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

DON'T GIVE UP ON WHAT MOVES YOU

A guide to your treatment for dizziness, lightheadedness or the feeling that you are going to black out

USE

NORTHERA (droxidopa) is a prescription medication used to reduce dizziness, lightheadedness, or the "feeling that you are about to black out" in adults who experience a significant drop in blood pressure when changing positions or standing (called symptomatic neurogenic orthostatic hypotension) and who have Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been established, and your doctor will decide if you should continue taking NORTHERA.

WARNING: SUPINE HYPERTENSION (this is high blood pressure while lying down)

When lying down, elevating the head and upper body lowers the risk of high blood pressure. Check your blood pressure in this position prior to starting and during NORTHERA treatment. If you experience high blood pressure, talk to your doctor about your NORTHERA treatment.

Please see complete Important Safety Information, including Boxed Warning for supine hypertension, on pages 26 and 27 and the full Prescribing Information at the end of this document.

LEARN MORE ABOUT SYMPTOMATIC nOH AND NORTHERA® (DROXIDOPA)

About Symptomatic nOH

Symptomatic nOH can occur in people who have Parkinson's disease, multiple system atrophy (MSA), or pure autonomic failure (PAF). People with symptomatic nOH may experience a sustained drop in blood pressure when standing up, changing positions, or standing for a long period of time. This may cause symptoms such as dizziness, lightheadedness, and the feeling that they are about to black out.

There is no cure for symptomatic nOH, but NORTHERA may help reduce these symptoms.

This brochure is intended to help you learn more about NORTHERA and its use in treating people with symptomatic nOH.

Do not take NORTHERA if you have a known allergy to NORTHERA or its ingredients.

What's Inside

Please see complete Important Safety Information, including Boxed Warning for supine hypertension, on pages 26 and 27 and the full Prescribing Information at the end of this document.

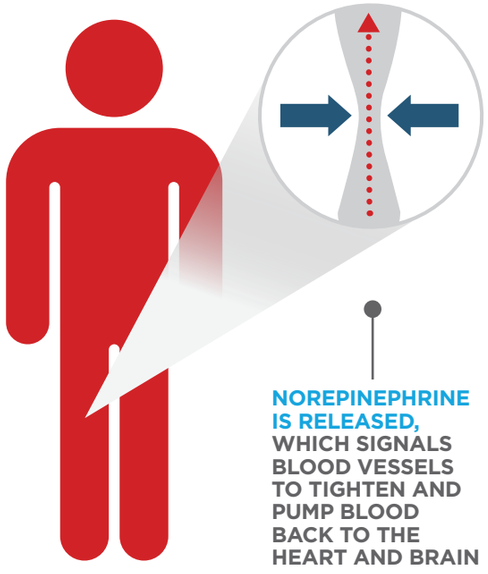
What Causes Symptomatic nOH?

After you stand up,
gravity pulls the blood toward the lower part of your body, lowering your blood pressure. When this happens, your nervous system typically releases a chemical called norepinephrine, which signals your blood vessels to tighten, or constrict. This raises your blood pressure and makes it easier for your body to pump blood back up to the heart and brain.

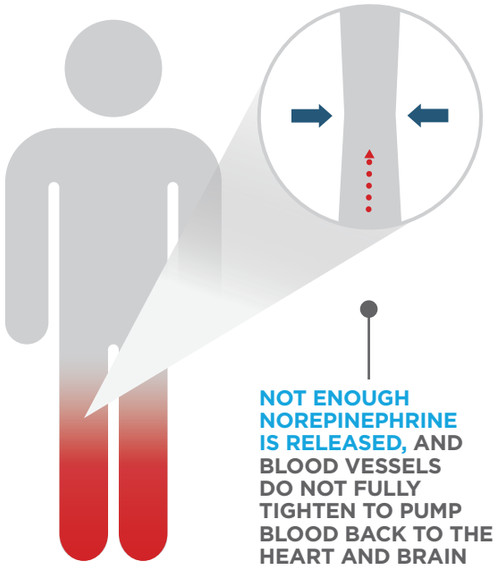
If you have a nervous system disorder,
such as Parkinson's disease or MSA, your body may not release enough norepinephrine when you stand. As a result, your blood vessels are unable to tighten as they should. Your blood pressure may remain low after standing, which prevents blood from moving back up to your heart and brain.

This reduced blood supply to your brain is what can cause symptoms like dizziness, lightheadedness, and the feeling that you are about to black out.

Without nOH (normal blood flow)



With nOH (decreased blood flow)



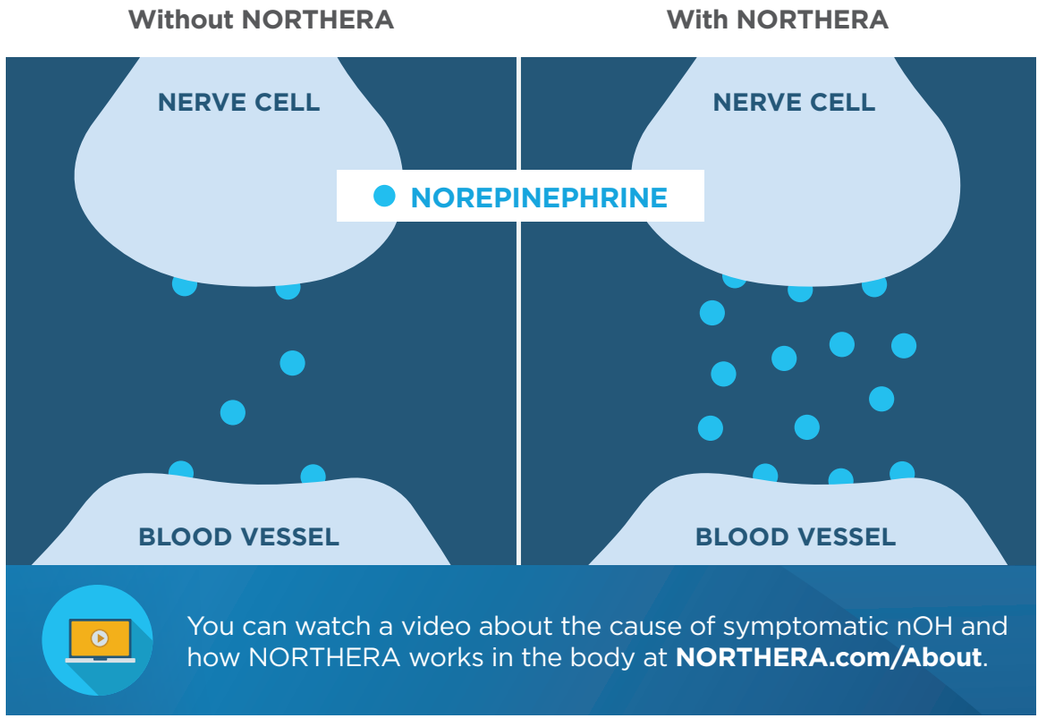
Important Risk Information

NORTHERA may cause high blood pressure when lying down, which could lead to strokes, heart attacks, and death. To reduce this risk of supine hypertension, take your late afternoon dose of NORTHERA at least 3 hours before going to bed.

Information About NORTHERA® (droxidopa)

How NORTHERA Works

The exact way NORTHERA works is unknown. However, one of the effects of NORTHERA is a small and temporary increase in norepinephrine, a chemical in the body that signals your blood vessels to tighten and helps to regulate blood pressure.



This is a graphical representation for illustrative purposes only.

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WHAT MOVES MARYGAIL

When my dad first started experiencing symptoms of nOH, he would say, “I’m dizzy” when he got up. And when he got out of bed, he would say, “I’m seeing black,” or “I feel like I’m going to black out.”

We found a neurologist who specialized in treating movement disorders, like Parkinson’s, and he read all of my dad’s medical information, including blood pressure readings we had taken in different positions. The doctor said, “I think this is symptomatic neurogenic orthostatic hypotension.” He also told us that there’s a medication called NORTHERA® (droxidopa) that is used to help manage certain symptoms of nOH in people with Parkinson’s, like my dad.

In my dad’s experience, NORTHERA helped improve his dizziness when standing up.

—MARYGAIL, CARE PARTNER TO HER FATHER, RALPH, WHO HAS PARKINSON’S DISEASE AND SYMPTOMATIC nOH

Important Risk Information

If you have coronary artery disease, irregular heartbeat, or heart failure, NORTHERA may worsen the symptoms of these disorders. Call your doctor if your symptoms become worse.

Spending time with my dad.

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FIRST AND ONLY

NORTHERA® (droxidopa) is the first and only FDA-approved treatment specifically studied in patients with symptomatic nOH.

PATIENTS SAW AN IMPROVEMENT IN SYMPTOMS OF DIZZINESS, LIGHTHEADEDNESS, AND THE FEELING THAT YOU ARE ABOUT TO BLACK OUT BY WEEK 1

The FDA approval of NORTHERA was based on a clinical study of 171 adults with Parkinson's disease and symptomatic nOH. Patients rated their symptoms on a scale of 0 to 10, with 0 being no symptoms at all and 10 being the most severe. After being treated for 1 week, patients taking NORTHERA reported a change of almost 1 point on the symptom scale compared to patients taking placebo (sugar pill), and reported a reduction in these symptoms.

Before starting the study, patients on average rated their symptoms of dizziness, lightheadedness, and the feeling of being about to black out at about 5 on the scale.

73%
OF PATIENTS TAKING NORTHERA
had a reduction of these symptoms by 1 point or more on the symptom scale

COMPARED WITH
59%
OF PATIENTS TAKING PLACEBO

NORTHERA MAY NOT WORK FOR EVERYONE

Three clinical studies did not show a clear benefit from taking NORTHERA. The effectiveness of NORTHERA beyond 2 weeks of treatment has not been established, and your doctor will decide if you should continue taking NORTHERA.

THE SAFETY OF NORTHERA WAS BASED ON:

3 SHORT-TERM STUDIES

2 LONG-TERM STUDIES

The most common side effects of NORTHERA in the short-term studies were headache, dizziness, nausea, and high blood pressure.

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Information About Taking NORTHERA® (droxidopa)

NORTHERA is a capsule that is **taken by mouth 3 times per day**. Here is some information about taking NORTHERA:

Always take NORTHERA as prescribed by your doctor.

Take NORTHERA with or without food, but make sure you take it the same way every time.

Take your late afternoon dose of NORTHERA at least 3 hours before bedtime to reduce the risk of supine hypertension (high blood pressure when lying down).

Take NORTHERA as scheduled.
If you miss a dose:

- **Take your next dose at the regularly scheduled time.**
- **Do not take 2 doses to make up for the dose you missed.**

Take NORTHERA capsules whole. (Do not open the capsule.)

Do not stop taking NORTHERA without talking to your doctor first.

Taking NORTHERA with other medications may cause side effects. Tell your doctor if you take prescription or over-the-counter medicines, vitamins, or herbal supplements.

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Finding the Right Dose

When you start NORTHERA, your doctor will want to find the dose that works best for you. Your doctor will likely start you on NORTHERA at a low dose. Based on how you feel, he or she may increase the amount you take until you reach the dose that best manages your symptoms. This process is called titration.

When NORTHERA was studied in clinical trials, doses were increased every 1 to 2 days. Your doctor will determine if and when your dose should be increased.

To hear doctors describe titration and dosing for NORTHERA, visit **NORTHERA.com/Dosing.**

How Will I Know If NORTHERA Is Working?

One way to tell if NORTHERA is working is to keep track of your nOH symptoms and whether they have been reduced. Monitoring and recording your nOH symptoms will also help your doctor determine if you're taking the right dose of NORTHERA. This is especially important after your doctor makes changes to your dose.

Important Risk Information

NORTHERA may cause allergic reactions. Stop taking NORTHERA and contact your doctor right away, or go to the nearest emergency room if you experience any signs or symptoms of an allergic reaction such as: fast heartbeat, nausea, vomiting, swelling, trouble breathing, hives, or rash. NORTHERA contains tartrazine (FD&C Yellow No. 5), which may also cause an allergic reaction, especially if you have had a reaction to aspirin.

Understanding Supine Hypertension

If you have symptomatic nOH, you may experience **supine hypertension, which is high blood pressure when lying down**. Like with low blood pressure when standing, the damage caused by your underlying nervous system disorder (such as Parkinson's disease or MSA) can also affect your body's ability to control your blood pressure when lying down. NORTHERA® (droxidopa) may cause or worsen supine hypertension, which can increase the risk of strokes and other cardiovascular events.

You can reduce the risk of supine hypertension by:

Elevating the head of your bed at least 30 degrees when lying down

Taking your late afternoon dose of NORTHERA at least 3 hours before bedtime

It is important to monitor your blood pressure before starting NORTHERA to set a baseline for yourself. This will help you and your doctor understand whether you are regularly experiencing high blood pressure when lying down due to your symptomatic nOH or if the cause may be due to taking NORTHERA.

Talk to your doctor about any concerns you may have about supine hypertension.

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"I do sleep with the head of my bed elevated because my doctor was very clear that NORTHERA may cause high blood pressure when lying down, which could cause serious side effects."

—GAIL, LIVES WITH PARKINSON'S DISEASE AND SYMPTOMATIC nOH

Visit NORTHERA.com/PatientDiary

to download your patient diary, which makes it easy to keep track of your NORTHERA dose, your nOH symptoms, and your blood pressure readings.

WHAT MOVES BOB?

The first symptom of nOH that I noticed was feeling lightheaded when I walked up stairs or a long way across the university campus where I work. Sometimes when I stood up, it felt like I had a weight on my head.

One of my favorite things to do is cook. It's relaxing for me, and I find it very rewarding to make a meal for the people I love. However, cooking often requires a great deal of standing, and sometimes I have to make adjustments due to feeling lightheaded. I would need to sit to chop food or ask my wife to help me watch things on the stove.

My neurologist prescribed me NORTHERA® (droxidopa) to help manage my symptomatic nOH. Taking NORTHERA has helped relieve my lightheadedness and the feeling that I'm going to black out.

—BOB, LIVES WITH PAF AND SYMPTOMATIC nOH

Important Risk Information

The most common side effects with NORTHERA are headache, dizziness, nausea, and high blood pressure.

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Prescription Coverage

Health insurance can be a confusing topic. Your health insurance plan will determine what is and isn't covered financially, how much you will pay for prescriptions, and what additional savings you may be eligible for. Let's take a look at your options under Medicare and commercial coverage.

Medicare	Commercial health insurance
Provided by the federal government	Offered by privately owned companies
For people 65 and older, or those with certain disabilities	Provided by your employer, or purchased on your own through the Affordable Care Act or otherwise
Optional prescription drug coverage (Medicare Part D)	

Medicare Part D and Your Prescription Coverage

Medicare is a federal health insurance program for people aged 65 and older, and/or people with certain disabilities. Medicare also provides prescription drug coverage through its Part D program. If you're enrolled in Medicare Part A or Part B, then you're eligible for Part D prescription coverage. Part D is optional, so to take part, you need to enroll in a Medicare Prescription Drug Plan or a Medicare Advantage Plan.

Every Medicare Part D plan is different, and many things can affect your prescription drug costs. For instance, what you pay for NORTHERA® (droxidopa) could depend on which "stage" of Part D coverage you're in: deductible, initial coverage, coverage gap, or catastrophic coverage.

The information provided in this brochure regarding Medicare Part D, Low Income Subsidy (LIS), and insurance coverage in general is being provided for informational purposes only.

Part D plans have many nuances that are not necessarily reflected in these materials. These nuances could impact program eligibility and coverage details for individual patients.

To learn more about Medicare Part D, visit **medicare.gov/drug-coverage-part-d**. Remember, not every Part D plan is the same. If you have questions about your personal Part D plan, contact your insurer.

Enrolling in Medicare Part D

In most cases, you can only enroll in or make changes to your Part D prescription drug coverage during the Fall Open Enrollment period (October 15 through December 7). Please note:

- Your new **Part D coverage would begin January 1** of the following year.
- Certain situations or life events may allow you to make changes outside of the Fall Open Enrollment period, such as:
  - Moving out of your plan's service area
  - Moving into a nursing home or a similar institution
  - Getting or losing Medicaid

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Medicare's Extra Help Program Could Help You Pay Less for NORTHERA® (droxidopa)

Medicare's Extra Help, also known as the Low Income Subsidy (LIS), can help people with limited income get NORTHERA and other medications at a lower cost. The amount of this subsidy someone receives is determined by comparing the person's income and assets to the Federal Poverty Level. See **medicare.gov/medicare-and-you** for details.

How to find out if you're eligible for Extra Help

- You're automatically enrolled in Extra Help if you're "dual eligible," meaning you're enrolled in both Medicare and Medicaid.
- Otherwise, you can check your eligibility and apply for Medicare Extra Help by getting in touch with Social Security:

Online: **socialsecurity.gov/i1020**

Phone: **1-800-772-1213**

When you can enroll: If you wish to apply for Extra Help, you may do so at any time.

Discover ways to get coverage and financial support under Medicare Part D

- Visit the Medicare Plan Finder at **medicare.gov/find-a-plan** to help you locate Part D plans based in your area.
- Call **1-800-MEDICARE (1-800-633-4227).**
- Call your State Health Insurance Assistance Program (SHIP) for free personalized health insurance counseling. To get the most up-to-date SHIP phone numbers, visit **shiptacenter.org.**

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 healthcare professionals' independent medical judgments regarding patients for whom NORTHERA may be appropriate.

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Commercial Insurance for NORTHERA® (droxidopa)

Commercial insurance, also known as private insurance, is coverage that you get from your employer or buy directly from insurance companies through the marketplace.

Under commercial insurance, coverage for medications, including NORTHERA, varies from plan to plan. Many plans have networks of participating pharmacies, and you generally will pay less for prescriptions filled at one of these "in-network" pharmacies. The information provided here is for your information only. Contact your insurer for information regarding your coverage.

Here are a few common terms you might come across if you have commercial insurance:

Prior authorization: Before agreeing to cover your prescription, your plan asks your doctor to provide information about why you need NORTHERA.

Step therapy: You may be required to try a certain medication before your plan will agree to cover your prescription for NORTHERA.

Formulary: A formulary is a list of generic and brand-name prescription medicines covered by your plan.

Premium: The premium is a monthly fee that is charged by your insurance plan.

Out-of-pocket costs: After the premium is paid, any *additional* costs that are not covered by your insurance (for example, your deductible or copayments) are considered "out-of-pocket" costs.

NORTHERA Commercial Copay Assistance Program

The NORTHERA Commercial Copay Assistance Program can help eligible commercial patients with their copays for NORTHERA.

Image above is not a real Commercial Copay Assistance card*

To be eligible, patients must

- Be aged 17 years or older.
- Have commercial prescription insurance.
- Have a valid prescription for NORTHERA that is not eligible for reimbursement through any state or federal healthcare programs.
- Meet all other eligibility requirements set forth in the NORTHERA Commercial Copay Assistance Program Terms and Conditions.

- 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 healthcare programs, including but not limited to Medicare or Medicaid, VA, DOD, or TRICARE.
- Pay at least $10 for each 30-day prescription.

Additional terms and conditions

- A maximum benefit limit may also apply; patients should confirm their out-of-pocket cost with their specialty pharmacy.
- To enroll in the NORTHERA Commercial Copay Assistance Program, either visit **NORTHERA.com/CopayAssistance** or call **1-855-820-6768** if you have questions.
- Complete terms and conditions for the NORTHERA Commercial Copay Assistance Program are enclosed in the pocket.

* Please note that a physical Commercial Copay Assistance card is not sent to participants. Copay information is sent electronically and should be printed out or written down so it can be shared with the specialty pharmacy over the phone.

This information is provided for informational purposes only. This information is subject to change, and Lundbeck makes no guarantees with regard to commercial plan coverage. Not all commercial coverage is the same, and nuances in your plan design may impact coverage for NORTHERA. If you have commercial insurance, contact your insurer for specific details regarding your coverage.

To determine your eligibility and enroll in the NORTHERA Commercial Copay Assistance Program, visit **NORTHERA.com/CopayAssistance**, or call **1-855-820-6768** with questions.

Please see complete Important Safety Information, including Boxed Warning for supine hypertension, on pages 26 and 27 and the full Prescribing Information at the end of this document.

4 Steps to Receiving Your NORTHERA® (droxidopa) Prescription

If your doctor has prescribed NORTHERA for your symptomatic nOH, here's what you can expect next:

Step 1: Processing your prescription

Your NORTHERA prescription will be filled by a specialty pharmacy. A specialty pharmacy is not like a regular drugstore where you pick your prescription up. Instead, the specialty pharmacy ships your medicine directly to your home.

The NORTHERA Support Center (NSC)

Your doctor has the option to send your prescription to the NSC instead of directly to a specialty pharmacy. If this is the case, your first phone call will be from an NSC support representative who will walk you through the prescription process outlined below. For more information on the NSC please see page 24.

Step 2: Determining insurance coverage

The specialty pharmacy will work with your insurance company to determine coverage for your NORTHERA prescription. This process could take a few days, during which you may receive a phone call from your specialty pharmacy to confirm some details.

It's important to always answer or return calls from the specialty pharmacy because they can't move forward without talking to you. **Keep in mind that these calls may appear as "Blocked" or "Unavailable" on your caller ID.** They will leave a voicemail asking you to return their call, but may not provide much detail beyond a callback number due to privacy laws.

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Step 3: Receiving your NORTHERA medicine

When your coverage and payment details have been confirmed, the specialty pharmacy will call you to coordinate the shipment of your NORTHERA. They must confirm payment and your shipping address *each time* they fulfill your prescription. If you have any questions about your medicine, ask to speak directly to a pharmacist or contact your doctor.

If you have commercial insurance, you may qualify for the NORTHERA Commercial Copay Assistance Program. Visit NORTHERA.com/CopayAssistance to find out if you're eligible. See page 21 of this brochure for more details.

Step 4: NORTHERA prescription refills

If your doctor prescribes refills, your prescription should be automatically refilled every 30 days. If you're a week away from needing a refill and have not heard from the specialty pharmacy, you should contact them to make sure everything is on track.

Remember, if you are eligible for the NORTHERA Commercial Copay Assistance Program, **be sure to mention this** to the specialty pharmacy each time you schedule your next shipment. Give them your Commercial Copay Assistance Program information (BIN, Group, PCN and ID numbers), located on your printout confirmation.

Important phone numbers

My specialty pharmacy: _____

My doctor's office: _____

My insurance company: _____

To reach the NORTHERA Support Center (NSC), call 1-844-601-0101 Monday-Friday, 8 AM-8 PM, EST.

More information about the NSC can be found on page 24.

Support Along the Way

In the event that your doctor sends your prescription to the NORTHERA Support Center (NSC) instead of directly to the specialty pharmacy, the NSC can assist you with the following:

Insurance coverage

- The NSC contacts your insurance carrier to confirm your coverage for NORTHERA, then provides that coverage information to both you and your doctor.
- If you are eligible, the NSC can enroll you in the NORTHERA Commercial Copay Assistance Program and provide information about any other financial assistance that may be available. See page 21 for details.

The StarterRx Program

The StarterRx Program provides a one-time, 30-day supply of NORTHERA to new, eligible, and commercially insured patients aged 17 years and older who have a valid NORTHERA prescription and an on-label diagnosis.

- Eligible commercially insured patients who have been prescribed NORTHERA by their doctor may qualify for the NORTHERA Commercial Copay Assistance Program or the StarterRx Program.
- **To learn more about the StarterRx Program, contact the NORTHERA Support Center toll-free at 1-844-601-0101, Monday–Friday, 8 AM–8 PM, EST.**
- Complete terms and conditions for the StarterRx Program are enclosed in the pocket.

Ongoing support

- The NSC will work with the specialty pharmacy to coordinate delivery of NORTHERA to your home. See page 22-23 for details.
- NSC representatives are also available to answer questions about any part of your treatment journey.

Complete terms and conditions for the NORTHERA Support Center are enclosed in the back pocket.

Please see complete Important Safety Information, including Boxed Warning for supine hypertension, on pages 26 and 27 and the full Prescribing Information at the end of this document.

Partnering With Your Doctor

Ongoing dialogue is key!
It is very important to tell your doctor how you're feeling and talk to him or her about your symptoms of nOH.

Use this page to write down any questions you have for your doctor, and then bring it to your next visit to write down the answers.

1 **Question:**

My doctor said:

2 **Question:**

My doctor said:

3 **Question:**

My doctor said:

“My doctor told me to take my late afternoon dose at least 3 hours before going to bed to reduce the risk of high blood pressure when lying down.”

—CAROL, LIVES WITH PARKINSON’S DISEASE AND SYMPTOMATIC nOH

Use and Important Safety Information

NORTHERA® (droxidopa) is a prescription medication used to reduce dizziness, lightheadedness, or the “feeling that you are about to black out” in adults who experience a significant drop in blood pressure when changing positions or standing (called symptomatic neurogenic orthostatic hypotension (nOH)) and who have one of the following:

- Parkinson’s disease (PD), a neurodegenerative disease that causes slowness in muscle movement as well as shaking in the hands
- Multiple system atrophy (MSA), a Parkinson’s-like disorder with more widespread effects on the brain and body
- Pure autonomic failure (PAF), a neurodegenerative disease that results in frequent drops in blood pressure upon standing
- Dopamine beta-hydroxylase deficiency, a condition where the body cannot make enough of the hormones that help regulate blood pressure
- Non-diabetic autonomic neuropathy, an inability to maintain blood pressure upon standing that can be caused by a number of rare diseases

Effectiveness beyond 2 weeks of treatment has not been established, and your doctor will decide if you should continue taking NORTHERA.

WARNING: SUPINE HYPERTENSION (this is high blood pressure while lying down)

When lying down, elevating the head and upper body lowers the risk of high blood pressure. Check your blood pressure in this position prior to starting and during NORTHERA treatment. If you experience high blood pressure, talk to your doctor about your NORTHERA treatment.

- Do not take NORTHERA if you have a known allergy to NORTHERA or its ingredients.
- NORTHERA may cause high blood pressure when lying down, which could lead to strokes, heart attacks, and death. To reduce this risk of supine hypertension, take your late afternoon dose of NORTHERA at least 3 hours before going to bed.
- Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening side effect reported with NORTHERA. Call your doctor right away and go to the nearest emergency room if you develop these signs and symptoms: high fever, stiff muscles, movements that you cannot control, confusion or problems thinking, very fast or uneven heartbeats, or increased sweating. NORTHERA should be stopped immediately if NMS is diagnosed.
- If you have coronary artery disease, irregular heartbeat, or heart failure, NORTHERA may worsen the symptoms of these disorders. Call your doctor if your symptoms become worse.
- NORTHERA may cause allergic reactions. Stop taking NORTHERA and contact your doctor right away, or go to the nearest emergency room if you experience any signs or symptoms of an allergic reaction such as: fast heartbeat, nausea, vomiting, swelling, trouble breathing, hives, or rash. NORTHERA contains tartrazine (FD&C Yellow No. 5), which may also cause an allergic reaction, especially if you have had a reaction to aspirin.
- The most common side effects with NORTHERA are headache, dizziness, nausea, and high blood pressure.
- Taking NORTHERA with other medications may cause side effects. Tell your doctor if you take prescription or over-the-counter medicines, vitamins, or herbal supplements.
- You should not breastfeed during treatment with NORTHERA.
- If you plan to become or are currently pregnant, talk to your doctor as it is not known if NORTHERA could harm your unborn baby.
- Take NORTHERA the same way each time, either with or without food.
- If you miss a dose of NORTHERA, take your next dose at the regularly scheduled time. Do not double the dose.

Please see the full Prescribing Information at the end of this document, including Boxed Warning for supine hypertension, or go to www.NORTHERA.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Patients who have limited financial resources and who do not have insurance coverage for NORTHERA® (droxidopa) may qualify for assistance through the Lundbeck Patient Assistance Program. Eligibility criteria apply. Visit NORTHERA.com for more information.

Terms and Conditions for the Northera® (droxidopa) Copay Assistance Program

Only commercially insured patients age 17 and older whose insurance policy provides coverage for Northera® (droxidopa) and who are not reimbursed for the entire cost of the prescription are eligible for the copay assistance (the "Offer"). Patients are not eligible for the Offer if they are self-pay or if the prescription is eligible to be reimbursed, in whole or in part, by any state or federal healthcare programs, including but not limited to Medicare or Medicaid, Medigap, VA, DOD, or TRICARE. In addition, patients may not use the Offer if they are Medicare-eligible and enrolled in an employer-sponsored health plan or prescription drug benefit program for retirees.

The Offer is valid only for use with a valid prescription for Northera at the time the prescription is filled by the pharmacist and dispensed to the patient. The Offer applies only to prescriptions filled before the program expires or terminates. The copay prescriptions shall not be submitted for reimbursement to any public third-party payer, including Medicaid or Medicare, or any other similar federal or state healthcare program. Patients are responsible for complying with any obligations or requirements imposed by their insurance plans.

The Offer is not transferable. The selling, purchasing, trading, or counterfeiting of the Offer is prohibited by law. The Offer has no cash value and may not be used in combination with any other discount, coupon, rebate, free trial, or similar offer for the specified prescription.

Lundbeck reserves the right to rescind, revoke, terminate, or amend the Offer without notice. The Offer is intended to comply with all applicable laws and regulations, including, without limitation, the federal Anti-Kickback Statute, its implementing regulations, and related guidance interpreting the federal Anti-Kickback Statute. The Offer is not health insurance. The Offer is valid only in the USA where allowed by law. There is no future purchase requirement associated with the Offer. Patient questions and requests to discontinue participation in the program can be directed to 1-844-601-0101 (8:00 am-8:00 pm ET, Monday through Friday).

Eligible commercially insured patients age 17 and older with a valid Northera prescription may participate in this program. Patients must pay at least $10 for each 30-day prescription. A maximum benefit limit may also apply. If the patient's total out-of-pocket pharmacy bill exceeds the cap established by Lundbeck, the patient will be responsible for the additional balance. Patients should confirm their out-of-pocket cost with their pharmacy at the time the pharmacy calls to dispense the prescription. By participating in the Copay Assistance Program, the patient acknowledges and agrees that he/she is eligible to participate and that he/she understands and agrees to comply with the General and Copay Assistance Terms and Conditions.

To the Pharmacist:

- Submit transaction to McKesson Corporation using BIN #610524
- Input card information as secondary coverage and transmit using the COB segment of the NCPDP transaction. Applicable discounts will be displayed in the transaction response
- Acceptance of this card and your submission of claims are subject to the LoyaltyScript® program. Terms and Conditions posted at **www.mckesson.com/mprstnc**
- For questions regarding claim transmission, call the LoyaltyScript® program at **1-800-657-7613** (8:00 am-8:00 pm ET, Monday through Friday)
- For questions regarding patient eligibility or other issues, call the Northera Support Center at **1-844-601-0101** (8:00 am-8:00 pm ET, Monday through Friday)

Terms and Conditions for Northera® (droxidopa) Informational Patient Support

Informational support provided through the Lundbeck Northera Support Center ("Informational Support") is available for eligible Northera patients only. Informational Support should not replace conversations between patients and their healthcare providers or their office staff, is not insurance or a guarantee of coverage or assistance, and has no independent value.

Patients are eligible for Informational Support if they have a valid prescription for Northera and a request is submitted to the Northera Support Center using a completed Northera Treatment Form. Informational Support includes insurance coverage information related to Northera and, depending on patient eligibility, information regarding other Lundbeck patient support programs. Separate applications may be required for Lundbeck programs to determine patient eligibility.

There may be other ways for patients to obtain assistance verifying insurance coverage for, and/or affording the cost of Northera. Questions regarding other possible sources of patient support should be directed to the patient's healthcare provider.

There is no purchase requirement associated with Informational Support. Informational Support is only provided in the USA where allowed by law. Informational Support is intended to comply with all applicable laws and regulations, including, without limitation, the federal Anti-Kickback Statute, its implementing regulations, and related guidance interpreting the federal Anti-Kickback Statute. Lundbeck reserves the right to rescind, revoke, or amend Informational Support without notice. Questions regarding Informational Support that may be available to a patient and opt-out requests should be directed to the Northera Support Center: Monday-Friday, 8:00 am to 8:00 pm, ET. 1-844-601-0101.

Terms and Conditions for the Northera® (droxidopa) StarterRx Program

Only new, commercially insured Northera patients age 17 years and older with an approved indication for Northera are eligible for the Northera StarterRx Program ("StarterRx"). Patients are not eligible for StarterRx if they are self-pay or if the prescription is eligible to be reimbursed, in whole or in part, by any state or federal healthcare programs, including but not limited to Medicare or Medicaid, Medigap, VA, DOD, or TRICARE. In addition, patients may not participate in StarterRx if they are Medicare-eligible and enrolled in an employer-sponsored health plan or prescription drug benefit program for retirees.

To be eligible for StarterRx, patients must have a Northera prescription that is consistent with the labeling for Northera. Patients are only eligible if they have never enrolled, either directly or through their healthcare provider, with the Northera Support Center and/or if they have never received StarterRx. To participate, the prescription for StarterRx must be submitted with a completed Northera Treatment Form to the Northera Support Center. Claims for product provided through StarterRx shall not be submitted for reimbursement to any private or public third-party payer, including Medicaid or Medicare, or any other state or federal healthcare program. Patients are responsible for complying with any obligations or requirements imposed by their insurance plans. Any product provided through StarterRx is intended solely for the patient for whom it has been prescribed.

Lundbeck reserves the right to rescind, revoke, or amend StarterRx without notice. StarterRx is intended to comply with all applicable laws and regulations, including, without limitation, the federal Anti-Kickback Statute, its implementing regulations, and related guidance interpreting the federal Anti-Kickback Statute. StarterRx is not health insurance. StarterRx is valid only in the USA where allowed by law. There is no future purchase requirement associated with StarterRx. Patient questions and requests to discontinue participation in StarterRx can be directed to 1-844-601-0101 (8:00 am -8:00 pm, ET, Monday through Friday). By participating in StarterRx, the patient acknowledges and agrees that he/she is eligible to participate and that he/she understands and agrees to comply with these terms and conditions.

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.

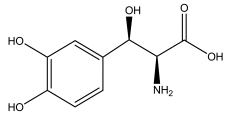
8.5 Geriatric Use
A total of 197 patients with symptomatic nOH aged 75 years or above were included in the NORTHERA clinical program. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified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

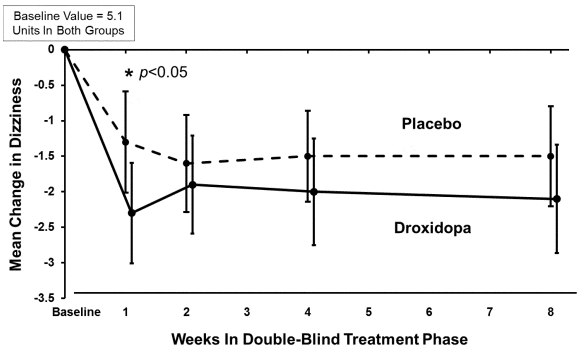
Efficacy was measured using the OHSA Item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at Week 1, in patients who had completed titration and 1 week of maintenance therapy.

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).

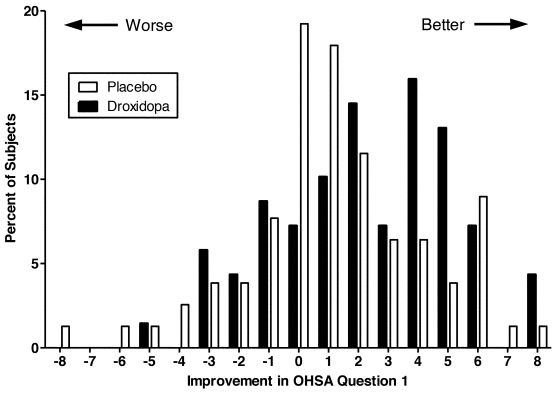
Figure 1. Mean Change in OHSA Item 1 Score by Week in Study 306B



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.

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