VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Northera® (droxidopa capsules – Chelsea Therapeutics)

DATE REVIEWED: 11/20/2019

OVERVIEW

Northera, a norepinephrine-type product, is indicated for the treatment of orthostatic dizziness, lightheadedness or the "feeling that one is 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 [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.[1] According to the prescribing information, the effectiveness beyond 2 weeks of treatment has not been established and should be evaluated periodically. The mechanism of action of Northera is unknown. Northera is a synthetic amino acid analog that is metabolized to norepinephrine by dopa-decarboxylase, which is found throughout the body. Northera is thought to exert its effects through norepinephrine, which increases blood pressure (BP) by inducing peripheral arterial and venous vasoconstriction. Northera has a Boxed Warning regarding supine hypertension. Northera may cause or exacerbate supine hypertension in patients with NOH. Supine BP should be measured prior to initiating Northera and after dose increases.

Disease Overview

OH is a sustained reduction in SBP of at least 20 mmHg or DBP of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table.[2] OH is caused by an excessive fall in a patient's cardiac output or by defective or inadequate vasoconstrictor mechanisms. OH may be symptomatic or asymptomatic, with only symptomatic OH requiring treatment.[3] NOH is a specific subset of this condition, in which OH is due to inadequate release of norepinephrine from sympathetic vasomotor neurons leading to vasoconstrictor failure.[2] NOH is a rare, chronic and often debilitating condition that is associated with PD (prevalence: 16% to 58%), MSA (prevalence: 60% to 75%), and PAF (prevalence: 100%) and with peripheral neuropathies and ganglionopathies that affect the autonomic nerves.[2,3] Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue, and fainting upon standing up.[2] These symptoms can adversely affect patients' quality of life and ability to conduct activities of daily living that involve standing or walking. Many patients with NOH have supine hypertension (i.e., high BP when lying down) even before treatment of hypotension is initiated. Patients with autonomic failure and the elderly are also susceptible to significant decreases in BP associated with meals. This may be exacerbated by large meals, meals high in carbohydrates, and alcohol intake. Medications may increase the frequency of symptomatic NOH, such as alpha-adrenergic antagonists (e.g., benign prostatic hypertrophy medications), antidepressants (particularly, tricyclic antidepressants), antipsychotics, and dopaminergic agonists (e.g., antiparkinsonian medications).[3]

Treatment of symptomatic NOH is aimed at increasing standing SBP into the range of compensatory cerebrovascular autoregulation (approximately 50 to 150 mmHg).[4,5] A variety of nonpharmacologic approaches have been used to treat symptoms of NOH, including arising slowly, elevating the head of the bed, and/or wearing elastic stockings.[6] Spreading total daily carbohydrate intake to multiple smaller meals has been shown to decrease OH symptoms.[7] Adequate salt and fluid intake may be useful (e.g., dietary sodium intake of at least 10 g/day and fluid intake of greater than 2 L/day) in patients without concomitant renal dysfunction.[6] These nonpharmacologic interventions should be considered first in the treatment of

NOH. Unapproved pharmacologic agents include fludrocortisone (volume expansion and pressor effect), desmopressin (nasal spray or oral) [volume expansion], dihydroergotamine (oral) [pressor effect], indomethacin (oral or intravenous) [pressor effect], pyridostigmine, and erythropoietin (treatment of anemia of chronic autonomic failure can improve orthostatic intolerance).[6-8] Midodrine, an alpha$_1$-agonist, is the only other medication approved with a similar indication (treatment of symptomatic OH) to Northera.[9]

Clinical Efficacy

Northera was evaluated in one 12-month, open-label study which demonstrated the maintenance of improvements from baseline in patient-reported NOH symptom severity and impact on daily activities.[6] Small studies have been published for the use of Northera in hemodialysis patients to prevent orthostatic hypotension (OH)[10,11] and also in restoring neurologic deficit in chronic stoke patients.[12]

Guidelines

According to the **American Academy of Neurology (AAN) practice parameter on treatment of nonmotor symptoms of PD (2010)**, there have been few placebo controlled trials of treatment for OH in PD, and the available data are insufficient to make a recommendation on the use of specific treatments for OH in PD.[13] Small studies have used domperidone, fludrocortisone, and indomethacin. While studies are lacking for mineralocorticoids, alpha-sympathomimetics, and pyridostigmine, they have pharmacologic actions that are consistent with improvement in OH. The only medications currently approved to treat OH are midodrine and Northera.

Consensus panel recommendations initiated by the American Autonomic Society and the National Parkinson Foundation for the screening, diagnosis, and treatment of NOH and associated supine hypertension were published in 2017.[14] Once a patient is diagnosed with NOH, the goals of treatment should be to reduce the burden of symptoms (especially falls), prolong standing time, and restore independence in activities of daily living. The recommendations propose a four-step treatment algorithm for NOH: assessing and adjusting pre-existing medications that may be causing or exacerbating NOH, utilizing non-pharmacologic approaches (e.g., blood volume repletion, increased salt intake, physical conditioning, compression garments, elevating the head of the bed), implementing single-agent pharmacologic treatment, and with great caution, combining pharmacologic treatments. After each step, a 2-week assessment period is recommended to establish whether sufficient symptomatic benefit has been achieved before moving onto the next step. Recommended treatments include midodrine, Northera, fludrocortisone, and pyridostigmine. The initial choice of NOH treatments should be individualized and should consider severity, comorbid disease (especially cardiac or renal failure), and treatment goals. Based on the experience of the consensus panel, the recommendation is to titrate to maximum tolerable dose of a single medication and then, if symptomatic benefit is not obtained, consider switching to a different medication or adding a second agent and titrate from its lowest starting dose.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Northera. Because of the specialized skills required for evaluation and diagnosis of patients treated with Northera as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Northera to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for the duration noted below.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Northera is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Neurogenic Orthostatic Hypotension (NOH).** Approve for 1 year if the patient meets the following criteria (a, b, c, d, and e):
   - **a)** Patient is ≥ 18 years of age; AND
   - **b)** Patient has been diagnosed with symptomatic NOH due to primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], and pure autonomic failure [PAF]), dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy; AND
   - **c)** Northera has been prescribed by or in consultation with a cardiologist or a neurologist; AND
   - **d)** Patient has tried two other medications (e.g., fludrocortisone, desmopressin, dihydroergotamine, indomethacin, pyridostigmine, erythropoietin, midodrine); AND
   - **e)** Patient has initiated non-pharmacological measures including but not limited to elevation of the head of the bed, orthostatic compression garments, and appropriate physical training.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Northera has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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OTHER REFERENCES UTILIZED

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