIENT/GUARDIAN NAME (PLEASE PRINT):	DATE:
Jane Doe	Jane Doe	10/16/2020

RELATIONSHIP TO PATIENT: ☑ Self ☐ Spouse ☐ Other[a] _____

AUTHORIZED REPRESENTATIVE CONSENT (OPTIONAL)

I further authorize the NORTHERA Support Center to discuss my treatment with the following authorized representative(s).

AUTHORIZED REPRESENTATIVE (1) NAME (PLEASE PRINT):
John Doe

RELATIONSHIP TO PATIENT: ☑ Spouse ☐ Child ☐ Other: _____

AUTHORIZED REPRESENTATIVE (2) NAME (PLEASE PRINT):
Emily Doe

RELATIONSHIP TO PATIENT: ☐ Spouse ☑ Child ☐ Other: _____

[a]Please note documentation proving Power of Attorney may be required.

Northera® (droxidopa) capsules 100 mg • 200 mg • 300 mg

Red and underlined fields are required

NORTHERA Treatment Form

PATIENTS MUST SIGN THE HIPAA RELEASE ON PAGE 1 IN ORDER TO RECEIVE ALL SUPPORT SERVICES OFFERED BY THE NSC.

1 Patient Information

PATIENT FIRST, LAST NAME: Jane Doe		DOB (MM/DD/YYYY): 09/24/1956	GENDER: ☐ M ☒ F
MAILING ADDRESS: 123 Napa Court	CITY: Naperville	STATE: IL	ZIP CODE: 60563
PRIMARY PHONE: (773) 555-0123 ☒ Home ☐ Cell ☐ Work	☐ CHECK HERE IF PATIENT IS IN THE HOSPITAL. DISCHARGE DATE:		
SECONDARY PHONE: (773) 555-0444 ☐ Home ☒ Cell ☐ Work	EMAIL: janedoe@emaildomain.com		
PREFERRED CONTACT TIME: ☐ Morning ☐ Afternoon ☐ Evening	☒ I AUTHORIZE THE NSC TO DISCUSS MY TREATMENT WITH: John Doe		
PRIMARY LANGUAGE: English			

2 Patient Insurance Attach copies of both sides of patient's pharmacy benefit card(s) OR complete the following

PRIMARY INSURANCE: United Healthcare	ID NUMBER: 123456789
PHONE: (773) 555-4544	CARDHOLDER NAME: Jane Doe
PLAN NUMBER: 123-45678-91	GROUP NUMBER: 456789

RELATIONSHIP TO CARDHOLDER: ☒ Self ☐ Spouse ☐ Child ☐ Other:

☐ CHECK IF NO COVERAGE

3 Clinical Information

Has a clinical evaluation of the patient's current medications been performed to evaluate for any medications that may precipitate hypotension? ☒ Yes ☐ No

Patient concomitant medications: None

☐ Drug allergies: _____

☐ No known drug allergies (NKDA)

Will the patient be monitored for supine hypertension prior to and during treatment? ☒ Yes ☐ No

Does the patient have any contraindications to the use of NORTHERA (eg, hypersensitivity to NORTHERA or any of its components)? ☐ Yes ☒ No

WHAT IS THE PATIENT'S PRIMARY DIAGNOSIS? (CHECK ONE OF THE FOLLOWING):

- ☒ G20 Parkinson's disease (PD)
- ☐ G23.2 Striatonigral degeneration
- ☐ G90.3 Multi-system degeneration of the autonomic nervous system
- ☐ G90.9 Disorder of the autonomic nervous system, unspecified*
- ☐ G99.0 Autonomic neuropathy in diseases classified elsewhere*

*NORTHERA is not indicated for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) caused by diabetic autonomic neuropathy.

- ☐ Dopamine beta-hydroxylase (DBH) deficiency
  Attach chart notes supporting the clinical diagnosis.
- ☐ Non-diabetic autonomic neuropathy (NDAN)
  Attach chart notes supporting the clinical diagnosis.
- ☐ Other (Include ICD code): _____
  Attach chart notes supporting the clinical diagnosis.

SYMPTOMATIC CONDITION(S) (CHECK ONE OR ALL THAT APPLY):

- ☒ Neurogenic orthostatic hypotension (nOH)
- ☒ R42 Dizziness and giddiness
- ☒ I95.1 Orthostatic hypotension
- ☐ I95.89 Other hypotension
- ☒ R55 Syncope and collapse
- ☐ Other (Include ICD code): _____

Has the patient tried and failed or is intolerant to midodrine? ☒ Yes ☐ No

Has the patient tried and failed or is intolerant to fludrocortisone? ☐ Yes ☒ No

Has the patient tried any of the following non-pharmacologic interventions? (Check all that apply):

- ☒ Discontinuation of drugs, which can cause orthostatic hypotension (eg, diuretics, antihypertensive medications [primarily sympathetic blockers], anti-anginal drugs [nitrates], alpha-adrenergic antagonists, and antidepressants)
- ☒ Increased salt and water intake, if appropriate
- ☒ Raising the head of the bed 10 to 20 degrees
- ☒ Compression stockings
- ☐ Physical maneuvers to improve venous return
- ☐ Avoiding precipitating factors (eg, overexertion in hot weather, arising too quickly from supine to sitting or standing)
- ☐ Other: _____

SAMPLE DO NOT FAX

Northera® (droxidopa) capsules 100 mg • 200 mg • 300 mg

NORTHERA Treatment Form

Red and underlined fields are required

4 Prescriber Information

PRESCRIBER NAME: Dr. Chris Smith

SPECIALTY: ■ Neurologist ☐ Cardiologist ☐ Nephrologist ☐ Other: _____

NPI #: 757837956 **STATE ID:** 27.01.01.200

PRACTICE/FACILITY NAME:

OFFICE CONTACT NAME: Nurse Jen

MAILING ADDRESS: 123 S. Riverside Plaza, Suite 999

OFFICE CONTACT PHONE: (773) 555-6769

CITY: Chicago ***STATE:** IL **ZIP CODE:** 60606

OFFICE CONTACT FAX: (773) 555-4800

OFFICE/PRESCRIBER EMAIL:

5 Initial NORTHERA Prescription Information

PATIENT FIRST, LAST NAME: Jane Doe **DOB (MM/DD/YYYY):** 09/24/1956

MAILING ADDRESS: 123 Napa Court **CITY:** Naperville **STATE:** IL **ZIP CODE:** 60563 **PHONE:** (773) 555-0123

CHOOSE ONLY ONE OPTION BELOW.

■ A — STANDARD 24-HR SCHEDULE

NORTHERA 24-HOUR TITRATION SCHEDULE

Dispense: NORTHERA 100 mg capsules (30-day supply) Sig: To be filled by the pharmacy to reflect indicated titration schedule. Qty = 495 Refills = 0

Administer 3 times daily: when you get up in the morning, at midday, and in late afternoon (at least 3 hours before bed)

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-30[a]
100 mg	200 mg	300 mg	400 mg	500 mg	600 mg

Additional instructions:

☐ B — STANDARD 48-HR SCHEDULE

NORTHERA 48-HOUR TITRATION SCHEDULE

Dispense: NORTHERA 100 mg capsules (30-day supply) Sig: To be filled by the pharmacy to reflect indicated titration schedule. Qty = 450 Refills = 0

Administer 3 times daily: when you get up in the morning, at midday, and in late afternoon (at least 3 hours before bed)

Days 1 and 2	Days 3 and 4	Days 5 and 6	Days 7 and 8	Days 9 and 10	Days 11-30[a]
100 mg	200 mg	300 mg	400 mg	500 mg	600 mg

Additional instructions:

☐ C — CUSTOM SCHEDULE

NORTHERA CUSTOM TITRATION SCHEDULE

Dispense: NORTHERA 100 mg capsules (Qty sufficient for 30-day supply) Sig: To be filled by the pharmacy to reflect indicated titration schedule. Refills = 0

Day(s) ___ - ___	Day(s) ___ - ___	Day(s) ___ - ___	Day(s) ___ - ___	Day(s) ___ - ___	Day(s) ___ - ___	Day(s) ___ - 30[a]
100 mg ___ times daily	___ mg ___ times daily	___ mg ___ times daily	___ mg ___ times daily	___ mg ___ times daily	___ mg ___ times daily	___ mg ___ times daily

Additional instructions:

☐ D — CUSTOM SCHEDULE

NORTHERA FIXED SCHEDULE

The quantity will be calculated at the pharmacy based upon indicated schedule for a 30-day supply. Refills = 0

Dispense: NORTHERA ☐ 100 mg capsules ☐ 200 mg capsules ☐ 300 mg capsules Sig: Take _____ mg _____ time(s) daily

Additional instructions: Please dispense a 30-day supply unless otherwise noted

[a]**Continued effectiveness of NORTHERA should be assessed periodically.**

Prescriber Certification and Authorization: I certify that, to the full extent required by applicable law, I have obtained written permission from my patient named above (or from the patient's legal representative) to release to the patient support program, the NORTHERA Support Center ("the Program"), the patient's personal health information, both as provided on this form and such other personal health information as the Program may need (1) to perform a preliminary verification of the patient's insurance coverage for NORTHERA, (2) to assess the patient's eligibility for participation in the Program, (3) to enroll the patient in the Program, (4) to provide reimbursement support and other services to the patient in connection with the patient's prescription(s) on this form, and (5) for the other purposes identified on the Patient Authorization for Use and Disclosure of Personal Health Information. I authorize and appoint the Program to convey on my behalf the prescription(s) I signed for the patient and the other information included on this form to the dispensing pharmacy chosen by or for the patient. I agree that the Program may contact me, including without limitation via email, fax, and telephone, to seek additional information relating to the Program, NORTHERA, or the prescription(s) contained on this form.

I understand that any NORTHERA provided at no charge to the patient is provided on a complimentary basis. I will not submit or cause to be submitted any claims for payment or reimbursement for such products to any third-party payor, including a federal health care program. If I am or become in possession of such product, I will not resell or attempt to resell the product.

Write "Brand necessary" along with the signature for "Dispense as written."

PRESCRIBER SIGNATURE (SIGN BELOW)

Chris Smith — 10.16.2020

DISPENSE AS WRITTEN/WRITE BRAND NECESSARY **DATE**

PRODUCT SUBSTITUTION PERMITTED **DATE**

SIGNATURE STAMPS NOT ACCEPTABLE

*The prescriber is to comply with his/her state specific prescription requirements such as e-prescribing, state specific prescription form, fax language, etc. Non-compliance with state specific requirements could result in outreach to the prescriber. If choosing "Dispense as Written/Brand Necessary," additional information may be needed from the prescriber.

DRX-B-100413v3

Please see accompanying Important Safety Information, including Boxed Warning for supine hypertension, on page 5.
For more information, please see the accompanying NORTHERA full Prescribing Information, or go to NORTHERA.com.

Questions? Call the NSC toll-free at 844-601-0101

SAMPLE DO NOT FAX

NORTHERA® (droxidopa)

INDICATIONS AND USAGE

NORTHERA (droxidopa) is indicated 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 (nOH) caused by primary autonomic failure (Parkinson's disease [PD], 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 established. The continued effectiveness of NORTHERA should be assessed periodically.

IMPORTANT SAFETY INFORMATION

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA.

CONTRAINDICATIONS

- NORTHERA is contraindicated in patients who have a history of hypersensitivity to the drug or its ingredients.

WARNINGS AND PRECAUTIONS

- **Supine Hypertension:** NORTHERA therapy may cause or exacerbate supine hypertension in patients with nOH, which may increase the risk of cardiovascular events if not well managed, particularly stroke.
- **Hyperpyrexia and Confusion:** Cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with NORTHERA use during post-marketing surveillance. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.
- **Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure:** NORTHERA therapy may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Careful consideration should be given to this potential risk prior to initiating therapy.
- **Allergic Reactions:** Hypersensitivity reactions, including anaphylaxis, angioedema, bronchospasm, urticaria, and rash have been reported in post-marketing experience, with some resulting in emergency treatment. If a hypersensitivity reaction occurs, discontinue the drug and initiate appropriate therapy.

  This product contains FD&C Yellow No. 5 (tartrazine), which may also cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS

- The most common adverse reactions (>5% and ≥3% difference compared to placebo) were headache, dizziness, nausea, and hypertension.

DRUG INTERACTIONS

- Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension.
- Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.
- 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.

USE IN SPECIFIC POPULATIONS

- There are no available data on use of NORTHERA in pregnant women and risk of major birth defects or miscarriage. 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.
- The safety and effectiveness of NORTHERA in pediatric patients have not been established. No overall differences in safety or effectiveness were observed between patients aged 75 years and older and younger patients in clinical trials, but greater sensitivity of some older individuals cannot be ruled out.
- Clinical experience with NORTHERA in patients with severe renal function impairment (GFR <30 mL/min) is limited; therefore, dosing recommendations cannot be provided for these patients.

Please see the accompanying full Prescribing Information, including Boxed Warning for supine hypertension, or go to NORTHERA.com, or call the NSC at 844-601-0101.

Lundbeck

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DRX-B-100413v3 **NORTHERA.com**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NORTHERA® safely and effectively. See full prescribing information for NORTHERA.

NORTHERA® (droxidopa) capsules, for oral use
Initial U.S. Approval: 2014

WARNING: SUPINE HYPERTENSION

See full prescribing information for complete boxed warning.

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA *[see Warnings and Precautions (5.1)]*.

INDICATIONS AND USAGE

NORTHERA is indicated 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 (nOH) caused by primary autonomic failure (Parkinson's disease [PD], 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 established. The continued effectiveness of NORTHERA should be assessed periodically (1).

DOSAGE AND ADMINISTRATION

- Starting dose is 100 mg three times during the day (2.1)
- Titrate by 100 mg three times daily, up to a maximum dose of 600 mg three times daily (2.1)
- Take consistently with or without food (2.1)
- To reduce the potential for supine hypertension, elevate the head of the bed and give the last dose at least 3 hours prior to bedtime (2.1)
- Take NORTHERA capsule whole (2.1)

DOSAGE FORMS AND STRENGTHS

100 mg, 200 mg, and 300 mg capsules (3)

CONTRAINDICATIONS

History of hypersensitivity to the drug or its ingredients (4)

WARNINGS AND PRECAUTIONS

- NORTHERA may cause supine hypertension and may increase cardiovascular risk if supine hypertension is not well-managed (5.1)
- Hyperpyrexia and confusion (5.2)
- May exacerbate symptoms in patients with existing ischemic heart disease, arrhythmias, and congestive heart failure (5.3)
- Allergic reactions (5.4)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Lundbeck at 1-800-455-1141 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use of DOPA decarboxylase inhibitors may require dose adjustments for NORTHERA (7.2)

USE IN SPECIFIC POPULATIONS

- *Lactation:* Breastfeeding not recommended (8.2)
- *Patients with Renal Impairment:* Dosing recommendations cannot be provided for patients with GFR less than 30 mL/min (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SUPINE HYPERTENSION

Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue NORTHERA *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

NORTHERA is indicated 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 (nOH) caused by primary autonomic failure (Parkinson's disease [PD], 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 established. The continued effectiveness of NORTHERA should be assessed periodically.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily: upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Administer NORTHERA consistently, either with food or without food. Take NORTHERA capsule whole. Titrate to symptomatic response, in increments of 100 mg three times daily every 24 to 48 hours up to a maximum dose of 600 mg three times daily (i.e., a maximum total daily dose of 1,800 mg).

Monitor supine blood pressure prior to initiating NORTHERA and after increasing the dose.

Patients who miss a dose of NORTHERA should take their next scheduled dose.

3 DOSAGE FORMS AND STRENGTHS

NORTHERA capsules are available in 100 mg, 200 mg, and 300 mg strengths as specified below.

- 100 mg: Hard gelatin capsules with "Northera" on the white body and "100" on the light blue cap
- 200 mg: Hard gelatin capsules with "Northera" on the white body and "200" on the light yellow cap
- 300 mg: Hard gelatin capsules with "Northera" on the white body and "300" on the light green cap

4 CONTRAINDICATIONS

NORTHERA is contraindicated in patients who have a history of hypersensitivity to the drug or its ingredients *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Supine Hypertension

NORTHERA therapy may cause or exacerbate supine hypertension in patients with nOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Monitor blood pressure, both in the supine position and in the recommended head-elevated sleeping position. Reduce or discontinue NORTHERA if supine hypertension persists. If supine hypertension is not well-managed, NORTHERA may increase the risk of cardiovascular events, particularly stroke.

5.2 Hyperpyrexia and Confusion

Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with NORTHERA use during postmarketing surveillance. Observe patients carefully when the dosage of NORTHERA is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

NMS is an uncommon but life-threatening syndrome characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes. The early diagnosis of this condition is important for the appropriate management of these patients.

5.3 Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure
NORTHERA may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Careful consideration should be given to this potential risk prior to initiating therapy in patients with these conditions.

5.4 Allergic Reactions
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.

This product contains FD&C Yellow No. 5 (tartrazine) which may also cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity *[see Contraindications (4)]*.

6 ADVERSE REACTIONS
The following adverse reactions with NORTHERA are included in more detail in the Warnings and Precautions section of the label:
- Supine Hypertension *[see Warnings and Precautions (5.1)]*
- Hyperpyrexia and Confusion *[see Warnings and Precautions (5.2)]*
- May exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety evaluation of NORTHERA is based on two placebo-controlled studies 1 to 2 weeks in duration (Studies 301 and 302), one 8-week placebo-controlled study (Study 306), and two long-term, open-label extension studies (Studies 303 and 304). In the placebo-controlled studies, a total of 485 patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy were randomized and treated, 245 with NORTHERA and 240 with placebo *[see Clinical Studies (14)]*.

Placebo-Controlled Experience

The most commonly observed adverse reactions (those occurring at an incidence of greater than 5% in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group) in NORTHERA-treated patients during the three placebo-controlled trials were headache, dizziness, nausea, and hypertension. The most common adverse reactions leading to discontinuation from NORTHERA were hypertension or increased blood pressure and nausea.

Table 1. Most Common Adverse Reactions Occurring More Frequently in the NORTHERA Group

	Study 301 and Study 302 (1 to 2 Weeks Randomized Treatment)		Study 306 (8 to 10 Weeks Randomized Treatment)	
	Placebo (N=132) n (%)	NORTHERA (N=131) n (%)	Placebo (N=108) n (%)	NORTHERA (N=114) n (%)
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)

Note: n=number of patients. Adverse reactions that were reported in greater than 5% of patients in the NORTHERA group and with at least a 3% greater incidence in the NORTHERA group than in the placebo group were from Study 306.

Long-Term, Open-Label Trials with NORTHERA

In the long-term, open-label extension studies, a total of 422 patients, mean age 65 years, were treated with NORTHERA for a mean total exposure of approximately one year. The commonly reported adverse events were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).

6.2 Postmarketing 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
Nervous System Disorders: Cerebrovascular accident
Psychiatric Disorders: Psychosis, hallucination, delirium, agitation, memory disorder

7 DRUG INTERACTIONS
7.1 Drugs that Increase Blood Pressure
Administering NORTHERA in combination with other agents that increase blood pressure (e.g., norepinephrine, ephedrine, midodrine, and triptans) would be expected to increase the risk for supine hypertension.

7.2 Parkinson's Medications
Dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA.

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.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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).

8.4 Pediatric Use
The safety and effectiveness of NORTHERA in pediatric patients have not been established.

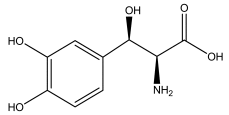
8.5 Geriatric Use
A total of 197 patients with symptomatic nOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment
NORTHERA and its metabolites are primarily cleared renally. Patients with mild or moderate renal impairment (GFR greater than 30 mL/min) were included in clinical trials and did not have a higher frequency of adverse reactions. Clinical experience with NORTHERA in patients with severe renal function impairment (GFR less than 30 mL/min) is limited.

10 OVERDOSAGE
10.1 Symptoms
There have been cases of overdose reported during postmarketing surveillance. A patient ingested 7,700 mg of 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 intracranial hemorrhage.

10.2 Treatment
There is no known antidote for NORTHERA overdosage. In case of an overdose that may result in an excessively high blood pressure, discontinue NORTHERA and treat with appropriate symptomatic and supportive therapy. Counsel patients to remain in a standing or seated position until their blood pressure drops below an acceptable limit.

11 DESCRIPTION
NORTHERA capsules contain droxidopa, which is a synthetic amino acid precursor of norepinephrine, for oral administration. Chemically, droxidopa is (–)-threo-3-(3,4-Dihydroxyphenyl)-L-serine. It has the following structural formula:



Droxidopa is an odorless, tasteless, white to off-white crystals or crystalline powder. It is slightly soluble in water, and practically insoluble in methanol, glacial acetic acid, ethanol, acetone, ether, and chloroform. It is soluble in dilute hydrochloric acid. It has a molecular weight of 213.19 and a molecular formula of $C_9H_{11}NO_5$.

NORTHERA capsules also contain the following inactive ingredients: mannitol, corn starch, and magnesium stearate. The capsule shell is printed with black ink. The black inks contain shellac glaze, ethanol, iron oxide black, isopropyl alcohol, n-butyl alcohol, propylene glycol, and ammonium hydroxide. The capsule shell contains the following inactive ingredients: 100 mg – gelatin, titanium dioxide, FD&C Blue No. 2, black and red iron oxide; 200 mg – gelatin, titanium dioxide, FD&C Blue No. 2, black and yellow iron oxide; 300 mg – gelatin, titanium dioxide, FD&C Blue No. 1, FD&C Yellow No. 5 (tartrazine), and FD&C Red No. 40. NORTHERA capsules differ in size and color by strength *[see Dosage Forms and Strengths (3)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The exact mechanism of action of NORTHERA in the treatment of neurogenic orthostatic hypotension is unknown. NORTHERA is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, which is extensively distributed throughout the body. NORTHERA is believed to exert its pharmacological effects through norepinephrine and not through the parent molecule or other metabolites. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction. NORTHERA in humans induces small and transient rises in plasma norepinephrine.

12.2 Pharmacodynamics

Peak droxidopa plasma concentrations are associated with increases in systolic and diastolic blood pressures. Droxidopa has no clinically significant effect on standing or supine heart rates in patients with autonomic failure.

Cardiac Electrophysiology

No prolongation of the QTc interval was observed with NORTHERA at single oral doses up to 2,000 mg, as shown in a dedicated thorough QT study.

12.3 Pharmacokinetics

Absorption

Peak plasma concentrations (C_{max}) of droxidopa were reached by 1 to 4 hours post-dose (mean of approximately 2 hours) in healthy volunteers. High-fat meals have a moderate impact on droxidopa exposure with C_{max} and area under the plasma concentration-time curve (AUC) decreasing by 35% and 20%, respectively. The C_{max} was delayed by approximately 2 hours with a high-fat meal.

Distribution

Pre-clinical studies suggest that droxidopa can cross the blood-brain barrier. Droxidopa exhibits plasma protein binding of 75% at 100 ng/mL and 26% at 10,000 ng/mL. The estimated apparent volume of distribution of droxidopa is about 200 L in humans.

Elimination

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

Metabolism

The metabolism of droxidopa is mediated by catecholamine pathway and not through the cytochrome P450 system. Droxidopa is initially converted to methoxylated dihydroxyphenylserine (3-OM-DOPS), a major metabolite, by catechol-O-methyltransferase (COMT), to norepinephrine by DOPA decarboxylase (DDC), or to protocatechualdehyde by DOPS aldolase. After oral dosing in humans, plasma norepinephrine levels peak within 3 to 4 hours but are generally very low (less than 1 ng/mL) and variable with no consistent relationship with dose. The contribution of the metabolites of droxidopa other than norepinephrine to its pharmacological effects is not well understood.

Excretion

The mean elimination half-life of droxidopa is approximately 2.5 hours in humans. The major route of elimination of droxidopa and its metabolites is via the kidneys in both animals and in humans. Studies in animals with radiolabeled drug showed that ~75% of the administered radioactivity was excreted in urine within 24 hours of oral dosing.

Specific Populations

There are no clinically relevant effects of age, body mass index, or sex on the pharmacokinetics of droxidopa. A population pharmacokinetic analysis suggests that hepatic function, assessed by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin, did not influence the exposure to droxidopa. The controlled clinical trials included patients with mild to moderate renal impairment. No dose adjustments are required in patients with mild to moderate renal impairment.

Drug Interaction Studies

No dedicated drug-drug interaction studies were performed for droxidopa. Patients in the Phase 3 trials with NORTHERA received concomitant levodopa/carbidopa, dopamine agonists, MAO-B inhibitors, COMT inhibitors and other medications used to treat Parkinson's disease. Carbidopa, a peripheral dopa-decarboxylase inhibitor, could prevent the conversion of NORTHERA to norepinephrine outside of the central nervous system (CNS). Patients taking NORTHERA with L-DOPA/dopa-decarboxylase inhibitor combination drugs had decreased clearance of NORTHERA, an increase in overall exposure (AUC) to droxidopa of approximately 100%, and an increase in overall exposure to 3-OM-DOPS of approximately 50%. However, in clinical trials, it was found that the decreased clearance was not associated with a significant need for a different treatment dose or increases in associated adverse events. Dopamine agonists, amantadine derivatives, and MAO-B inhibitors do not appear to affect NORTHERA clearance, and no dose adjustments are required.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have been conducted at dosages up to 1,000 mg/kg/day in mice and up to 100 mg/kg/day in rats with no indication of carcinogenic effects. Based on dose per unit body surface area, these two doses correspond to approximately 3 and 0.5 times, respectively, the maximum recommended total daily dose of 1,800 mg in a 60 kg patient. Droxidopa was clastogenic in Chinese hamster ovary cells (chromosome aberration assay), but was not mutagenic in bacteria (Ames assay), and was not clastogenic in a mouse micronucleus assay.

Studies in rats show that droxidopa has no effect on fertility.

13.2 Animal Toxicology and/or Pharmacology

In long-term chronic toxicity studies, 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.

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.

14 CLINICAL STUDIES

14.1 Studies in Neurogenic Orthostatic Hypotension

Clinical studies (described below) examined the efficacy of NORTHERA in the short-term (1 to 2 weeks) and over longer-term periods (8 weeks; 3 months). Studies 301 and 306B showed a treatment effect of NORTHERA at Week 1, but none of the studies demonstrated continued efficacy beyond 2 weeks of treatment.

Study 306B was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study in patients with symptomatic nOH and Parkinson's disease. Patients entering the study were required to have a decrease of at least 20 mm Hg or 10 mm Hg, respectively, in systolic or diastolic blood pressure, within 3 minutes after standing, as well as symptoms associated with neurogenic orthostatic hypotension. The study had an initial dose titration period that lasted up to 2 weeks in which patients received placebo or 100 to 600 mg of NORTHERA three times daily, followed by an 8-week treatment period.

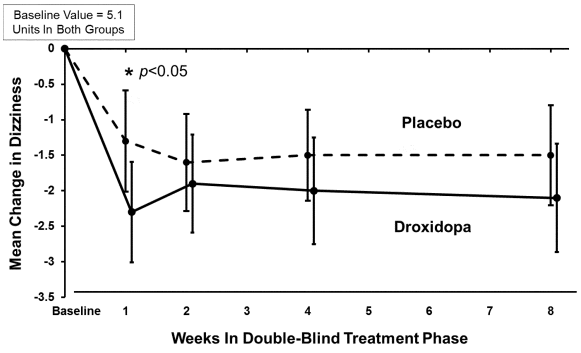
Efficacy was measured using the OHSA Item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at Week 1, in patients who had completed titration and 1 week of maintenance therapy.

A total of 171 patients were enrolled, and 147 patients were included in the efficacy analysis. The mean age was 72 years, and patients were mostly Caucasian. During the study, 94% of placebo-treated patients and 88% on NORTHERA were taking dopa-decarboxylase inhibitors; 17% of placebo-treated patients and 26% on NORTHERA were taking fludrocortisone. There were more premature discontinuations in the NORTHERA group (28%) than in the placebo group (20%).

In both groups, the mean baseline dizziness score was 5.1 on an 11-point scale. At Week 1, patients showed a statistically significant mean 0.9 unit decrease in dizziness with NORTHERA versus placebo (P=0.028), but the effect did not persist beyond Week 1. The data at all time points are shown in Figure 1.

Patients receiving NORTHERA also had a greater increase, compared to placebo, in the Week 1 lowest standing systolic blood pressure within 3 minutes after standing (5.6 mm Hg; P=0.032).

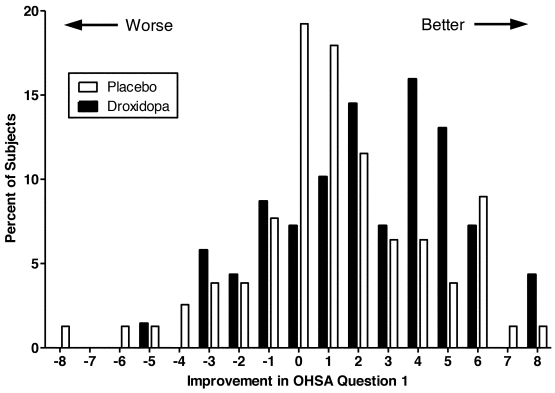
Figure 1. Mean Change in OHSA Item 1 Score by Week in Study 306B



Note: The graph is based on observed data only. The error bars are the 95% confidence interval of the mean change from baseline in OHSA Item 1 scores.

Figure 2. Distribution of Patients by Change in OHSA Item 1, Baseline to Week 1, in Study 306B

Figure 2 shows the distribution of changes from Baseline to Week 1 in the OHSA Item #1 score. Overall, the figure shows that patients treated with NORTHERA improved more than those treated with placebo.



Study 301 was a multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study in patients with symptomatic neurogenic orthostatic hypotension. The study included an initial open-label dose titration period, a 7-day washout period, and a randomized double-blind 7-day treatment period. To be eligible for enrollment, patients were required to have a decrease in systolic or diastolic blood pressure of at least 20 or 10 mm Hg, respectively, within 3 minutes after standing. The study was enriched, such that only patients who had been identified as "responders" during the titration period were randomized to NORTHERA or placebo. To be considered a responder, a patient had to demonstrate improvement on the OHSA Item #1 score by at least 1 point, as well as an increase in systolic blood pressure of at least 10 mm Hg post-standing, during the open-label dose titration period. Patients who dropped out during the titration period because of side effects or other reasons were also not included in the double-blind portion of the study.

Patients had a primary diagnosis of Parkinson's disease (n=60), pure autonomic failure (n=36), or multiple system atrophy (n=26). The mean age was 60 years, and most were Caucasian. 45% of patients were taking dopa-decarboxylase inhibitors, and 29% were taking fludrocortisone.

Efficacy was measured using the Orthostatic Hypotension Questionnaire (OHQ), a patient-reported outcome that measures symptoms of nOH and their impact on the patient's ability to perform daily activities that require standing and walking. The OHQ includes OHSA Item #1 as one of several components. A statistically significant treatment effect was not demonstrated on OHQ (treatment effect of 0.4 unit, *P*=0.19).

The mean baseline dizziness score on OHSA Item #1 ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") was 5.2 units on an 11-point scale. At Week 1 of treatment, patients showed a mean 0.7 unit decrease in dizziness with NORTHERA versus placebo (*P*=0.06).

Study 302 (n=101) was a placebo-controlled, 2-week randomized withdrawal study of NORTHERA in patients with symptomatic nOH. Study 303 (n=75) was an extension of Studies 301 and 302, where patients received their titrated dose of NORTHERA for 3 months and then entered a 2-week randomized withdrawal phase. Neither study showed a statistically significant difference between treatment arms on its primary endpoint. Considering these data, the effectiveness of NORTHERA beyond 2 weeks is uncertain, and patients should be evaluated periodically to determine whether NORTHERA is continuing to provide a benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NORTHERA capsules are supplied in the following dosage strengths:

100 mg: Hard gelatin, size 3 capsule, with an opaque light blue cap and an opaque white body, printed with "Northera" on body and "100" on cap, filled with a white to light brown powder.

200 mg: Hard gelatin, size 2 capsule, with an opaque light yellow cap and an opaque white body, printed with "Northera" on body and "200" on cap, filled with a white to light brown powder.

300 mg: Hard gelatin, size 1 capsule, with an opaque light green cap and an opaque white body, printed with "Northera" on body and "300" on cap, filled with a white to light brown powder.

100 mg 90-count bottle (NDC code# 67386-820-19)

200 mg 90-count bottle (NDC code# 67386-821-19)

300 mg 90-count bottle (NDC code# 67386-822-19)

16.2 Storage and Handling

NORTHERA capsules should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Elevations in Blood Pressure

Counsel patients that NORTHERA causes elevations in blood pressure and increases the risk of supine hypertension, which could lead to strokes, heart attacks, and death. Instruct patients to rest and sleep in an upper-body elevated position and monitor blood pressure. Instruct patients how to manage observed blood pressure elevations. To reduce the risk of supine hypertension, in addition to raising the upper body, the late afternoon dose of NORTHERA should be taken at least three hours before bedtime *[see Warnings and Precautions (5.1)]*.

Concomitant Treatments

Counsel patients about the concomitant use of drugs to treat other conditions that may have an additive effect with NORTHERA *[see Drug Interactions (7)]*.

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)]*.

Food

Patients should take NORTHERA the same way each time, either with food or without food *[see Dosage and Administration (2.1)]*.

Missed Dose

If a dose is missed, patients should take the next dose at the regularly scheduled time and should not double the dose.

Manufactured by:
Patheon, Whitby, ON L1N 5Z5, Canada
For:
Lundbeck, Deerfield, IL 60015, U.S.A.

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