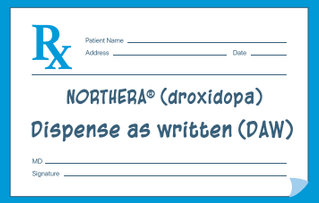

If you decide that NORTHERA® (droxidopa) is clinically appropriate for your patients, write "Dispense as written" on the prescription to help ensure patients receive their medication exactly as prescribed.

Distinctive. Effective. Focused.

NORTHERA is the only treatment *specifically studied* to reduce the classic symptoms of neurogenic orthostatic hypotension (nOH)[1,2]

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 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.

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.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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

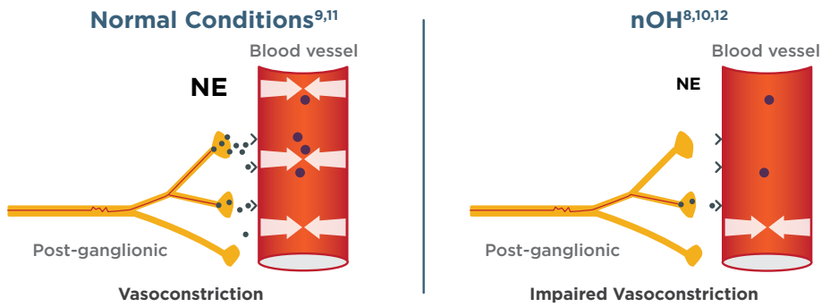
Identifying appropriate symptomatic nOH patients for NORTHERA® (droxidopa) therapy[1]

nOH is one of the various types of orthostatic hypotension (OH)[3-5]

Neurogenic[3,4]	Iatrogenic[3,4]	Non-neurogenic[3,4]
Parkinson's disease (PD)	Vasodilators	Hypovolemia
Multiple system atrophy (MSA)	Diuretics	Cardiac insufficiency
Pure autonomic failure (PAF)	Antihypertensives	Impaired venous return
Non-diabetic autonomic neuropathy	Other medications	
Dopamine beta-hydroxylase deficiency		

Symptomatic nOH is due to inadequate release of norepinephrine (NE) upon standing or changing positions[6,7]

- Due to reduced NE release from postganglionic sympathetic nerves, the autonomic nervous system fails to adequately regulate blood pressure in response to postural changes[6,8-10]
- Inadequate release of NE may lead to impaired vasoconstriction and cerebral hypoperfusion[6,10]
- This may result in the classic symptoms of nOH upon standing: dizziness, lightheadedness, or the "feeling that you are about to black out"[2,7,9]



Graphic adapted from: Palma JA, Kaufmann H. *Mov Disord Clin Pract.* 2017;4(3):298-308.[8]

Symptom assessment and orthostatic measurements are key in evaluating symptomatic nOH[2,5,7,10,13]

- Orthostatic measurements can play a role in the diagnosis of nOH. Measure your patient's blood pressure (BP) and pulse rate after supine for 5 minutes and again in a standing position, after 1 minute, and after 3 minutes[14,15]
- Due to inadequate NE release, heart rate remains fairly constant in nOH patients upon standing.[6,9,10] If a patient experiences a sustained drop in BP upon standing, with an increase in heart rate less than 15 bpm within 3 minutes, a diagnosis of nOH may be considered. However, an increase of more than 15 bpm within 3 minutes may suggest non-neurogenic orthostatic hypotension[5,9,10,13,14]

NORTHERA is an NE prodrug[1]

The exact mechanism of action of NORTHERA in the treatment of nOH is unknown. NORTHERA is directly metabolized into NE and is believed to exert its pharmacologic effects through NE.[1]

- NE increases blood pressure by inducing peripheral arterial and venous vasoconstriction[1]
- NORTHERA in humans induces small and transient rises in plasma NE[1]

NORTHERA is directly metabolized to NE by dopa-decarboxylase, the same mechanism by which levodopa is converted to dopamine[1,10,16]

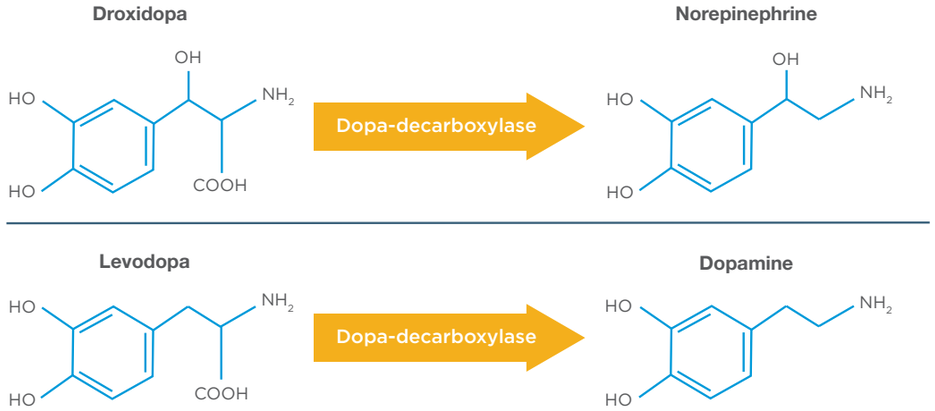


Figure adapted from Kaufmann H, Norcliffe-Kaufmann L, Palma JA. *Expert Rev Cardiovasc Ther.* 2015;13(8):875-891.[10]

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **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.

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Study 306B

Study design

- Study 306B (efficacy population, NORTHERA® [droxidopa] n=69; placebo n=78) was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in PD patients with symptomatic nOH (mean age of patients, 72 years)[1,17]
- The study had a dose titration period that lasted up to 2 weeks in which patients received placebo or NORTHERA (100 mg to 600 mg) 3 times daily, followed by an 8-week stable-dose treatment period[1,17]

Primary efficacy endpoint

The primary endpoint was change in Item 1 on the Orthostatic Hypotension Symptom Assessment (OHSA) scale at Week 1. Item 1 assessed patients' self-reported symptom ratings for dizziness, lightheadedness, feeling faint, or "feeling like you might black out."[1,17]

Key inclusion criteria[17]

1. **Clinical diagnosis of PD with symptomatic nOH**
2. **Documented decrease in systolic blood pressure (SBP) ≥20 mm Hg or diastolic blood pressure (DBP) ≥10 mm Hg within 3 minutes of standing**

Key exclusion criteria[17,18]

Taking vasoconstricting agents (e.g., ephedrine, dihydroergotamine, or midodrine) within 2 days or 5 half-lives (whichever was longer) of study entry.

Taking long-acting antihypertensive medication (use of short-acting antihypertensive medications at bedtime was permitted).

Sustained severe hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg in the seated or supine position, which was observed in 3 consecutive measurements over an hour).

Significant uncontrolled cardiac arrhythmia, unstable angina, congestive heart failure, or a history of myocardial infarction.

A score of ≤23 on the Mini–Mental State Examination.

Discontinuations

- There were more premature discontinuations in the NORTHERA group (28%)[a] vs the placebo group (20%)[b] during the study[17]
  - –24 randomized patients (18 NORTHERA, 6 placebo) dropped out of the study **prior to** the efficacy assessment at Week 1[17]
  - –18 randomized patients (7 NORTHERA, 11 placebo) dropped out of the study **after** the efficacy assessment at Week 1[17]
- The most common reason for discontinuation from all randomized patients (NORTHERA n=89; placebo n=85) was adverse events: 10 patients (11.2%) in the NORTHERA group and 6 patients (7.1%) in the placebo group[17]

[a]Based on 89 patients; 2 patients on NORTHERA were randomized but never treated.[17]
[b]Based on 85 patients; 1 patient on placebo was randomized but never treated.[17]

Concomitant medications

Concomitant medication use was common in Study 306B for patients taking both droxidopa and placebo.[17]

- 88% of NORTHERA patients and 94% of placebo-treated patients were taking dopa-decarboxylase inhibitors[1]
- 26% of NORTHERA patients and 17% of placebo-treated patients were taking fludrocortisone[1]

Concomitant Medications in Phase 3 Trials Included[1]:

- Levodopa/Carbidopa
- Dopamine Agonists
- Monoamine oxidase B (MAO-B) Inhibitors
- Catechol-O-methyl transferase (COMT) Inhibitors
- Other Medications Used to Treat PD

No dedicated drug-drug interaction studies were performed for droxidopa.[1]

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.

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Study 301[a]

Study design

- A Phase 3, multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose titration, followed by a 7-day washout period. Patients were then randomized into droxidopa and placebo groups. Randomization to end of study was 1 week (total efficacy population, n=162)[17]

Primary efficacy endpoint

- The primary efficacy endpoint was the mean change from randomization to the end of study in the Orthostatic Hypotension Questionnaire (OHQ) composite score, 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[1,17]

Study 302[b]

Study design

- A Phase 3, multicenter, multinational, randomized, placebo-controlled, double-blind, parallel-group withdrawal study. Open-label dose titration of droxidopa (up to 14 days) was followed by 7 days of open-label treatment. Patients were then randomized to droxidopa or placebo for 14 days (total efficacy population, n=101)[17]

Primary efficacy endpoint

- The primary efficacy endpoint was mean change from randomization to Day 14 on the OHSA Item 1 (dizziness, lightheadedness, and "feeling like you might black out")[17]

Study 303[c]

Study design

- A Phase 3, multicenter, multinational, 12-month, open-label study of the safety and efficacy of droxidopa that included a 2-week, double-blind, randomized-withdrawal, placebo-controlled period (following the first 3-month open-label droxidopa treatment) to evaluate the long-term effects of droxidopa treatment (total efficacy population, n=75). All patients entered this study from a prior droxidopa study (Study 301 or Study 302)[17]

Primary efficacy endpoint

- The primary efficacy endpoint was the mean change from randomization to Day 14 in the OHQ composite score following 3-month open-label droxidopa treatment[17]

[a]Study 301 included patients with primary autonomic failure and non-diabetic autonomic neuropathy with symptomatic nOH.[17]

[b]Study 302 included patients with primary autonomic failure, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy with symptomatic nOH.[17]

[c]Study 303 included patients with primary autonomic failure, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy with symptomatic nOH.[17]

Results

Studies 301, 302, and 303 failed to reach statistical significance in their primary endpoint analyses.[1]

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.[1]

WARNINGS AND PRECAUTIONS

- **Supine Hypertension:** NORTHERA® (droxidopa) 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.

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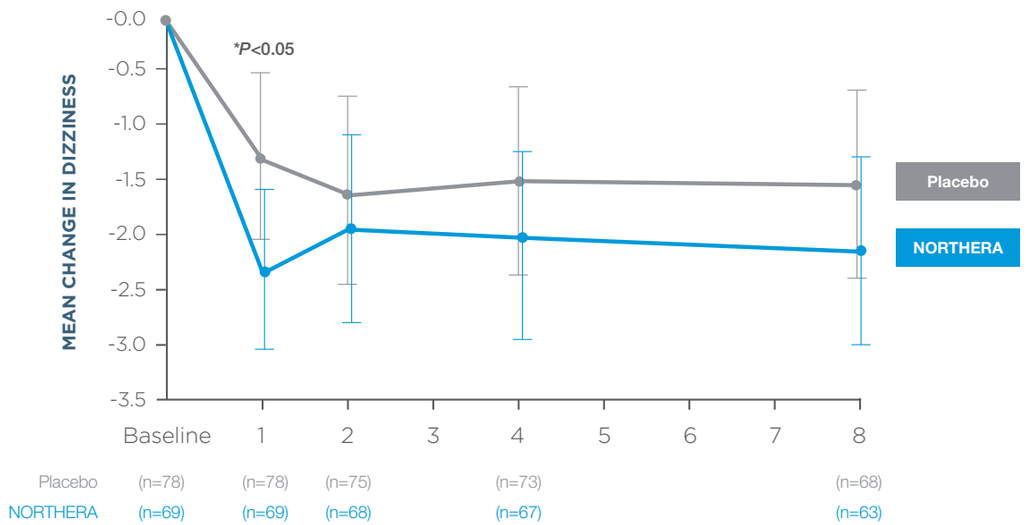
Study 306B: Primary endpoint

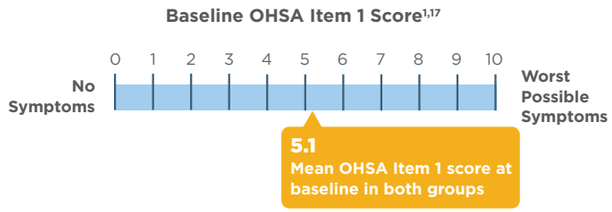
Patients on NORTHERA® (droxidopa) reported improvement in symptoms of orthostatic dizziness, lightheadedness, or "feeling like you might black out" at Week 1[1]

MEAN CHANGE IN OHSA ITEM 1 SCORE BY WEEK[1,17,a,b]



[a]The error bars are the 95% confidence intervals of the mean change from baseline in OHSA Item 1 scores.[1]
[b]Nonparametric analysis of covariance was used to determine treatment difference at Week 1, and the 2-sided *P*-value is reported.[17]

- At Week 1, patients on NORTHERA had a statistically significant mean decrease in symptoms vs placebo (*P*=0.028) as measured by OHSA Item 1 scores[1]
  - –The mean decrease in OHSA Item 1 score for NORTHERA vs placebo was 0.9 points[1]
  - –Statistical significance beyond Week 1 has not been demonstrated[1]
- OHSA is an 11-point scale for measuring patient-reported improvement of symptomatic nOH[17]
- Item 1 of the OHSA scale measures nOH symptoms of dizziness, lightheadedness, and "feeling like you might black out"[17]

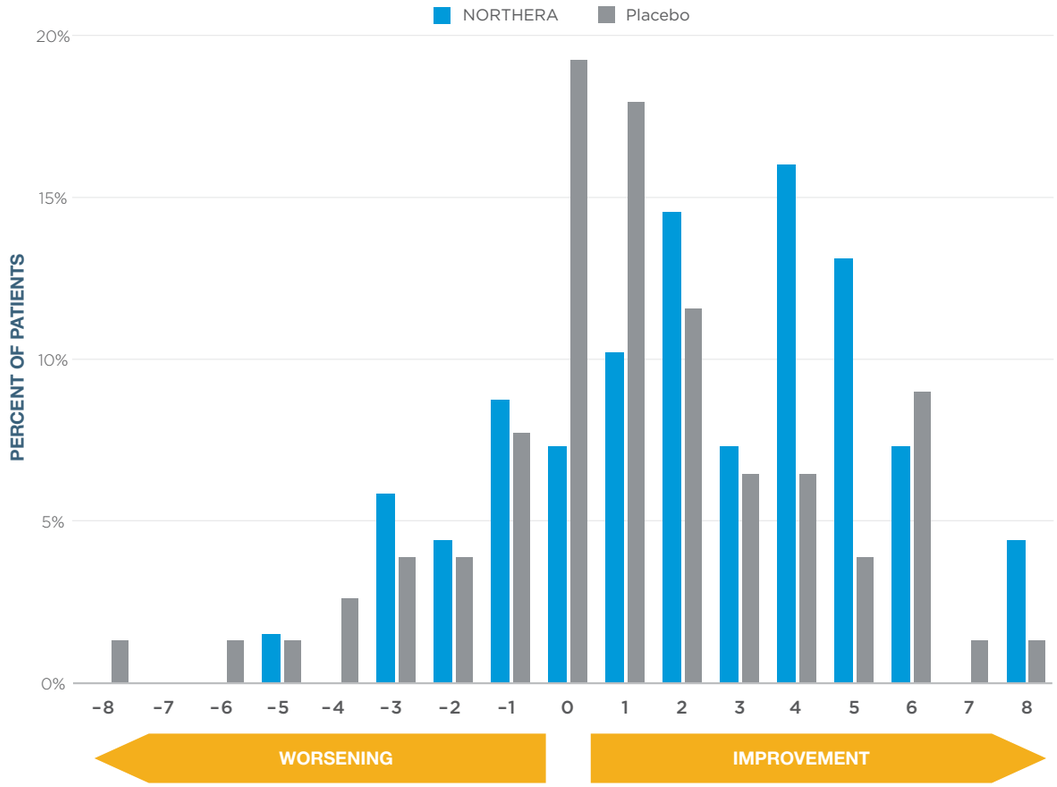


- When compared with placebo, patients on NORTHERA experienced a greater increase in Week 1 lowest standing SBP within 3 minutes after standing (5.6 mm Hg; *P*=0.032)[1]

Study 306B: Distribution by OHSA Item 1 score change

Overall, patients treated with NORTHERA improved more than those treated with placebo[1]

DISTRIBUTION OF PATIENTS BY POINT CHANGE IN OHSA ITEM 1, BASELINE TO WEEK 1[1]



- The mean decrease in OHSA Item 1 score of NORTHERA vs placebo was 0.9 points; some patients had a much greater improvement[1]

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.

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.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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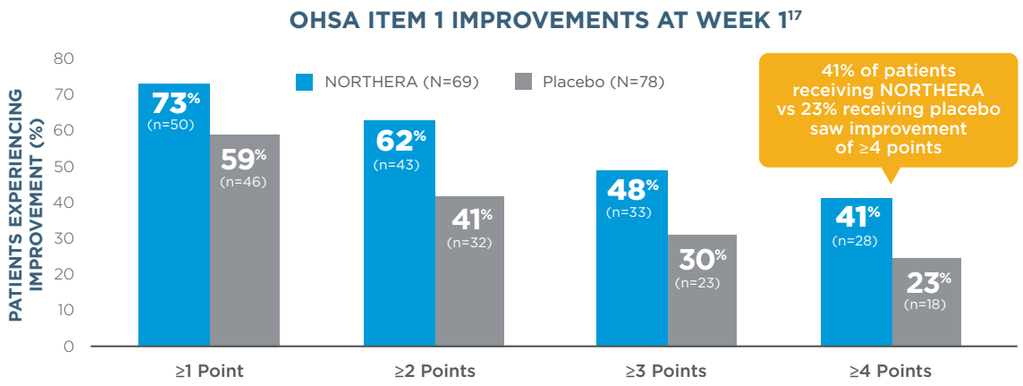
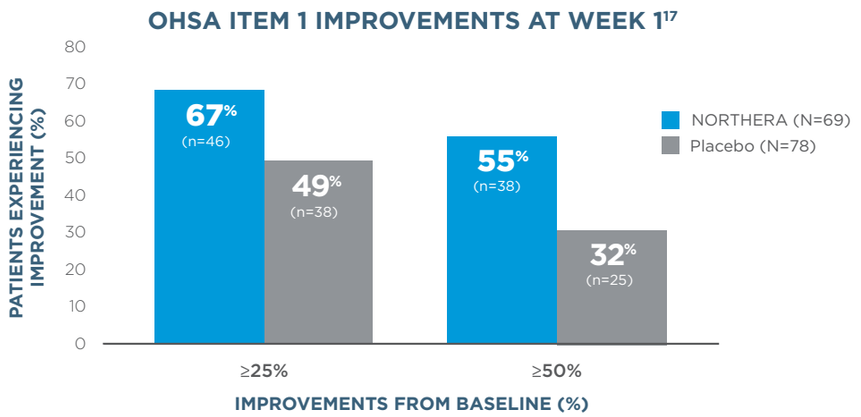
Study 306B: Secondary descriptive analyses

73% of NORTHERA® (droxidopa)-treated patients vs 59% of placebo patients reported an improvement in OHSA Item 1 scores[17]



Study 306B: Secondary descriptive analyses

At Week 1, more than half of NORTHERA-treated patients showed ≥50% improvement in OHSA Item 1 scores[17]



CONTRAINDICATIONS

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

ADVERSE REACTIONS

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

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 (glomerular filtration rate [GFR] <30 mL/min) is limited; therefore, dosing recommendations cannot be provided for these patients.

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.

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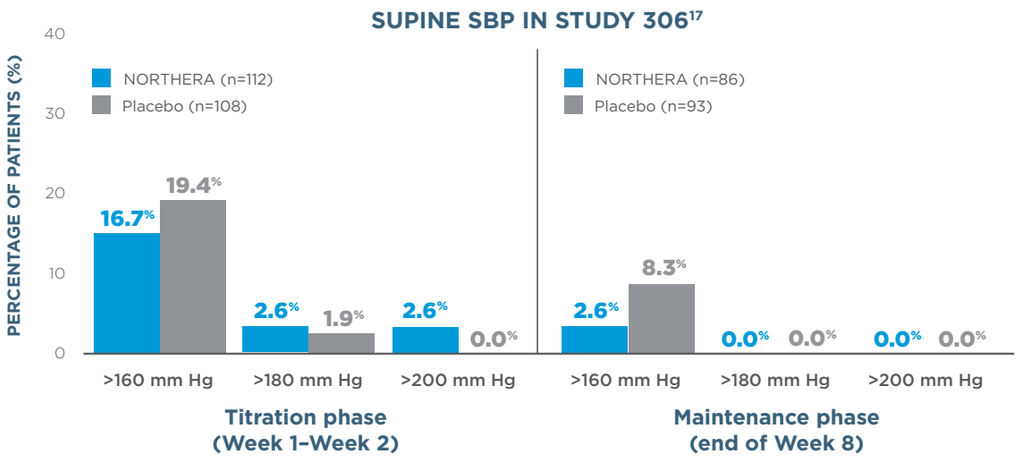
Study 306:

Supine blood pressure was measured at each study visit[17]



- **Overall, rates of supine hypertension (SBP >180 mm Hg at all supine measurements during the orthostatic standing test) were slightly higher in NORTHERA® (droxidopa) patients (7.9%) compared with placebo patients (4.6%)[17]**
- Supine blood pressure measurements were taken with upper body at 30-degree tilt 3 hours after administration of morning dose[17]
- Sustained severe hypertension (SBP ≥180 mm Hg or DBP ≥110 mm Hg in the seated or supine position observed in 3 consecutive measurements over an hour) at the screening visit was an exclusion criterion for the study[17]
  - –Dose escalation was stopped if supine SBP rose to ≥180 mm Hg or DBP to ≥110 mm Hg during dose escalation[17]
- To reduce the potential for supine hypertension, elevate the head of the bed and give the last dose of NORTHERA at least 3 hours prior to bedtime[1]

No prolongation of the QTc interval was observed in a QT study[1,17]

No prolongation of the QTc interval was observed with NORTHERA at single oral doses up to 2000 mg, as shown in a dedicated, thorough QT study in healthy volunteers.

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.

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.

Safety was assessed in controlled clinical trials and long-term, open-label studies

In the short-term, placebo-controlled studies, the most common adverse reactions were headache, dizziness, nausea, and hypertension[1]

	Study 306[1] (8 to 10 weeks randomized treatment)		Study 301 and 302[1] (1 to 2 weeks randomized treatment)	
Adverse reaction	**NORTHERA (N=114) n (%)**	**Placebo (N=108) n (%)**	**NORTHERA (N=131) n (%)**	**Placebo (N=132) n (%)**
Headache	15 (13.2)	8 (7.4)	8 (6.1)	4 (3.0)
Dizziness	11 (9.6)	5 (4.6)	5 (3.8)	2 (1.5)
Nausea	10 (8.8)	5 (4.6)	2 (1.5)	2 (1.5)
Hypertension	8 (7.0)	1 (0.9)	2 (1.5)	0 (0.0)

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.[1]

- The most common adverse reactions leading to discontinuation of NORTHERA were hypertension and nausea[1]

Long-term assessments of the safety of NORTHERA were conducted in both Study 303 and Study 304[1]

- Study 303 and Study 304 evaluated safety for 12 months and up to 36 months, respectively[1,17]
- 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 1 year. The commonly reported adverse reactions were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%)[1]

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NORTHERA® (droxidopa) can be titrated every 24 to 48 hours to symptomatic response[1]

RECOMMENDED NORTHERA TITRATION (total daily dose)[1]

START	TITRATE UP	MAINTAIN
300 mg (100 mg three times a day)	**300 mg** (100 mg three times a day) **every 24 to 48 hours to symptomatic response**	**Dosage strength based on symptomatic relief established through titration*** Higher-strength capsules allow patients to take fewer pills

*Recommended maximum dose 1800 mg (600 mg three times a day).[1]

- Monitor supine blood pressure prior to and during treatment and more frequently when increasing doses[1]
- Patients can download a diary at nOHdiary.com to track their symptoms and BP readings throughout treatment

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.[1]

Switching patients to higher-strength capsules may help reduce the number of pills taken daily.

For oral administration. Not actual sizes.

INDICATIONS AND USAGE

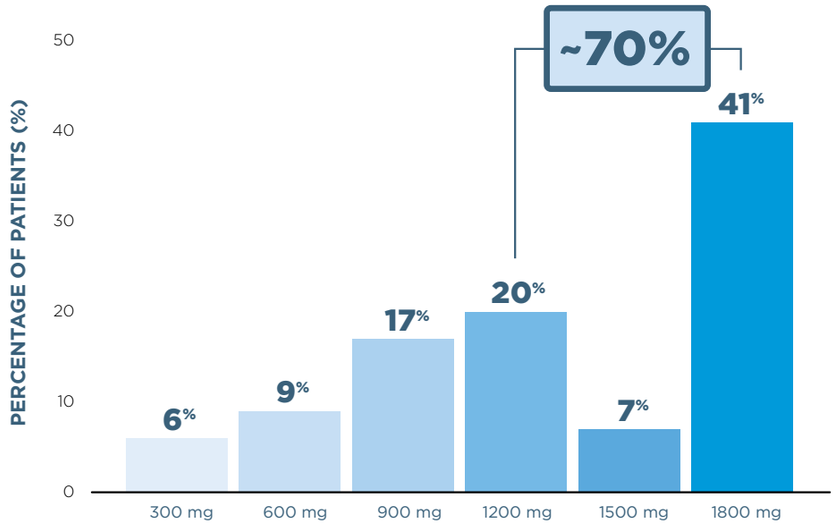
NORTHERA is indicated for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic nOH caused by primary autonomic failure (Parkinson's disease [PD], multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase 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.

WARNINGS AND PRECAUTIONS

- **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.

~70% of patients received a maintenance dose of at least 1200 mg (400 mg three times a day)[17]

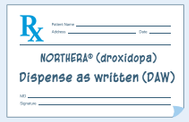
TOTAL DAILY DOSING EXPERIENCE (STUDY 306B; n=69)[17]



- About 40% of patients received the maximum total daily dose of 1800 mg (600 mg three times a day)[17]
- Dose escalation was stopped if[17]:
  - –Sustained supine SBP rose to ≥180 mm Hg or DBP to ≥110 mm Hg
  - –The patient became asymptomatic, reached the maximum dose, or was unable to tolerate side effects believed to be related to the study drug
- Fewer than 10% of patients remained at the starting dose of 300 mg (100 mg three times a day)[17]

The goal of nOH treatment: reduce symptoms reported by patients

Considering that nOH is due to autonomic dysfunction and often associated with an underlying neurodegenerative disorder, restoring BP to a normal range may not be a feasible treatment goal. Instead, therapy should focus on symptom improvement in nOH patients.[2,5,6,19]



If you decide that NORTHERA is clinically appropriate for your patients, write "Dispense as written" on the prescription to help ensure patients receive their medication exactly as prescribed.

ADVERSE REACTIONS

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

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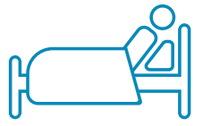
Important dosing information

NORTHERA® (droxidopa) should be taken 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.[1]

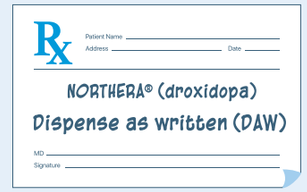
- NORTHERA capsules should be taken whole, the same way each time, either with food or without food[1]
- If a dose is missed, the next dose should be taken at the regularly scheduled time. The patient should not double the next dose[1]
- Patients should be advised to elevate the head of the bed when resting or sleeping[1]



- If supine hypertension is not well managed, NORTHERA may increase the risk of cardiovascular events, particularly stroke[1]
- Reduce or discontinue NORTHERA if supine hypertension persists[1]
- Use of or change in dose of dopa-decarboxylase inhibitors may require dose adjustments for NORTHERA[1]
- 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[1]
- 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[1]

Why "Dispense as written" matters

NORTHERA has been dedicated to helping provide relief from symptomatic nOH for several years for appropriate symptomatic nOH patients. If you decide that NORTHERA is clinically appropriate for your patients, write "Dispense as written" on the prescription or follow your state's instructions for indicating branded vs generic product to help ensure patients receive NORTHERA as intended.



CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- **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.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

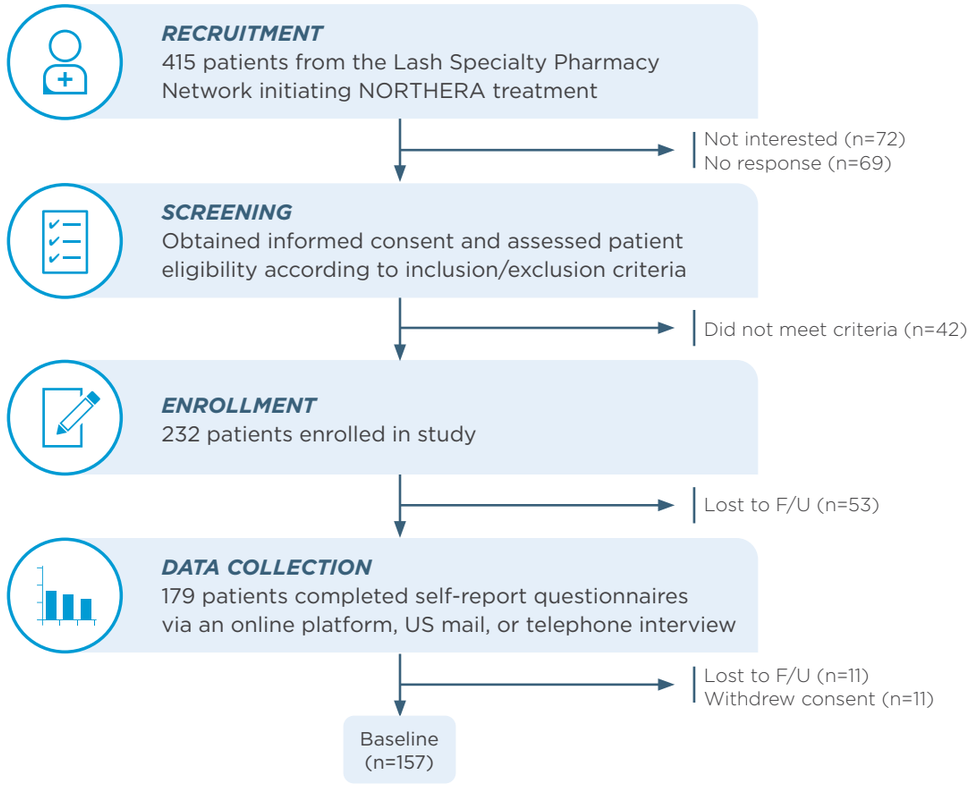
Northera®
(droxidopa) capsules
100 mg • 200 mg • 300 mg

Real-world experience

Observational study of patients prescribed NORTHERA® (droxidopa) followed up to 6 months[20]

Study design[1,17,20]

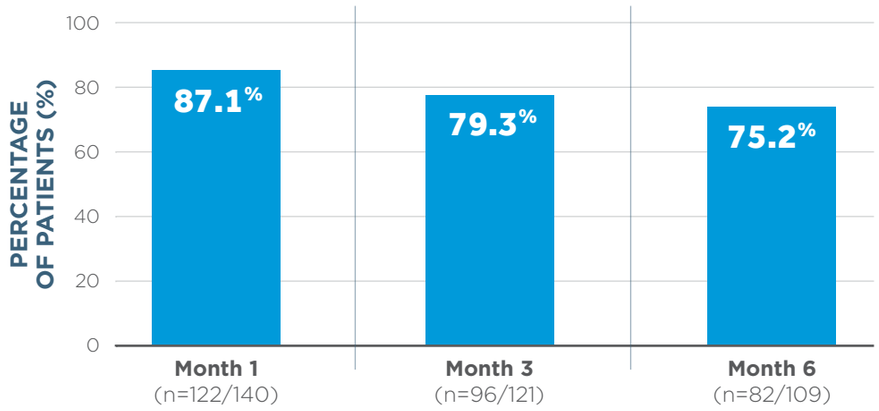
- A non-interventional, US-based, prospective cohort study of adult patients aged ≥18 years with a diagnosis of primary autonomic failure (PD, MSA, PAF), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy, who were newly prescribed NORTHERA (no treatment in the prior year) for symptomatic nOH
- Patients were enrolled through a central hub (HUB) by Lash Specialty Pharmacy Network, and continuation of NORTHERA beyond 2 weeks was at the prescriber's discretion
- Continued participation in the study was not a condition for continuing treatment with NORTHERA



Patient sample/sample characteristics[20]

- The 179 patients who completed the baseline surveys had a mean age of 62.8 years
- The mean total daily maintenance dose for NORTHERA was 1014.5 mg
- Baseline medication usage in >5% of patients included midodrine, fludrocortisone acetate, levodopa-carbidopa, pyridostigmine, dopamine agonists, pseudoephedrine or ephedrine, monoamine oxidase B inhibitors, carbidopa/levodopa/entacapone; however, information concerning continuation of baseline medications was not collected

PATIENTS REPORTING CONTINUING TREATMENT WITH NORTHERA[20]



- Not all patients who completed the questionnaire at Month 6 also did at baseline, Month 1, and Month 3. Similarly, not all patients who completed the questionnaire at Month 3 did at baseline and Month 1[17]

Effectiveness beyond 2 weeks of treatment has not been established. The continued effectiveness of NORTHERA should be assessed periodically. The RESTORE clinical study to assess the sustained effects of NORTHERA therapy in adult patients with symptomatic nOH is ongoing.[1,21]

Discontinuations[20]

- The most common reasons for discontinuation were adverse events, patient or prescriber choice, treatment with alternative medication, and other/unknown

Limitations[20]

- Recruitment and enrollment of patients were conducted by identifying eligible patients via the HUB. Patients who consented and were enrolled in the study may be different from those who did not consent
- 53 of the 232 patients enrolled in the study were lost to follow-up before completion of the baseline survey, which may have affected the observations of the study
- Observations relied on patient self-report, which could have resulted in recall bias or misclassification
- This was an uncontrolled study and no conclusions of statistical or clinical significance can be drawn

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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

Two options to prescribe NORTHERA® (droxidopa)

CHOOSE THE OPTION THAT WORKS BEST FOR YOU AND YOUR PATIENTS

Through the Northera Support Center (NSC)

The NSC can help your patient through the prescription process. Complete and fax the NORTHERA Treatment Form to the NSC.

Insurance coverage information

Coordinates with your patient, insurance provider, and you to confirm coverage and informs patients of available financial assistance options.

The StarterRx Program*

Provides a one-time 30-day supply to new, eligible, commercially insured patients age 17 and older with a valid prescription.

Ongoing support

Coordinates delivery of initial prescription and answers frequently asked questions throughout treatment.

Visit **StartNORTHERA.com** or contact the NSC at:
Phone: 1-844-601-0101 **Fax:** 1-844-601-0102

OR

Direct to a Specialty Pharmacy

Prescribe through your electronic medical record system with one of our in-network specialty pharmacies.

Accredo
Phone: 844-412-4764 **Fax:** 888-302-1028

AllianceRx Walgreens Prime
Phone: 888-347-3416 **Fax:** 877-231-8302

CVS Specialty
Phone: 877-437-8469 **Fax:** 844-691-1345

NO TREATMENT FORM REQUIRED

$10 As little as a **COPAY PER MONTH** for eligible patients*

Image above is not a real Commercial Copay Assistance card.

Commercially insured patients age 17 years and older with a valid NORTHERA prescription may pay as little as $10 per month through the NORTHERA Commercial Copay Assistance Program, if eligible. Copay assistance is available as allowed by individual states.†

For information on eligibility and how to obtain Commercial Copay Assistance for your patients, please

- Visit **NORTHERAhcp.com** or
- Call 1-855-820-6768

Steps to enroll a patient in the NORTHERA Commercial Copay Assistance Program

1. Healthcare provider prescribes **NORTHERA**
2. *Confirm eligibility* and enroll by calling **1-855-820-6768** OR by visiting **NORTHERAhcp.com/Copay**
3. Eligible patient *receives* specific Commercial Copay Assistance Program information (BIN/Group/PCN/ID numbers) at the time of enrollment
4. Eligible patient *provides* specific Commercial Copay Assistance Program information (BIN/Group/PCN/ID numbers) to the specialty pharmacy upon coordination of prescription fulfillment

Remind your patients to share their copay assistance information when the Specialty Pharmacy calls to coordinate prescription fulfillment.

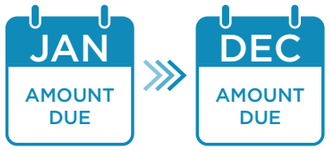
*Terms and Conditions for Commercial Copay Assistance follow this brochure. Patients are not eligible for this assistance if they are uninsured or if the prescription is eligible to be reimbursed, in whole or in part, by any state or federal health care programs, including but not limited to Medicare or Medicaid, Medigap, VA, DOD, or TRICARE. Maximum benefit limits may apply. Terms and Conditions for all NORTHERA patient support programs can be found at NORTHERAhcp.com.

†Certain states may not allow commercial copay support if a generic product is available. Please check the policies in your prescribing state for compliance.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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

Assistance is available when you prescribe NORTHERA® (droxidopa)



Medicare Part D plans are all different, and the amount your patient pays at the beginning of the year may be different by year's end.[22,23*]

Additional resources for finding coverage information and financial support under Medicare Part D[22]

Visit the Medicare Plan Finder at www.medicare.gov/find-a-plan

Call 1-800-MEDICARE (1-800-633-4227)

Visit the State Health Insurance Assistance Programs (SHIP) for free personalized health insurance counseling at www.shiptacenter.org

The NSC or your patient's Specialty Pharmacy may have information about independent foundation options for assistance with out-of-pocket drug costs for patients with Medicare

*HCPs and patients should contact a plan directly to confirm its specific requirements.

Eligible Medicare Part D patients may be able to access NORTHERA at a low cost[22]

"Extra Help" is a Low Income Subsidy (LIS) program that provides financial assistance to patients with limited income or resources by covering some or most of their Medicare prescription drug costs[22]

Patients who are "dual eligible" (qualify for both Medicare and Medicaid) or who receive Supplemental Security Income are automatically enrolled in Extra Help. Others can apply for Extra Help by[22]

- Visiting www.socialsecurity.gov/i1020
- Calling Social Security at 1-800-772-1213

If they qualify, patients can receive full or partial Extra Help benefits based on their income and assets in relation to the federal poverty level.

Patients can apply for Extra Help at any time without waiting for open enrollment periods.[22]

This information is subject to change. Lundbeck does not control the Medicare Part D plan terms or the Low Income Subsidy (LIS) program and does not make any guarantees regarding coverage. These programs have nuances that could impact program eligibility and coverage details for individual patients. Any information regarding these programs is not intended to imply disease prevalence or influence HCPs' independent medical judgments regarding patients for whom NORTHERA may be appropriate.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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

Use CoverMyMeds to streamline the prior authorization (PA) approval and appeals processes for NORTHERA® (droxidopa)[17,25]

covermymeds®

CoverMyMeds electronically connects providers, pharmacists, and health plans, helping patients to more quickly get the medication they need.[25]

After prescribing NORTHERA, initiate a PA using CoverMyMeds.

CoverMyMeds performance data for NORTHERA PA requests[17]*

87% of submitted NORTHERA ePA requests have a determination within **24 hours**

92% of submitted NORTHERA ePA requests have a determination within **48 hours**

77.5% average approval rate for submitted NORTHERA PA[17†]

ePA = electronic prior authorization.

*Based on May 2021 data.
†Based on May 2021 YTD data.

For additional information, call CoverMyMeds toll-free at **1-866-452-5017** or visit **www.CoverMyMeds.com**.

Standing by you

NORTHERA stands by you and your patients every step of the way, to support patient access to the medication they need. With a breadth of patient access support offerings and other resources—such as a patient diary, titration guide, and patient videos—you can continue to help them keep going.

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

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

Important Safety Information

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.

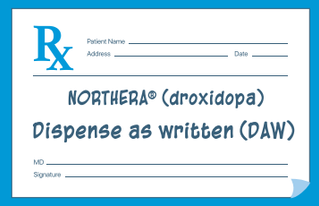
USE IN SPECIFIC POPULATIONS

- 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.

References: 1. NORTHERA [package insert]. Deerfield, IL: Lundbeck. **2.** Freeman R. Neurogenic orthostatic hypotension. *N Engl J Med.* 2008;358(6):615-624. **3.** Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. *Circulation.* 2009;119(1):139-146. **4.** Bradley JG, Davis KA. Orthostatic hypotension. *Am Fam Physician.* 2003;68(12):2393-2398. **5.** Gibbons CH, Schmidt P, Biaggioni I, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. *J Neurol.* 2017;264(8):1567-1582. **6.** Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res.* 2011;21(2):69-72. **7.** Kaufmann H, Malamut R, Norcliffe-Kaufmann L, et al. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. *Clin Auton Res.* 2012;22(2):79-90. **8.** Palma JA, Kaufmann H. Epidemiology, diagnosis, and management of neurogenic orthostatic hypotension. *Mov Disord Clin Pract.* 2017;4(3):298-308. **9.** Isaacson SH, Skettini J. Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa. *Vasc Health Risk Manag.* 2014;10:169-176. **10.** Kaufmann H, Norcliffe-Kaufmann L, Palma JA. Droxidopa in neurogenic orthostatic hypotension. *Expert Rev Cardiovasc Ther.* 2015;13(8):875-891. **11.** Charkoudian N, Rabbitts JA. Sympathetic neural mechanisms in human cardiovascular health and disease. *Mayo Clin Proc.* 2009;84(9):822-830. **12.** Jordan J, Shibao C, Biaggioni I. Multiple system atrophy: using clinical pharmacology to reveal pathophysiology. *Clin Auton Res.* 2015;25(1):53-59. **13.** Low PA. Neurogenic orthostatic hypotension: pathophysiology and diagnosis. *Am J Manag Care.* 2015;21(suppl 13):s248-s257. **14.** Shibao C, Lipsitz LA, Biaggioni I. Evaluation and treatment of orthostatic hypotension. *J Am Soc Hypertens.* 2013;7(4):317-324. **15.** Centers for Disease Control and Prevention. Measuring orthostatic blood pressure. https://www.cdc.gov/steadi/pdf/STEADI-Assessment-MeasuringBP-508.pdf. Accessed January 25, 2019. **16.** Di Stefano A, Sozio P, Cerasa LS. Antiparkinson prodrugs. *Molecules.* 2008;13(1):46-68. **17.** Data on file. Deerfield, IL: Lundbeck. **18.** Hauser RA, Isaacson S, Lisk JP, et al. Droxidopa for the short-term treatment of symptomatic neurogenic orthostatic hypotension in Parkinson's disease (nOH306B). *Mov Disord.* 2015;30(5):646-654. **19.** Isaacson SH. Managed care approach to the treatment of neurogenic orthostatic hypotension. *Am J Manag Care.* 2015;21(suppl 13):s258-s268. **20.** Francois C, Shibao CA, Biaggioni I, et al. Six-month use of droxidopa for neurogenic orthostatic hypotension. *Mov Disord Clin Pract.* 2019;6(3):235-242. **21.** U.S. National Library of Medicine. Sustained effect of droxidopa in symptomatic neurogenic orthostatic hypotension (RESTORE). Clinical Trials website. https://clinicaltrials.gov/ct2/show/results/NCT02586623. Accessed July 21, 2020. **22.** Centers for Medicare & Medicaid Services. Medicare & you: 2021. https://www.medicare.gov/Pubs/pdf/10050-Medicare-and-You.pdf. Accessed June 23, 2021. **23.** Medicare Interactive. Phases of Part D coverage. https://www.medicareinteractive.org/get-answers/medicare-prescription-drug-coverage-part-d/medicare-part-d-costs/phases-of-part-d-coverage. Accessed August 2, 2021. **24.** National Council on Aging. Part D Low-Income Subsidy (LIS/Extra Help). https://www.ncoa.org/article/part-d-low-income-subsidy-extra-help-eligibility-and-coverage-chart. Updated January 2021. Accessed August 2, 2021. **25.** CoverMyMeds. https://www.covermymeds.com/main/support/general/what-is-covermymeds/. Accessed May 13, 2020.

Please see the accompanying full Prescribing Information, including Boxed Warning for supine hypertension, or go to NORTHERAhcp.com.

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



If you decide that NORTHERA® (droxidopa) is clinically appropriate for your patients, write "Dispense as written" on the prescription to help ensure patients receive their medication exactly as prescribed.

Distinctive. Effective. Focused.

NORTHERA is the only treatment *specifically studied* to reduce the classic symptoms of neurogenic orthostatic hypotension (nOH)[1,2]

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 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.

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.

- **Patients on NORTHERA reported an improvement in symptoms of orthostatic dizziness, lightheadedness, or "feeling like you might black out" at Week 1 compared to placebo, as measured by OHSA Item 1 scores[1]**
- **73% of NORTHERA-treated patients vs 59% of placebo patients reported an improvement in these symptoms in a secondary descriptive analysis at Week 1[17]**
- **At Week 1, more than half of NORTHERA-treated patients showed ≥50% improvement in OHSA Item 1 scores in a secondary descriptive analysis[17]**
- **NORTHERA is contraindicated in patients who have a history of hypersensitivity to the drug or its ingredients[1]**
- **The most common adverse reactions (>5% and ≥3% difference compared to placebo) were headache, dizziness, nausea, and hypertension[1]**
- **Titrate each patient every 24 to 48 hours to symptomatic response[1]**

Please see Important Safety Information, including Boxed Warning for supine hypertension, on Page 14. For more information, see the accompanying full Prescribing Information, or go to NORTHERAhcp.com.

Lundbeck

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

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*

*Sections or subsections omitted from the full prescribing information are not listed.

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.

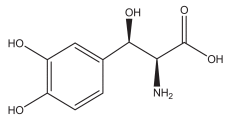
8.5 Geriatric Use
A total of 197 patients with symptomatic nOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified 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.

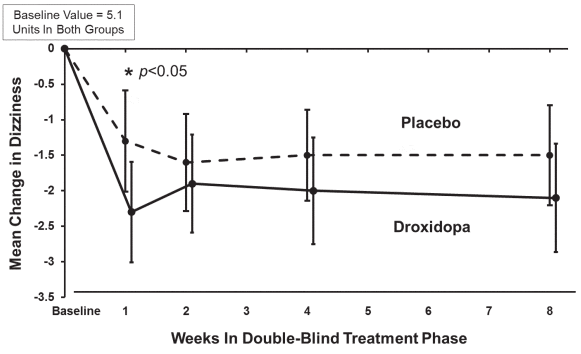
Efficacy was measured using the OHSA Item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at Week 1, in patients who had completed titration and 1 week of maintenance therapy.

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).

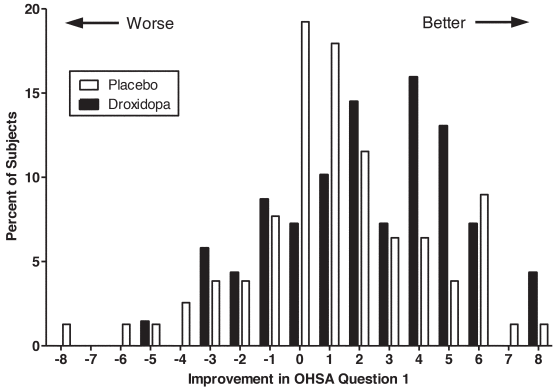
Figure 1. Mean Change in OHSA Item 1 Score by Week in Study 306B



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.

 DRX-L-00010v2