PHARMACY COVERAGE GUIDELINE

Droxidopa oral
NORTHERA™ (droxidopa) oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Northera (droxidopa) or generic droxidopa is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Nephrologist, or Cardiologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of symptomatic neurogenic orthostatic hypotension (NOH) caused by **ONE** of the following conditions:
    a. Parkinson's disease
    b. Multiple system atrophy

c. Pure autonomic failure
d. Dopamine beta-hydroxylase deficiency
e. Non-diabetic neuropathy

4. **For Northera and other generic droxidopa:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic droxidopa by CIVICASCRIPT** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Orthostatic hypotension is documented after 5-minutes of supine rest and within 2-5 minutes upon standing or head-up tilt on a tilt table is **ONE** of the following:
   a. A decrease of at least 20 millimeters of mercury (mmHg) in systolic blood pressure (SBP)
   b. A decrease of at least 10 mmHg in diastolic blood pressure (DBP)

6. Individual has persistent and consistent symptoms of orthostatic dizziness, lightheadedness, or feelings of about to black out

7. Non-pharmacologic measures have been maximized to include:
   a. Intake of fluid and salt has been liberalized or maximized, where appropriate
   b. Use of fitted elastic/compression stockings or abdominal binder, unless contraindicated or not tolerated
   c. Head of the bed has been elevated
   d. Individual is instructed on how to change position from supine to standing in gradual stages

8. A comprehensive medication review has been performed to either reduce or discontinue agents that contribute or cause orthostatic hypotension, if clinically safe to do so

9. Individual has failure (at least a 30-day trial), contraindication per FDA label, intolerance, or is not a candidate for simultaneous use of **fludrocortisone AND midodrine**

10. Individual does not have renal impairment (glomerular filtration rate (GFR) of less than 30 mL/min)

11. Individual is not currently taking any other drugs which cause severe adverse reactions or drug interaction requiring discontinuation such as non-specific monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine, tranylcypromine, linezolid)

Initial approval duration: 1 month, renewal requires documentation of reduction in orthostatic symptoms **and** an increase in blood pressure for approval

- **Criteria for continuation of coverage (renewal request):** Northera (droxidopa) or generic droxidopa is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Nephrologist, or Cardiologist

2. Individual's condition has responded while on therapy with response defined as a sustained reduction in dizziness, lightheadedness, feeling faint, or feeling like the patient may black out **and** an increase in SBP of 10 mmHg within 3 min of standing

3. **For Northera and other generic droxidopa:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic droxidopa by CIVICASCRIPT** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

4. Individual has been adherent with the medication and all non-pharmacologic measures as deemed appropriate for the individual patient

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Persistent supine hypertension
    b. Neuroleptic Malignant Syndrome (NMS)-like reaction with hyperpyrexia and confusion
    c. Hypersensitivity reactions such as anaphylaxis, angioedema, bronchospasms, urticaria, and rash

6. Individual does not have renal impairment (glomerular filtration rate (GFR) of less than 30 mL/min)

7. Individual is not currently taking any other drugs which cause severe adverse reactions or drug interaction requiring discontinuation such as non-specific monoamine oxidase inhibitors (e.g., isocarboxazid, phenelzine, tranylcypromine, linezolid)

Renewal duration: 6 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

Description:

Generic droxidopa or brand Northera (droxidopa) 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 (MSA), and pure autonomic failure (PAF)], dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. The effectiveness of droxidopa beyond 2 weeks of treatment has not been established, continued effectiveness of droxidopa should be assessed periodically.

Droxidopa is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, which is extensively distributed throughout the body. It is believed to exert its effects through norepinephrine and

not through the parent molecule. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction.
Use of droxidopa is associated with a risk of increased blood pressure while lying down (supine hypertension), individuals must sleep with their head and upper body elevated. In addition, it may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure.

Orthostatic hypotension:

- Orthostatic hypotension may be categorized as neurogenic or non-neurogenic in origin
- Non-neurogenic causes include disorders that result in cardiac impairment, reduced intravascular volume and electrolyte loss, venous pooling/vasodilation, and iatrogenic from use of numerous medications
    - Age related orthostatic hypotension is considered a non-neurogenic cause of orthostatic hypotension
- Neurogenic causes include Parkinson's disease (PD), pure autonomic failure (PAF), and multiple system atrophy (MSA)
- Orthostatic hypotension is a physical finding and is defined as a documented decrease of ≥ 20 millimeters of mercury (mmHg) in systolic blood pressure (SBP) or a ≥ 10 mmHg decrease in diastolic blood pressure (DBP) within 3 minutes upon standing or a head-up tilt on a tilt table
- Symptoms of orthostatic hypotension include dizziness, lightheadedness, blurred vision, fatigue and fainting when a person stands
- There are known predisposing factors that cause or contribute to orthostatic hypotension such as dehydration, deconditioning, poor nutrition, aging, and others, as well as numerous drugs such as diuretics, antihypertensive agents, anti-anginal agents, antidepressants, alpha-blockers, and others
- Management of orthostatic hypotension involves liberalizing and maximizing fluid and sodium intake (where appropriate), elevation of head of the bed, a comprehensive review of medications used to reduce the doses or discontinue agents that contribute to orthostatic hypotension (if safe to do so), patient education on how to change position from supine to standing in gradual stages, and use of fitted elastic stockings
- Pharmacologic agents used to treat orthostatic hypotension include fludrocortisone and midodrine
- Midodrine is the only other FDA-approved medication for symptomatic orthostatic hypotension
    - Midodrine is a direct acting agonist for peripheral alpha-1 adrenoreceptors
    - It is a pro-drug that is activated to desglymidodrine, the active receptor agonist
        - Desglymidodrine is 15 times more potent than the parent compound and is primarily responsible for the therapeutic effect
    - The pressor effect is due to both arterial and venous constriction
    - The dose should be titrated from 2.5 mg to 10 mg three times a day
- Fludrocortisone is commonly used off-label to treat orthostatic hypotension

- Fludrocortisone, is a synthetic mineralocorticoid, is considered agent of first choice for orthostatic hypotension and is used in individuals who are not are unable to increase plasma volume effectively with liberalized fluid and salt intake
- It has a long duration of action and is well-tolerated by most individuals
- Fludrocortisone increases blood volume and enhances the sensitivity of blood vessels to circulating catecholamines
- Other potential actions include enhancing norepinephrine release from sympathetic neurons and increasing vascular fluid content
- Treatment is initiated with a 0.1 mg tablet and can be increased to 1 mg daily although little benefit is obtained by increasing beyond 0.5 mg daily

- Other off-label treatments that are less commonly used include ephedrine, desmopressin, dihydroergotamine, erythropoietin, indomethacin, octreotide, pyridostigmine, and yohimbine

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Northera (droxidopa) product information, revised by Lundbeck Pharmaceuticals, LLC. 07-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Droxidopa product information, revised by Ajanta Pharma USA, Inc. 11-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 25, 2024.

Palma JA, Kaufmann H. Mechanisms, causes, and evaluation of orthostatic hypotension. In: UpToDate, Aminoff MJ, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated August 16, 2024. Accessed December 29, 2024.

Palma JA, Kaufmann H. Treatment of orthostatic and postprandial hypotension. In: UpToDate, Aminoff MJ, Kowey P, Goddeau RP (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through November 2024. Topic last updated August 16, 2024. Accessed December 29, 2024.