Northera (droxidopa) Prior Authorization with Quantity Limit Program Summary

This program applies to FlexRx Closed, FlexRx Open, FocusRx, GenRx Closed, GenRx Open, Health Insurance Marketplace, and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
8/1/2023	10/1/2016

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Northera® (droxidopa)* Capsule	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 should be assessed periodically.	* Generic available	1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Orthostatic Hypotension	Orthostatic hypotension (OH) is defined as a blood pressure decrease greater than or equal to 20mmHg systolic or greater than or equal to 10mmHg diastolic recorded within 3 minutes after that patient stands.(2-6) OH can impair perfusion to organs above the heart, resulting in symptoms of hypoperfusion in these tissues. OH is a frequent problem in the general population, especially in the elderly.(2-4,6) The overall prevalence of OH in patients greater than 65 years is approximately 20%.(2) It can result from a variety of medical conditions, such as IV volume depletion, blood pooling from varicose veins, severe anemia, medications, and physical deconditioning. In these cases, OH usually improves once the underlying cause is treated. In a minority of patients, OH occurs due to decreased norepinephrine release from sympathetic nerves, which leads to defective vasoconstriction when in the upright position. This is referred to as neurogenic orthostatic hypotension (nOH). nOH occurs frequently in patients with neurodegenerative disorders such as Parkinson's disease, Lewy Body dementia, multiple system atrophy, and pure autonomic failure.(2-6) An estimated 30-50% of Parkinson's disease patients have nOH.(2,4) When present, symptoms are similar to those observed with OH. However, in contrast to vasovagal (neutrally mediated) syncope, syncope in nOH occurs without signs of autonomic activation such as diaphoresis, tachycardia, nausea, or abdominal discomfort.(2) The goal of nOH treatment is not to normalize standing blood pressure, but to reduce symptom burden so as to improve quality of life. The steps in management include: 1) correcting aggravating factors, 2) implementing non-pharmacological measures, and 3) drug therapies. The correction of aggravating factors includes management of medications contributing to the nOH through the reduction of IV volume, induction of vasodilation, and interference with norepinephrine. The correction of anemia and

	vitamin deficiencies is also included. Non-pharmacological management includes insuring proper blood volume, adjusting sodium intake, physical conditioning, avoid increased core body temperature, compression garments, and head-up position while sleeping.(2) Pharmacological options include midodrine and droxidopa, as well as off-label use of fludrocortisone and pyridostigmine for nOH.(2-6) 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.(3)
Efficacy(1)	Clinical studies examined the efficacy of Northera in the short-term (1-2 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 two weeks of treatment. Study 301: 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 306B: 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	Northera has a Boxed Warning for 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.(1)

REFERENCES

Number	Reference
1	Northera prescribing information. Lundbeck LLC. July 2019.
2	Palma JA, Kaufmann H. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension. Mov Disord Clin Pract. 2017 May-Jun;4(3):298-308.
3	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.
4	2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol. 2017 Aug;70(5):e39-e110.
5	Brignole M, Moya A, de Lange FJ, et al. 2018 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Syncope. Eur Heart J. 2018 June;39(21):1883-1948.
6	Kalra DK, Raina A, Sohal S. Neurogenic Orthostatic Hypotension: State of the Art and Therapeutic Strategies. Clin Med Insights Cardiol. 2020;14:1-12.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Northera	droxidopa cap	100 MG ; 200 MG ; 300 MG	M ; N ; O ; Y	O ; Y		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Northera	Droxidopa Cap 100 MG	100 MG	450	Capsules	30	DAYS			
Northera	Droxidopa Cap 200 MG	200 MG	180	Capsules	30	DAYS			
Northera	Droxidopa Cap 300 MG	300 MG	180	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Northera	droxidopa cap	100 MG ; 200 MG ; 300 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Northera	Droxidopa Cap 100 MG	100 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Northera	Droxidopa Cap 200 MG	200 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx
Northera	Droxidopa Cap 300 MG	300 MG	FlexRx Closed ; FlexRx Open ; FocusRx ; GenRx Closed ; GenRx Open ; Health Insurance Marketplace/BasicRx ; KeyRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation

Module	Clinical Criteria for Approval

Target Agent(s) 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:
      1. The prescriber has performed baseline (prior to therapy with the requested agent) blood pressure readings while the patient is sitting or supine (laying face up) AND also within 3 minutes of standing from a supine position **AND**
      2. 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**
      3. The patient has persistent and consistent symptoms of neurogenic orthostatic hypotension (nOH) caused by ONE of the following:
         A. Primary autonomic failure (Parkinson's disease [PD], multiple system atrophy, or pure autonomic failure) **OR**
         B. Dopamine beta-hydroxylase deficiency **OR**
         C. Non-diabetic autonomic neuropathy **AND**
      4. The prescriber has assessed the severity of the patient's baseline (prior to therapy with the requested agent) symptoms of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out **AND**
      5. The prescriber has assessed and adjusted, if applicable, any medications known to exacerbate orthostatic hypotension (e.g., diuretics, vasodilators, beta-blockers) **AND**
      6. ONE of the following:
         A. The patient has tried and had an inadequate response to midodrine **OR**
         B. The patient has an intolerance or hypersensitivity to therapy with midodrine **OR**
         C. The patient has an FDA labeled contraindication to midodrine **OR**
         D. The patient is currently being treated with the requested agent as indicated by ALL of the following:
            1. A statement by the prescriber that the patient is currently taking the requested agent **AND**
            2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND**
            3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR**
         E. The prescriber has provided documentation that midodrine cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **OR**
   B. The patient has another FDA approved indication for the requested agent **AND**
2. If the patient has an FDA approved indication, ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND**
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Brand	Generic Equivalent
Northera	droxidopa

   A. The patient's medication history includes the required generic equivalent as indicated by:
      1. Evidence of a paid claim(s) **OR**

Module	Clinical Criteria for Approval
	2. The prescriber has stated that the patient has tried the generic equivalent AND the generic equivalent was discontinued due to lack of effectiveness or an adverse event **OR** B. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** C. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** D. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent **OR** E. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** F. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 1 month NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's 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: 1. The patient has had improvement in severity from baseline symptoms (prior to therapy with the requested agent) of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out **AND** 2. The patient had an increase in systolic blood pressure from baseline (prior to therapy with the requested agent) of at least 10 mmHg upon standing from a supine (laying face up) position **OR** B. BOTH of the following: 1. The patient has another FDA approved indication for the requested agent **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following: **Brand** / **Generic Equivalent** Northera / droxidopa

Module	Clinical Criteria for Approval
	A. The patient's medication history includes the required generic equivalent as indicated by: 1. Evidence of a paid claim(s) **OR** 2. The prescriber has stated that the patient has tried the generic equivalent AND the generic equivalent was discontinued due to lack of effectiveness or an adverse event **OR** B. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** C. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** D. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent **OR** E. The patient is currently being treated with the requested agent as indicated by ALL of the following: 1. A statement by the prescriber that the patient is currently taking the requested agent **AND** 2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND** 3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR** F. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) is greater than the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) is greater than the program quantity limit **AND** B. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: Initial - 1 month; Renewal - 3 months

