Subject: Northera (droxidopa)	**Original Effective Date:** 7/10/2018
Policy Number: MCP-313	**Revision Date(s):**
Review Date:	
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of Northera (droxidopa) for the treatment of adult patients with **neurogenic orthostatic hypotension** when appropriate criteria are met.

The intent of the Northera (droxidopa) policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies. This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Orthostatic hypotension (OH)** is defined as a decrease in systolic BP > 20 mmHg or diastolic BP > 10 mmHg within 3 minutes after standing. Orthostatic hypotension may or may not be accompanied by symptoms (e.g., dizziness, lightheadedness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, head or neck ache). Orthostatic hypotension increases with age and is reported to affect approximately 30% of those over the age of 65.
  - Etiology
    - Drug-induced orthostatic hypotension is most common cause of OH
    - 25% of orthostatic syncope due to age-related orthostatic hypotension
    - Syncope due to OH may be caused by primary autonomic failure associated with:
      - pure autonomic failure
      - multiple system atrophy
      - Parkinson disease with autonomic failure
      - Lewy body dementia
      - Common causes include illness, autonomic dysfunction, volume depletion, cardiovascular impairment, endocrine dysfunction, and drugs **[Refer to Appendix 1: Medications that may cause or exacerbate OH]**

- **Neurogenic orthostatic hypotension (nOH)**
  - nOH a result of the inability of the autonomic nervous system to adequately release norepinephrine in order to regulate blood pressure after changes in posture, and can be seen in patients with Parkinson's disease, pure autonomic failure, and multiple system atrophy (Isaacson S, et al. 2014)
  - Patients may experience a sustained decrease in blood pressure upon standing, as well as supine hypertension (Isaacson S, et al. 2014).
  - It is reported that Parkinson's disease affects approximately one to 1.5 million Americans, with an estimate of 20%4 to 37-58% of patients with Parkinson's disease with symptomatic NOH. (Metzler M, et al. 2013)
  - Multiple system atrophy is a rare disorder, but the prevalence rate of orthostatic hypotension in these patients is estimated to be 75%, and 100% in patients with pure autonomic failure, also a rare condition. (Metzler M, et al. 2013)
- Pharmacologic management may include:
  - **Midodrine (an alpha1-adrenergic agonist) is FDA approved for symptomatic NOH and is PREFERRED.** (Jankovic J, et al.; Low PA, et al.; Wright RA, et al)
  - Fludrocortisone, has been used to increase plasma volume, and therefore blood pressure. Fludrocortisone has been used off-label as monotherapy or in combination with other treatments for orthostatic hypotension. (Low PA, et al. Metzler M et al. 2013)
  - **With limited evidence and lack of head-to-head data on midodrine and droxidopa, the place in therapy should be determined on a case-by-case basis based on patient response and tolerability to alternate agents available with consideration of cost-effectiveness.**

- **Droxidopa** is a synthetic amino acid precursor of norepinephrine. After conversion to norepinephrine, it may increase blood pressure by causing vasoconstriction of peripheral arteries and veins.
  - Droxidopa is a prodrug of norephinephrine. Norepinephrine increases peripheral vascular resistance.
  - The exact mechanism of action of droxidopa in the treatment of NOH is unknown; however, by increasing norepinephrine levels, droxidopa has been associated with improvements in standing BP and in NOH symptoms. Droxidopa is thought to exert its beneficial effects through the production of norepinephrine and not through the parent molecule or other metabolites.

- **EFFICACY**
  - Patients with symptomatic NOH treated with droxidopa experienced an improvement in symptoms compared to placebo as measured by the change in the Orthostatic Hypotension Questionnaire (OHQ) overall composite score (primary endpoint: droxidopa -1.83 vs. placebo -0.93; difference 0.90, P=0.003), composite symptom score and composite symptom-impact score (secondary endpoints)
  - Treatment with droxidopa increased standing systolic blood pressure compared to placebo (difference 7.3 mm Hg; P<0.001)

  References: 1) PI; 2) Droxidopa. Medical Review. Center for Drug Evaluation and Research. Drugs@FDA. Food and Drug Administration Web site; 3) Kaufmann H, et al. 2014.

- If droxidopa is initiated, it should be noted that only patient responders were enrolled in the published pivotal clinical trial of droxidopa (Study 301)**. Therefore, initial patient response and tolerability to droxidopa should be assessed (with discontinuation if there is no clinical benefit or intolerable adverse effects); with continued effectiveness of droxidopa reassessed periodically due to the benefit beyond 2 weeks of treatment not yet been established in clinical trials.**

- Droxidopa (Northera) appears to be **only marginally effective for treatment of the symptoms of neurogenic orthostatic hypotension.** It may decrease the risk of falling in some patients with Parkinson's disease. (The Medical Letter on Drugs and Therapeutics. 2015 Jun 22;57(1471):92-3)

- **Effectiveness beyond 2 weeks is uncertain, and patients should be evaluated periodically to determine whether droxidopa is continuing to provide a benefit.**

- Droxidopa carries a **boxed warning** of the increased risk of supine hypertension, which can cause stroke. It is recommended that patients sleep with their head and upper body elevated with routine monitoring of BP.

FDA INDICATIONS

- **Neurogenic orthostatic hypotension**
  Treatment of orthostatic dizziness, light-headedness, or the "feeling that you are about to black out" in adults with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.

Available as: Capsules: 100 mg, 200 mg, 300 mg

FDA Approved: February 18, 2014

- *Droxidopa was approved under the FDA accelerated approval program, as it is the only product approved for the treatment of NOH caused by primary autonomic failure (i.e., Parkinson disease, multiple system atrophy, pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy.*
- *Droxidopa received orphan-product designation from FDA for the treatment of neurogenic symptomatic orthostatic hypotension in patients with primary autonomic failure, dopamine-beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy*

Black Box Warnings: Droxidopa product labeling includes a boxed warning regarding supine hypertension. Monitor supine blood pressure 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.

REMS: No REMS at the time of this writing

CLASSIFICATION: Sympathomimetics

RECOMMENDATIONS/COVERAGE CRITERIA

Northera (droxidopa) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified cardiologist, neurologist, or nephrologist. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis **[ALL]**

- ❒ Diagnosis of symptomatic neurogenic orthostatic hypotension (nOH)
- ❒ ALL of the following documentation: [ALL]
  - ❍ Orthostatic hypotension documented on test of active standing or tilt-table test
  - ❍ Decrease of at least 20 mmHg in systolic blood pressure or 10 mmHg diastolic blood pressure within three minutes after standing from a sitting position
  - ❍ nOH is caused by ONE (1) of the following diagnoses: [ONE]
    - Primary autonomic failure (i.e., Parkinson's disease, multiple system atrophy, or pure autonomic failure)
    - Dopamine beta-hydroxylase deficiency
    - Non-diabetic autoimmune neuropathy
- ❒ Assessment of the severity of baseline symptoms of dizziness, lightheadedness, feeling faint, or feeling like the individual may black out. Documentation required (*effectiveness of therapy assessed for/if continuation of therapy is requested*)

3. Age/Gender/Restrictions [ALL]

- ❒ 18 years of age or older
  - *Safety and efficacy of droxidopa have not been established in pediatric patients.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

❒ **Non-Pharmacological Interventions**
Non-pharmacologic therapy have been tried and is ineffective. Documentation demonstrating that the member has tried non-pharmacologic interventions to treat their condition. [ALL]

NOTE: List below is not all-inclusive and if other non-pharmacologic therapies have been tried, please submit documentation for review by pharmacy/medical director.

- ❍ Discontinuation of medications that may cause or exacerbate OH: Clinical evaluation of ALL member's current medications to evaluate for any medications that may precipitate hypotension.
  Refer to Appendix 1: Medications that may cause or exacerbate OH

  Informational Note: Medications that may increase the frequency of symptomatic NOH include alpha-adrenergic antagonists (e.g., benign prostatic hypertrophy medications), antidepressants (particularly, tricyclic antidepressants), antipsychotics, and dopaminergic agonists (e.g., antiparkinsonian medications).

- ❍ Lifestyle modifications, including:
  - Arising too quickly from supine to sitting or standing
  - Avoiding overheating
  - Avoiding straining/coughing/walking in hot weather; hot environment
  - Maintaining hydration
  - Raising the head of the bed 10 to 20 degrees
  - Using custom-fitted elastic stockings

- ❍ Performance of physical counter-maneuvers such as: crossing legs stooping, squatting and tensing muscles

- ❍ Meal modification (if symptoms appear to be associated with eating) such as: Avoiding large meals; Ingesting meals low in carbohydrates; Minimizing alcohol intake; Drinking water with meals; Avoiding activities or sudden standing immediately after eating

Informational Note: When non-pharmacologic measures do not sufficiently prevent symptoms of OH, pharmacologic interventions should be considered. Most widely used agents for treatment of OH are fludrocortisone and midodrine.

❒ **Pharmacologic Treatments**
Inadequate response,† clinical intolerance, contraindication, or inappropriate for member's condition required for the following therapies. Documentation required: [ALL]
†*Inadequate response is defined as failure to achieve and maintain improvement in OH symptoms after a compliant trial on the recommended dose for a sufficient period*

- ❍ midodrine (ProAmatine)
  AND
- ❍ ONE (1) of the following medications, unless contraindicated or clinically significant adverse effects are experienced. Documentation required. [ONE]
  - fludrocortisone (Florinef)
  - desmopressin
  - dihydroergotamine
  - indomethacin
  - pyridostigmine
  - erythropoietin

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to droxidopa or any component of the formulation, such as FD+C Yellow No. 5 (tartrazine)
  - *Reactions may include anaphylaxis, angioedema, bronchospasm, rash, and urticaria; emergency treatment may be necessary. Discontinue use and initiate immediate medical support if a hypersensitivity reaction occurs*
  - *Product contains FD+C yellow number 5 (tartrazine) which may cause allergic reactions (e.g., bronchial asthma), particularly in patients with aspiring hypersensitivity*
- ❒ Younger than 18 years
  - *Safety and efficacy have not established in pediatric patients*

Informational Note: No specific drug-drug interaction studies were performed for droxidopa; however, patients in clinical trials have received droxidopa with concomitant levodopa/carbidopa, dopamine agonists, monoamine oxidase B inhibitors, COMT inhibitors, and other medications used to treat Parkinson disease.

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Northera (droxidopa) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Subsequent authorizations will require the Member to have an office visit and re-assessment for this condition beyond 2 weeks of treatment to determine if continuation of treatment with requested medication is medically necessary. Chart notes or consultation notes (if applicable) must be submitted for initial request and for continuation of treatment requests beyond 2 weeks of treatment

  NOTE: It should be noted that only patient responders were enrolled in the published pivotal clinical trial of droxidopa (Study 301). Therefore, initial patient response and tolerability to droxidopa should be assessed (with discontinuation if there is no clinical benefit or intolerable adverse effects); with continued effectiveness of droxidopa reassessed periodically due to the benefit beyond 2 weeks of treatment not yet been established in clinical trials.

2. Compliance [ALL]

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including: [ALL]
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

  NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL]

Northera (droxidopa) therapy may be authorized when therapy has demonstrated efficacy as evidenced by: [ALL]

- ❒ Continued effectiveness of Northera (droxidopa) documented through: [ALL]
  - ❍ Improvement in the symptoms of neurogenic orthostatic hypotension, such as decreased dizziness, decreased lightheadedness, decreased fainting
  - ❍ Periodic assessments of blood pressure

4. **Discontinuation of Treatment [ANY]**
   Discontinue treatment if ANY of the following conditions applies: [ANY]
   - ❑ Intolerable adverse effects or drug toxicity
     - ❍ Hyperpyrexia and Confusion
       - *Case reports of a symptom complex resembling neuroleptic malignant syndrome (NMS) have been reported with droxidopa during post-marketing surveillance. Patients should be observed carefully if the dose of droxidopa is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics. Although NMS is uncommon, it can be life-threatening where early diagnosis is important to ensure appropriate treatment. NMS is characterized by fever or hyperthermia, muscle rigidity, involuntary movements, altered consciousness, and mental status changes.*
     - ❍ Ischemic Heart Disease, Arrhythmias, and Congestive Heart Failure
       - *Droxidopa may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure. Consider risk vs. benefit prior to initiating therapy in patients with these conditions*.
     - ❍ Allergic Reactions
       - *Droxidopa contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions, including bronchial asthma, in certain susceptible persons (e.g., patients with aspirin hypersensitivity).*
   - ❑ Persistent and uncorrectable problems with adherence to treatment
   - ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms

   <u>Contraindications/Exclusions/Discontinuations</u>
   - ❒ Non-FDA approved indications
   - ❒ Hypersensitivity to droxidopa or any component of the formulation, such as FD+C Yellow No. 5 (tartrazine)
     - *Reactions may include anaphylaxis, angioedema, bronchospasm, rash, and urticaria; emergency treatment may be necessary. Discontinue use and initiate immediate medical support if a hypersensitivity reaction occurs*
     - *Product contains FD+C yellow number 5 (tartrazine) which may cause allergic reactions (e.g., bronchial asthma), particularly in patients with aspiring hypersensitivity*
   - ❒ Younger than 18 years
     - *Safety and efficacy have not established in pediatric patients*

5. **Labs/Reports/Documentation required [ALL]**
   All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

   NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

1. Recommended Dosage [ALL]

- ❒ **Orthostatic hypotension, Neurogenic:** The 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.

  Titrate as needed in increments of 100 mg 3 times daily every 24 to 48 hours.

  NOTE: Efficacy beyond 2 weeks of treatment not established

2. Authorization Limit [ALL]

- ❒ Quantity limit: Maximum dose of 600 mg three times daily (OR a maximum total daily dose of 1,800 mg)
- ❒ Dispensing limit: [ALL]
  - ❍ Up to a **2-week** supply may be dispensed at a time
- ❒ Duration authorization: [ALL]
  - ❍ Initial: 2 weeks (14 days)
    - *Per label, effectiveness for use beyond 2 weeks of treatment has not been established and continued effectiveness should be assessed periodically.*
  - ❍ Continuation: 2 weeks (14 days).

    Re-authorization is required every 2 weeks to determine effectiveness of therapy and continued need based on documented positive clinical response. Subsequent renewals will be authorized upon verification of marked clinical improvement demonstrated by objective improvement in these selected markers. Refer to 'Continuation of Therapy' section.
  - ❍ **Total approval duration (per 365 days): 4 weeks (28 days)**

3. Route of Administration [ALL]

- ❒ Northera (droxidopa) is considered a **self-administered** medication
  - *Northera (droxidopa) is deemed appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.*
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider. These agents must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy addresses the coverage of Northera (droxidopa) for the treatment of adult patients with **neurogenic orthostatic hypotension** when appropriate criteria are met.

All other uses of Northera (droxidopa) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered not medically necessary. This is subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF CLINICAL EVIDENCE

Orthostatic hypotension (OH) is a reduction in systolic blood pressure due to orthostatic stress, common in older patients that may result in syncope (Chisholm P. et al 2017). Syncope is syndrome of transient loss of consciousness secondary to cerebral hypoperfusion characterized by rapid onset, short duration, and complete spontaneous recovery.Dynamed 2018

Neurogenic orthostatic hypotension (nOH) occurs in many neurodegenerative and metabolic diseases and is also associated with aging. Lightheadedness and dizziness are common symptoms, but weakness, fatigue, and cognitive dysfunction also occur.

Lifestyle modifications such as avoiding rapid changes in posture, increasing fluid and salt intake, and wearing compression stockings can be helpful, but pharmacotherapy may be necessary for patients with persistent symptoms. Midodrine, an alpha1-selective adrenergic agonist, was FDA-approved earlier for treatment of severe symptomatic OH based on its effectiveness in increasing standing blood pressure, but symptomatic or functional improvement in patients with NOH has not been documented (Med Lett Drugs Ther. 2015 Jun 22) . Other drugs commonly used (off-label) to treat symptomatic NOH include fludrocortisone and pyridostigmine (Berger, MJ et al. 2014).

PIVOTAL TRIALS

EFFICACY

The efficacy of droxidopa was evaluated through two short-term placebo-controlled studies over 1-2 weeks (studies 301 and 302).

Study 301 (Kaufmann H, et al. 2014)

- Phase 3 multicenter, multinational, double-blind trial that randomized 162 patients (61.6% of 263 patients who were considered responders) [i.e., > 1 unit on the OHQ item 1 ("dizziness, lightheadedness, feeling faint, and feeling like you might black out"), in addition to > 10 mm Hg increase in SBP from baseline after an open-label droxidopa optimization protocol) with symptomatic NOH due to Parkinson's disease (N=66), multiple symptom atrophy (N=26), pure autonomic failure (N=54), or nondiabetic autonomic neuropathy (N=8), with a decrease in systolic BP > 20 mmHg or diastolic BP > 10 mmHg within 3 minutes after standing, to treatment with droxidopa or placebo.
- Subjects:
  - age 18 or older
  - 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.
  - 97% Caucasian, 52% male, with a mean age of 563; 45% of participants were taking dopa-decarboxylase inhibitors, and 29% were taking fludrocortisone
- 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.
- 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. **Responders were then randomized to a seven day treatment period with droxidopa (n=82) or placebo (n=80).**

- The Orthostatic Hypotension Questionnaire (OHQ) consists of 10 items, 6 which address NOH symptoms (e.g., dizziness/lightheadedness, vision disturbance, weakness, fatigue, trouble concentrating, head/neck discomfort), and 4 that ask the patient to consider the impact of NOH on daily activities in the preceding week (e.g., that require "standing a short time," "standing a long time," "walking a short time," and "walking a long time"). A Likert scale is used to score the item from 0 (not bothered/no interference) to 10 (worst possible/complete interference). A composite symptom score and a composite symptom-impact score (each an average of the item scores that are not rated 0 at baseline), as well as an overall composite score (average of the symptom and symptom-impact composite scores), are computed based on patient response.
- The primary efficacy endpoint was change in overall composite score from randomization to end of study (at Week 1 analysis). Secondary endpoints included: change in symptom score; change in symptom-impact composite score; and change in individual OHQ items. Additional endpoints included change in standing systolic BP from randomization to end of the study.
- Results
  - Patients with symptomatic nOH (who previously responded to open-label droxidopa) treated with droxidopa for one week experienced a statistically significant improvement in OHQ composite score, composite symptom score, composite symptom-impact score, and increase in standing systolic BP compared to placebo.
  - There was a statistically significant improvement noted in four of the six components of the symptom score (dizziness/lightheadedness, vision disturbance, weakness, fatigue), as well as all four of the symptom-impact items (standing short time, standing long time, walking short time, walking long time).
- Post-hoc subgroup analyses showed statistically significant differences favoring droxidopa in OHQ composite score as well as standing systolic BP only for patients with pure autonomic failure, or for non-users of dopa-decarboxylase inhibitors. It was noted that it is difficult to assess efficacy by subgroup as each contained fewer than 50 patients.
- Safety Considerations
  - In Study 301, during double-blind treatment, no falls occurred in the droxidopa treatment group compared to 3.7% of patients on placebo. Cardiac adverse events were reported in 3.0% of patients during the open-label dose titration phase of droxidopa, most frequently reported as palpitations (1.9%). During the treatment phase, no cardiac adverse events and no serious adverse events were reported. At the end of the study, 4 patients (4.9%) receiving droxidopa experienced supine hypertension (defined as systolic BP > 180 mm Hg), which was reported in 2 patients (2.5%) in the placebo group.
  - According to data from long-term, open-label extension trials (N=422), the most common adverse events reported were falls (24%), urinary tract infections (15%), headache (13%), syncope (13%), and dizziness (10%).[PI]

Reference: Kaufmann H et al. (2014): Droxidopa for neurogenic orthostatic hypotension; A randomized, placebo-controlled, phase 3 trial. Neurology 83:328-335.

Study 302

Study 302 (n=101) was designed similarly to Study 301. It was a multi-center, multi-national, double-blind, placebo-controlled, 2-week randomized withdrawal study of droxidopa in patients with symptomatic NOH.

- There was an initial dose titration phase of up to 14 days followed by seven days of open-label treatment and a 14-day randomized withdrawal period. Inclusion and exclusion criteria were similar to those in Study 301.
- Endpoints included the primary efficacy endpoint of the mean change in the OHSA Item #1 (dizziness/lightheadedness) and secondary endpoints of blood pressure, global assessment evaluations, and symptom and activity measurements using OHQ scores.
- Results from this study did not reveal a statistically significant difference between the treatment and placebo arms with respect to the primary endpoint of OHSA Item #1 or the secondary endpoint of blood pressure.

Reference: FDA Briefing Document: Cardiovascular and Renal Drug Advisory Committee Meeting.

SAFETY

- Clinical trials consisted of patients with Parkinson's disease, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy. The most common adverse reactions (>5%) include headache, dizziness, nausea, hypertension, and fatigue.
- Across clinical trials, the most common adverse reactions leading to discontinuation of therapy were hypertension and nausea.

CLINICAL PRACTICE GUIDELINES

NOTE: Droxidopa (Northera) have not been addressed in clinical practice guidelines as of this writing in March 2018

European Federation of Neurological Societies: orthostatic hypotension (Lahrmann H, et al, 2011)

- In patients with orthostatic hypotension, these guidelines recommend the use of fludrocortisone, midodrine, octreotide, and droxidopa for the pharmacologic treatment of orthostatic hypotension.
- Fludrocortisone (level C) is listed as first-line monotherapy, and midodrine (level A) is suggested for use as monotherapy or combination therapy with fludrocortisone.
- Droxidopa (level A) is recommended for use for effective treatment of orthostatic hypotensions associated with dopamine beta-hydroxylase deficiency.

DEFINITIONS

Orthostatic Hypotension

- ≥ 20-mm Hg decrease in systolic blood pressure or ≥ 10-mm Hg decrease in diastolic blood pressure within 3 minutes of standing compared to sitting or supine[Dynamed]
- Decrease in systolic blood pressure ≥ 30 mm Hg in patients with hypertension (supine systolic blood pressure ≥ 160 mm Hg) (Freeman R. et al; Chisholm P et al.)
- Absolute standing systolic blood pressure < 90 mm Hg in patients with low baseline blood pressure (Chisholm P et al.)

APPENDIX

Appendix 1: Non-Pharmacologic Measures for Treatment of OH

NOTE: Table below is a reference only and may not all-inclusive of every causative agent. If the suspected/causative agent is not listed below, confirm the status of the agent and its association with OH.

NON PHARMACOLOGIC MEASURES FOR TREATMENT OF OH *Discontinuation of medications that may cause or exacerbate OH*
Alpha blockers (e.g., terazosin)
Antidepressants (e.g., SSRIs, trazodone, MAOIs, tricyclic antidepressants)
Antihypertensive drugs (e.g., sympathetic blockers)
Antiparkinsonism drugs (e.g., levodopa, pramipexole, ropinirole)
Antipsychotic drugs (e.g., olanzapine, risperidone)
Beta-blocker drugs (e.g., propranolol)
Diuretics (e.g., hydrochlorothiazide, furosemide)
Skeletal muscle relaxants (e.g., tizanidine)
Narcotic analgesics (e.g., morphine)
Phosphodiesterase inhibitors (e.g., sildenafil, tadalafil)
Sedatives/hynotics (e.g., temazepam)
Vasodilators (e.g., hydralazine, nitroglycerin, calcium channel blockers)

CODING INFORMATION

The codes listed in the policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

CPT	Description
NA	

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10	Description [For dates of service *on or after* 10/01/2015]
I95.1	Orthostatic hypotension
F02.2	Syncope and collapse

*CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

REFERENCES

PACKAGE INSERT, FDA, DRUG COMPENDIA

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