NORTHERA™ (droxidopa) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member’s specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms “experimental” and “investigational” are considered to be interchangeable.

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Description:

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 Northera (droxidopa) beyond 2 weeks of treatment has not been established, continued effectiveness of Northera (droxidopa) should be assessed periodically.

NOH 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.

Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue and fainting when a person stands.
Orthostatic hypotension is a physical finding and is defined as a documented decrease of greater than or equal to 20 millimeters of mercury (mmHG) in systolic blood pressure (SBP) or a greater than or equal to 10 mmHG decrease in diastolic blood pressure (DBP) within 3 minutes upon standing or a head-up tilt on a tilt table.

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, use of fitted elastic stockings, etc.

Other pharmacologic agents used to treat orthostatic hypotension include Fludocortisone and Midodrine. Midodrine is the only other FDA-approved medication for symptomatic orthostatic hypotension. Fludrocortisone is commonly used off-label to treat orthostatic hypotension. Other off-label treatments that are less commonly used are Ephedrine, Desmopressin, Dihydroergotamine, Erythropoietin, Indomethacin, Octreotide, Pyridostigmine, and Yohimbine.

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 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.

Northera (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 Northera (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.
NORTHERA™ (droxidopa) oral capsule (cont.)

Definitions:

Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened
A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer's labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record
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Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline. This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Northera (droxidopa) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. Incomplete forms will be returned.

- Initial therapy: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Northera (droxidopa) is considered medically necessary when ALL of the following criteria are met:
  1. The medication is prescribed by EITHER a neurologist OR a cardiologist
  2. Individual is 18 years of age and older
  3. Medical record documentation of a confirmed diagnosis of neurogenic orthostatic hypotension (NOH) caused by ONE of the following conditions:
     - Parkinson’s disease
     - Multiple system atrophy
     - Pure autonomic failure
     - Dopamine beta-hydroxylase deficiency
     - Non-diabetic neuropathy
  4. NOH is accompanied by the following symptoms: orthostatic dizziness, lightheadedness, or feelings of about to black out
  5. Orthostatic hypotension is documented on 3 separate occasions as a decrease of greater than or equal to 20 millimeters of mercury (mm HG) in systolic blood pressure (SBP) or a greater than or equal to 10 mm HG decrease in diastolic blood pressure (DBP) within 3 minutes by EITHER of the following:
NORTHERA™ (droxidopa) oral capsule (cont.)

- Upon standing
- Head-up tilt on a tilt table

6. **ALL** of the following non-pharmacologic measures have been maximized:
   - Intake of fluid and salt has been either liberalized or maximized, where appropriate
   - Uses fitted elastic/compression stockings, unless contraindicated
   - Uses abdominal binder, unless contraindicated
   - Head of the bed has been elevated
   - Individual instructed on how to change position from supine to standing in gradual stages

7. Comprehensive medication review has been performed to either reduce or discontinue agents that contribute or cause orthostatic hypotension, if safe to do so

8. Simultaneous use of fludrocortisone **AND** midodrine cannot be used due to **ONE** of the following:
   - Failed or is not effective
   - Experience significant adverse drug event
   - Has a contraindication to their use

9. Absence of **ALL** of the following exclusions:
   - Persistent supine hypertension
   - Individual with creatinine clearance of < 30 mL/min
   - Woman who is breast feeding an infant or child

- **Continuation of coverage (renewal request):** Northera (droxidopa) is considered **medically necessary** with documentation of **ALL** of the following:

  1. The individual has benefited from therapy but remains at high risk
  2. The condition has not progressed or worsened while on therapy
  3. Individual has not developed any contraindications or other exclusions to its continued use

- **Northera (droxidopa) for all other indications not previously listed is considered experimental or investigational** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Drug induced orthostatic hypotension
- Vitamin B-6 deficiency
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- Folate deficiency

Resources:


FDA-approved indication and dosage:

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<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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| NORTHERA 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 caused by primary autonomic failure (Parkinson's disease, 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 demonstrated. The continued effectiveness of NORTHERA should be assessed periodically. | - Starting dose is 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  
- Take consistently with or without food  
- To reduce the potential for supine hypertension, elevate the head of the bed and give the last dose at least 3 hours prior to bedtime  
- Take NORTHERA capsule whole |