



Louisiana

droxidopa (Northera[®])

Policy # 00460

Original Effective Date: 03/20/2015

Current Effective Date: 03/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider the use of droxidopa (Northera[®])[†] for the treatment of symptomatic neurogenic orthostatic hypotension to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for droxidopa (Northera) will be considered when all of the following criteria are met:

- Patient is 18 years of age or older; AND
- Patient has a diagnosis of symptomatic neurogenic orthostatic hypotension due to primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy; AND
- Patient has failed non-pharmacologic therapy (eg elevation of the head of the bed, compression garments, appropriate physical training); AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- Patient has failed therapy with midodrine unless there is clinical evidence or patient history that suggests midodrine will be ineffective or cause an adverse reaction to the patient; AND
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
- For re-approval beyond the one month initial approval: Patient is experiencing (and maintaining) improvement in the symptoms of neurogenic orthostatic hypotension.
*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of droxidopa (Northera) when patient selection criteria are not met (with the exception of those denoted in the patient selection criteria as **not medically necessary****) to be **investigational**.*

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of droxidopa (Northera) when the patient has NOT failed therapy with midodrine, unless there is clinical evidence or patient history that suggests midodrine will be ineffective or cause an adverse reaction to the patient, to be **not medically necessary**.**

Based on review of available data, the Company considers the use of droxidopa (Northera) when the patient has NOT failed non-pharmacologic therapy (eg elevation of the head of the bed, compression garments, appropriate physical training) to be **not medically necessary**.**

Based on review of available data, the Company considers the use of droxidopa (Northera) beyond one month when the patient has NOT shown improvement in the symptoms of neurogenic orthostatic hypotension to be **not medically necessary**.**

Background/Overview

Northera is metabolized to norepinephrine by dopa-decarboxylase, which is found throughout the body. Northera's effects are thought to be brought on by the norepinephrine molecule, which increases blood pressure by inducing peripheral arterial and venous vasoconstriction. Northera's recommended dose is 100mg three times daily and can be titrated up to 600mg three times daily.

Neurogenic Orthostatic Hypotension (NOH)

Orthostatic hypotension is a sustained reduction in systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table. Once a patient stands, their blood volume is redistributed due to gravity, causing a pooling of blood in the lower extremities. Due to the pooling of blood, venous blood return to the heart falls and cardiac filling pressure is reduced, resulting in diminished stroke volume and cardiac output. In response, sympathetic outflow to the heart and blood vessels increases and cardiac vagal nerve activity decreases. These autonomic adjustments increase vascular tone, heart rate and cardiac contractility, and stabilize arterial blood pressure. When standing, contraction of lower body skeletal muscle prevents excessive pooling and augments venous return to the heart. Neurogenic orthostatic hypotension is a specific subset of this condition, in which the patient's orthostasis is due to inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure. Neurogenic orthostatic hypotension is a rare, chronic and often debilitating condition that is associated with Parkinson's disease, multiple system atrophy (MSA), pure autonomic failure (PAF) and with peripheral neuropathies and ganglionopathies that affect the autonomic nerves. Many patients with NOH have supine hypertension (i.e., high blood pressure when lying down) even before treatment of hypotension is initiated. Some of these patients have decreases in blood pressure upon standing that fulfill criteria for orthostatic hypotension even though their blood pressure remains at or above the normal range. Patients with autonomic failure and the elderly are also susceptible to significant decreases in blood pressure associated with meals. This may be exacerbated by large meals, meals high in carbohydrates, and alcohol intake. Medications that may increase the frequency of symptomatic NOH include alpha-adrenergic antagonists (e.g., benign prostatic hypertrophy medications),

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antidepressants (particularly, tricyclic antidepressants), antipsychotics, and dopaminergic agonists (e.g., antiparkinsonian medications). The American Academy of Neurology (AAN) practice parameter on the treatment of non-motor symptoms of Parkinson's disease mentions midodrine (available generically) and Northera, but does not provide a place in therapy for these medications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Northera was approved in 2014 for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that one is about to black out" in adult patients with symptomatic NOH due to primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Clinical studies 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 neurogenic orthostatic hypotension and Parkinson's disease. The study had an initial dose titration period that lasted up to 2 weeks in which patients received placebo or 100 to 600mg of Northera three times daily, followed by an 8 week treatment period. Efficacy was measured using the OHSA (Orthostatic Hypotension Symptoms Assessment) item #1 score ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") at week 1, in patient who had completed titration and 1 week of maintenance therapy. 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 vs. placebo (p=0.028), but the effect did not persist beyond week 1.

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. The study was enriched, such that only patients who had been identified as 'responders' during the titration period were randomized to Northera or placebo. Efficacy was measured using the Orthostatic Hypotension Questionnaire (OHQ), a patient-reported outcome that measures symptoms of neurogenic orthostatic hypotension 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).

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Study 302 (n=101) was a placebo-controlled, 2-week randomized withdrawal study of Northera in patients with symptomatic neurogenic orthostatic hypotension. 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.

References

1. Northera [package insert]. Lundbeck. Deerfield, IL. Revised 08/2014
2. Northera. Express Scripts Drug Evaluation. Revised 06/2014.

Policy History

Original Effective Date: 03/20/2015

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03/05/2015 Medical Policy Committee review
03/20/2015 Medical Policy Implementation Committee approval. New policy.
03/03/2016 Medical Policy Committee review
03/16/2016 Medical Policy Implementation Committee approval. No change to coverage.
03/02/2017 Medical Policy Committee review
03/15/2017 Medical Policy Implementation Committee approval. No change to coverage.
03/01/2018 Medical Policy Committee review
03/21/2018 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 03/2019

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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