Northera® (droxidopa) Prior Authorization with Quantity Limit Program Summary

This program applies to the Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the prior authorization (PA) requirement for Northera is to encourage appropriate selection of symptomatic neurogenic orthostatic hypotension (NOH) patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. Criteria will limit the approved dose for Northera to at or below the maximum FDA labeled dose. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET AGENT
Northera® (droxidopa)

QUANTITY LIMIT TARGET AGENTS- RECOMMENDED LIMITS

Brand (generic)	GPI	Multisource Code	Quantity per Day Limit
Northera (droxidopa)			
100 mg capsule	38700030000130	M, N, O, or Y	15 capsules
200 mg capsule	38700030000140	M, N, O, or Y	6 capsules
300 mg capsule	38700030000150	M, N, O, or Y	6 capsules

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Northera (droxidopa) will be approved when ALL of the following are met:

1. ONE of the following
    A. The patient has a diagnosis of neurogenic orthostatic hypotension (NOH) AND ALL of the following
        i. The patient is 18 years of age or over
        AND
        ii. The prescriber has performed baseline blood pressure readings while the patient is sitting or in supine position AND also within 3 minutes of standing from a supine (lying face up) position
        AND
        iii. The patient has a decrease of at least 20 mmHg in systolic blood pressure or 10 mmHg diastolic blood pressure within three minutes after standing
        AND
        iv. The patient has persistent and consistent symptoms of neurogenic orthostatic hypotension (NOH) caused by ONE of the following:
            1. Primary autonomic failure [Parkinson's disease (PD), multiple system atrophy, or pure autonomic failure]
            OR

2. Dopamine beta-hydroxylase deficiency
   OR
3. Non-diabetic autonomic neuropathy

AND

v. The prescriber has assessed the severity of the patient's baseline symptoms of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out
AND

vi. The prescriber has assessed and adjusted, if applicable, any medications known to exacerbate orthostatic hypotension (e.g., diuretics, vasodilators, beta-blockers)
AND

vii. ONE of the following:
1. The patient has tried and failed midodrine
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to midodrine

OR

B. The patient has another FDA approved diagnosis for the requested agent

AND

2. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g. cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
AND
3. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND
4. ONE of the following:
   A. The requested quantity (dose) is NOT greater than the program quantity limit
      OR
   B. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

      OR
   C. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit
         AND
      ii. The requested quantity (dose) is greater than the FDA labeled dose
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 1 month

Renewal Evaluation
Northera (droxidopa) will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the Prime Therapeutics prior authorization process
   AND
2. ONE of the following:

A. The patient has a diagnosis of neurogenic orthostatic hypotension (NOH) **AND** BOTH of the following:
    i. The patient has demonstrated improvement in severity from baseline symptoms of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out
    AND
    ii. The patient had an increase in systolic blood pressure from baseline of at least 10 mmHg upon standing from a supine (laying face up) position

OR

B. The patient has another FDA approved diagnosis for the requested agent

AND

3. The prescriber is a specialist in the area of practice related to the patient's diagnosis (for example: cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
AND
4. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
AND
5. ONE of the following:
    A. The requested quantity (dose) is NOT greater than the program quantity limit
    OR
    B. ALL of the following
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
        AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit

    OR

    C. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) is greater than the FDA labeled dose
        AND
        iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of Approval: 3 months

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent	Indication	Dose
Northera® (droxidopa)	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	100 mg three times during the day. Titrate by 100 mg three times daily, up to a maximum dose of 600 mg three times daily

CLINICAL RATIONALE

Orthostatic hypotension (OH) is a common condition that is defined as a sustained reduction of greater than 20 mmHg or 10 mmHg in systolic and diastolic blood pressure, respectively, upon standing for three minutes or less.[2,4,8] It can occur as a result of several different causes including dehydration, volume depletion, and vasodilation. Symptoms can be disabling and include dizziness, lightheadedness, and/or syncope. OH can negatively impact daily activities including standing and walking, as well as increase risk for falls. The frequency of OH increases with age and is common in the elderly, affecting approximately 16% of community dwellers over age 65 and up to 50% of institutionalized patients (e.g. nursing homes). Of note, OH is an independent predictor of mortality and is associated with increased incidences of coronary artery disease, stroke, and heart failure. Midodrine, a peripheral selective alpha-1-adrenergic agonist is most often used in the treatment of chronic orthostatic hypotension (and in neurocardiogenic syncope). Its efficacy in treatment has been shown in open-label and double-blind studies.[9]

Neurogenic orthostatic hypotension (NOH) is one type of OH that involves failed compensatory autonomic reflexes in the central nervous system.[3,4,7] NOH occurs in patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, or dopamine beta-hydroxylase deficiency. The decrease in or absence of norepinephrine released from sympathetic nerve terminals of vasomotor neurons results in the failed vasoconstriction of systemic circulation upon standing. When present, symptoms are similar to those observed in OH. Supine hypertension (defined as blood pressure greater than 180 mmHg [systolic] or 110 mmHg [diastolic]) commonly observed in the spectrum of NOH may also be due to the loss of homeostatic mechanisms to control blood pressure fluctuations. NOH is associated with increased mortality rates for diabetes, hypertension, Parkinson's disease, and patients receiving dialysis.[3] The prevalence of NOH in Parkinson's disease ranges from 16-58%.[7]

The goal of treatment should not be to normalize standing blood pressure but the principal treatment goals should serve to reduce the burden of symptoms (especially falls), prolong standing time, and improve the physical capabilities of the patients to restore independence in activities of daily living. A treatment algorithm for NOH that encompasses a 4-step hierarchical process is proposed: (1) assessing and adjusting pre-existing medications, (2) utilizing non-pharmacologic approaches, (3) implementing single-agent pharmacologic treatment, and (4) with great caution, combining pharmacologic treatments.[10]

One of the keys to initial success is to complete a comprehensive medication review so that adjustments in regimens can be made as needed. Many medications (including those commonly used for treatment of PD, hypertension, or bladder symptoms) can lower blood pressure and exacerbate the symptoms of NOH. Discontinuation or dose reduction of medications which can potentially aggravate orthostatic symptoms such as diuretics, vasodilators, and medications with negative chronotropic properties such as beta blockers may be sufficient to resolve symptoms of NOH in some patients. Non pharmacological options include ensuring normal blood volume, adjusting sodium intake, physical conditioning, avoid increased core body temperature, anemia and vitamin/mineral deficiency in diet, compression garments, and head-up position while sleeping. Pharmacological options include midodrine and droxidopa, as well as off-label use of fludrocortisone and pyridostigmine for NOH. One of the challenges associated with treating NOH pharmacologically is the limited availability of clinical evidence and lack of comparative effectiveness studies. Once initial therapy has begun, symptomatic benefit, including impact on activities of daily living, and changes in blood pressure need to be assessed frequently. Little data exists to determine efficacy and safety of different combinations of therapy compared to monotherapy for nOH. Based on the experience of the consensus panel, the recommendation is to appropriately titrate to maximum tolerable dose of a single agent and then, if symptomatic benefit is not obtained, consider switching to a different therapy or adding a second agent and titrate from its lowest starting dose.[10]

EFFICACY

The efficacy of droxidopa was evaluated through two short term placebo-controlled studies over 1-2 weeks (studies 301 and 302), and two long-term open label extension studies (studies 303 and 304). Two similarly designed 8-week placebo-controlled studies were also completed (306A [exploratory] and 306B).

Study 301:[1,4] Patients with symptomatic neurogenic orthostatic hypotension (NOH) participated in this multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study. Patients were age 18 or older, and were required to have a clinical diagnosis of symptomatic NOH due to one of the following: Parkinson's disease, pure autonomic failure, multiple system atrophy, non-diabetic autonomic neuropathy, or dopamine-beta-hydroxylase deficiency. Exclusion criteria included use of long-acting antihypertensives or norepinephrine reuptake inhibitors, severe supine hypertension, vasoconstrictor agent use within two days before baseline, and significant hepatic, cardiac, renal or systemic disease. After the initial screening, patients went through open-label dose titration period followed by a seven day wash-out period (n=263).

Of the 263 patients who participated in dose randomization, 162 (61.6%) were identified as responders and entered the double-blind phase of the study. Responders were defined as demonstrating improvement on the Orthostatic Hypotension Symptom Assessment (OHSA) Item #1 score by at least one point and an increase in systolic blood pressure of at least 10 mmHg upon standing. The OHSA Item #1 referred to dizziness, lightheadedness, feeling faint, and feeling like you might black out (see monograph appendix for more information). Responders were then randomized to a seven day treatment period with droxidopa (n=82) or placebo (n=80).

Patients in the treatment period had an average age of 60 years and a primary diagnosis of Parkinson's disease (n=60), pure autonomic failure (n=36) or multiple system atrophy (n=26). Patients were allowed to continue taking dopa-decarboxylase inhibitors (45% of patients) and fludrocortisones (29% of patients).

Efficacy was established within the treatment period through utilizing the Orthostatic Hypotension Questionnaire (OHQ, see monograph appendix for more information), which measures the symptoms of NOH and their impact on the patient's daily activities. The OHQ was

administered at baseline, randomization, and at the end of the study. The pre-specified primary efficacy endpoint was the change in overall composite score from randomization to end of study. Secondary endpoints were individual OHQ items and changes in symptom and symptom impact scores. Blood pressure was also measured throughout the study.

Results revealed a statistically significant improvement in the OHQ composite score from randomization to the end of the study (p=0.003). Several symptom items revealed differences between droxidopa and placebo including dizziness/lightheadedness (item 1 for randomization), vision disturbance, weakness, and fatigue. Differences from placebo were also observed on all symptom-impact items. Standing systolic blood pressures increased an average of 11.2 mmHg in patients receiving droxidopa versus 3.9 mmHg with placebo.

Study 302:[1,6] Study 302 (n=101) was designed similarly to Study 301. It was a multi-center, multi-national, double-blind, placebo-controlled, 2-week randomized withdrawal study of droxidopa in patients with symptomatic NOH. There was an initial dose titration phase of up to 14 days followed by seven days of open-label treatment and a 14-day randomized withdrawal period. Inclusion and exclusion criteria were similar to those in Study 301. Endpoints included the primary efficacy endpoint of the mean change in the OHSA Item #1 (dizziness/lightheadedness) and secondary endpoints of blood pressure, global assessment evaluations, and symptom and activity measurements using OHQ scores. Results from this study did not reveal a statistically significant difference between the treatment and placebo arms with respect to the primary endpoint of OHSA Item #1 or the secondary endpoint of blood pressure.

Study 303:[1,6] This study (n=75) was an extension of studies 301 and 302. In this study, a three month open-label treatment period was followed by a 2-week double-blind, placebo-controlled, randomized-withdrawal period. After the withdrawal period, patients entered a nine month open-label study. Patients included in the study were those who had a symptomatic response to droxidopa in either Study 301 or 302. The primary efficacy endpoint was the change in OHQ score from randomization to the end of the two week treatment period. Secondary endpoints included individual items on the OHQ, global clinical assessments, and blood pressure. Results from this study did not reveal a statistically significant difference between the treatment and placebo arms.

Study 305:[6] This study was a multicenter, open-label study to assess the effect of droxidopa on a 24-hour blood pressure profile in patients with symptomatic NOH due to primary autonomic failure, dopamine-beta-hydroxylase deficiency, or non-diabetic neuropathy. Patients (n=18) included in this study had been a part of the post-titration washout phase of Study 301 and had planned to participate in Study 303. Patients were given a 24-hour blood pressure monitoring device and completed 24-hour assessments at baseline and at four weeks of droxidopa treatment under Study 303. No efficacy analysis was completed, as the intent of the study was to rule out postural supine night-time hypertension. A statistically significant increase in blood pressure was observed in patients when on droxidopa.

Study 306A:[5] This study was an interim analysis of the 51 patients enrolled in a phase 3 study of droxidopa versus placebo. Patients were required to be 18 years of age or over, have a diagnosis of Parkinson's disease, and NOH symptoms (decrease upon standing of 20 mmHg or 10 mmHg in systolic or diastolic blood pressure, respectively). Data was collected via the patient-reported OHQ and the study investigator rating on the Clinical Global Impression-Severity (CGI-S) scale. Exclusion criteria included current use of vasoconstrictive agents or long-acting antihypertensive medications, sustained severe hypertension (greater than 180/110 mmHg when seated or supine) or a Mini-Mental State Examination score below 23. Patients received droxidopa (n=24) or placebo (n=27) for a titration period of up to two weeks that was followed by eight weeks of treatment. Dosing ranged from 100 mg to 600 mg three times daily. Patients were allowed to take fludrocortisone if the dosing had been consistent throughout the two weeks prior to the start of the study drug, but patients were not allowed to be on midodrine.

Over the 8 weeks of the study, droxidopa failed to show benefit over placebo by the primary end point of the change in OHQ composite score from baseline to week 8 (p=0.98, see Figure 2 below). Mean standing blood pressure change did favor droxidopa at week 1 (p=0.04). Though not statistically significant, some improvement in dizziness/lightheadedness at week 1 (p=0.24) and in reported falls (p=0.16) were observed.

Study 306B[1]**:** Study 306B was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study that consisted of an initial dose titration period followed by an 8-week treatment period. Patients (n=171) in the study had symptomatic NOH and Parkinson's disease, and were required to have a decrease of at least 20 mmHg or 10 mmHg, respectively, in systolic or diastolic blood pressure within three minutes after standing. Dosing was titrated to patient response and ranged from 100 mg to 600 mg three times daily. Data was collected throughout an eight week treatment period. At week 1, patients demonstrated a statistically significant decrease (0.9-unit) in dizziness as reported on the OHSA Item #1 11-point scale (p=0.028). This effect did not continue beyond week 1.

Safety[1]
Northera does contain a Black Box Warning**:** Supine hypertension: Supine blood pressure should be monitored 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 droxidopa.

Droxidopa is contraindicated in those with history of hypersensitivity to the drug or its ingredients.

The most common adverse reactions (>5%) include headache, dizziness, nausea, hypertension, and fatigue.

Across clinical trials, the most common adverse reactions leading to discontinuation of therapy were hypertension and nausea.

REFERENCES

1. Northera prescribing information. Lundbeck LLC. February 2017.
2. Biaggioni I (2014): New Developments in the Management of Neurogenic Orthostatic Hypotension. *Curr Cardiol Rep* 16:542.
3. Arbique D, Cheek D, Welliver M, Vongpatanasin W (2014): Management of Neurogenic Orthostatic Hypotension. *JAMDA* 15:234-239.
4. Kaufmann H *et al.* (2014): Droxidopa for neurogenic orthostatic hypotension; A randomized, placebo-controlled, phase 3 trial. *Neurology* 83:328-335.
5. Hauser RA, Hewitt LA, and Isaacson S (2014): Droxidopa in Patients with Neurogenic Orthostatic Hypotension Associated with Parkinson's disease (NOH306A). *J Parkinson's Disease* 4:57-65
6. FDA Briefing Document: Cardiovascular and Renal Drug Advisory Committee Meeting. Accessed 10 November 2014 at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381154.pdf
7. Metzler M, Duerr S, Granata R, Krismer F, Robertson D, and Wenning GK (2013): Neurogenic orthostatic hypotension: pathophysiology, evaluation, and management. *J Neurol.*260(9):2212-2219.
8. Goldstein D, Sharabi Y. Neurogenic Orthostatic Hypotension. A Pathophysiological Approach. *Circulation*. 2009;119:139-146. http://circ.ahajournals.org/content/119/1/139. Accessed on 12/1/2014.

9. Kaufmann, Horacio, MD., et al. Treatment of orthostatic and postprandial hypotension. UpToDate. Last updated May 2015.
10. Gibbons, Christopher H., et al. The Recommendations of a Consensus Panel for the Diagnosis, and Treatment of Neurogenic Orthostatic Hypotension and Associated Supine Hypertension. *J Neurol* (2017) 264: 1567-1582.