Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: droxidopa capsules, oral

Month/Year of Review: January 2015
Generic Name: droxidopa
PDL Class: None

End date of literature search: October 13, 2014
Brand Name (Manufacturer): Northera™ (Lundbeck)
Dossier Received: October 13, 2014

FDA Approved Indication:
Droxidopa is indicated for the treatment of orthostatic dizziness, light-headedness, 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 or pure autonomic failure), dopamine beta-hydroxylase deficiency, and nondiabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been demonstrated. The continued effectiveness of droxidopa should be assessed periodically.[1]

Research Questions:
- Is droxidopa more effective than currently available alternative agents for the treatment of symptomatic neurogenic orthostatic hypotension?
- Is droxidopa safer than currently available agents?
- Are there subgroups of patients in which droxidopa may be safer or more effective than other drugs to treat neurogenic orthostatic hypotension?

Conclusions:
- There is insufficient evidence directly comparing the efficacy or safety of droxidopa to other pharmacological interventions for symptomatic neurogenic orthostatic hypotension.
- There is insufficient evidence demonstrating efficacy of droxidopa on clinically relevant outcomes for symptomatic orthostatic hypotension, such as quality-of-life, symptom relief and fall rates.
- There is low quality evidence demonstrating short-term relief of symptoms over the first 7 days of therapy, based on one item addressed in the 10-item Orthostatic Hypotension Questionnaire, in patients with Parkinson's disease and orthostatic hypotension. Efficacy beyond 7 days is questionable.
- There is moderate quality evidence documenting high attrition during initial treatment with droxidopa, primarily due to lack of drug effectiveness.
- There is insufficient evidence to determine what subpopulation droxidopa might be more effective.

Recommendations:

- Prior authorization should be added to ensure appropriate use due to low quality data suggesting short-term symptomatic relief of orthostatic hypotension and lack of long-term efficacy and safety data. See **Appendix 2**.

Background:

Neurogenic orthostatic hypotension (nOH), a subtype of orthostatic hypotension, results from the failure of the autonomic nervous system (ANS) to regulate blood pressure with inadequate release of norepinephrine (NE) in response to postural change. Thus, blood pressure falls upon standing and inadequately maintains cerebral perfusion, resulting in symptoms such as lightheadedness, dizziness and syncope. This condition can be observed in patients with primary autonomic failure, such as with Parkinson's disease (PD), multiple system atrophy (MSA) and pure autonomic failure (PAF), but can also be observed in conditions such as dopamine beta-hydroxylase (DBH) deficiency and non-diabetic autonomic neuropathy (NDAN). In contrast, orthostatic hypotension can be caused by volume depletion, dehydration and vasodilation, and is not associated with dysfunction of the autonomic nervous system. Symptomatic nOH can occur in up to 20% of patients with PD and is more common with long duration of PD, more disease severity, increased age and levodopa usage. Symptoms may vary throughout the day and may abate and recur over time.[2]

Orthostatic hypotension is a clinical sign defined as a decrease in systolic blood pressure (SBP) of at least 20 mmHg and diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing. Patients with nOH may experience daily fluctuations in SBP and DBP and symptoms may vary, or may not occur until several minutes after standing.[2,3]

Avoidance of factors that may induce nOH is recommended first line and includes educating the patient about conditions that may precipitate hypotension. These factors include warm temperatures, such as a hot bath or shower, which can cause venous pooling; prolonged recumbence during daytime and sudden head-up postural change, especially in the morning; and post-prandial conditions, especially after carbohydrate-rich meals. Maintaining adequate hydration and salt intake have an important role in the management of nOH. Individualized exercise training often improves nOH.[4]

Pharmacological management of nOH may be added when patients have persistent symptoms despite management utilizing nonpharmacological measures. Medications that may lower blood pressure or have anticholinergic effects should be discontinued if possible. There are limited data for the pharmacological management of symptoms of nOH. Fludricortisone is a synthetic mineralocorticoid initially recommended for orthostatic hypotension. Fludricortisone retains sodium and water and requires high dietary salt and adequate fluid intake to be effective. Fludricortisone may also exacerbate heart failure symptoms in susceptible patients. Midodrine is an alpha-adrenergic agonist with FDA approval for nOH and is can be used in combination with fludricortisone. Midodrine increases blood pressure by increasing peripheral vascular resistance but has a short duration of action and must be administered multiple times per day. Midodrine should also be avoided near bedtime as it can result in increased supine blood pressure. Other agents that have been utilized for nOH include pyridostigmine, pseudoephedine/ephedrine, desmopressin and erythropoietin; each with limited evidence of effectiveness and obviously uncomfortable or dangerous side effects.[4]

Droxidopa has been marketed in Japan since 1989 for freezing of gait in patients with PD and orthostatic hypotension during hemodialysis. In Europe, blood pressure levels have been studied in a non-controlled, open-label trial of 33 nOH patients with MSA and PAF.[5] More recently, droxidopa was evaluated by the FDA in Phase 3 clinical trials.

The FDA accelerates approval of drugs for serious or life-threatening conditions based on a surrogate endpoint or intermediate clinical measure that is *reasonably likely* to predict clinical benefit. Under these circumstances, droxidopa was approved in February 2014 based on short-term relief of dizziness that the FDA felt *reasonably likely* to predict long-term relief of dizziness. Approval under these conditions is subject to the FDA requirement that the applicant study droxidopa with due diligence to further verify and describe the clinical benefits of the drug in an adequate, well-controlled clinical trial.[6] Clinical outcomes of significance in this population include long-term symptom relief of dizziness and lightheadedness and prevention of falls, as well as adequate improvement quality-of-life and functional capacity.[4]

Clinical Efficacy:

There were four Phase 3 clinical trials conducted in the development of droxidopa (studies 301, 302, 303 and 306). Study 305 was a 24-hour blood pressure monitoring study and Study 304 was a long-term, open-label study collecting safety data. Data from Study 301 yielded the principal evidence of the effectiveness of droxidopa. Study 302 was a randomized withdrawal study running concurrently with study 301 that did not succeed on its primary endpoint of item 1 of the Orthostatic Hypotension Questionnaire (OHQ) (see description below). Study 303, made up of participants from study 301 and 302, also had negative findings.[6]

The effectiveness of droxidopa was evaluated using the OHQ. The OHQ is comprised of 10 self-assessment symptom and activity questions: 6 items pertaining to symptoms (e.g., item 1 pertains to dizziness/lightheadedness), and 4 items pertaining to daily activities (e.g., standing and walking). The patient rates each item from both sections on a scale from 0 to 10, with 10 being the worst possible symptoms or interference with a activity. The composite OHQ score is the unweighted average of the 10 subscores of each item. In reviewing droxidopa, the FDA felt item 1 was the preferred method of evaluating the effectiveness of droxdiopa over the cumulative OHQ score because it represents core symptoms of nOH, whereas other items of OHQ have not been documented to be disease-defining symptoms.[6]

All studies enrolled adult patients with nOH, defined as a decrease in SBP of at least 20 mmHg or in DBP of at least 10 mmHg within 3 minutes upon standing that is associated with primary autonomic failure (PD, MSA, PAF), DBH deficiency, or NDAN. Patients with diabetes mellitus and those with significant cardiac, renal or hepatic disease were excluded.[6]

The two positive studies the FDA used to grant approval of droxidopa are summarized below. Both trials are considered low quality studies due to high selection bias and detection bias. In general, only patients who tolerated droxidopa and appeared to have a favorable symptom response during the open-label titration period were randomized for data analysis. Multiple protocol amendments also hinder the validity of these results.

Study 301

Study 301 was a poor quality phase 3, randomized, multi-center, parallel-group, placebo-controlled, double-blind trial with an initial open-label dose titration, followed by a 7-day washout period, which was followed by a 7-day double-blind, randomized treatment period.[7] The study was designed to evaluate the efficacy and safety of droxidopa (n=82) compared to placebo (n=80) in patients who previously demonstrated a response to, and tolerance of, droxidopa.

All eligible patients (n=263) entered an open-label, dose titration phase to find an optimal dose for each patient. Patients were initiated at 100 mg orally three times daily (TID), then titrated by 100 mg TID until one or more of the following criteria were met: i) the patient became asymptomatic (i.e., score of 0 on item 1

of the OHQ) and had an improvement in standing SBP of at least 10 mmHg from baseline; ii) sustained SBP greater than 180 mmHg or DBP greater than 110 mmHg after 3 minutes standing, or 5 minutes sitting, or in the supine position; iii) unable to tolerate side effects; or iv) reached the maximum dose of 600 mg TID.[7] Only patients (n=168) who tolerated droxidopa and had a favorable response in the open-label titration period, as outlined in the protocol above, were included in the randomized treatment phase and included in the assessment of endpoints. Thus, 95/263 (36%) of the initially eligible patients were considered droxidopa treatment failures.

Baseline characteristics were similar between groups with an average age of 57 years. About half the patients were male and nearly all patients were white. Mean OHQ composite scores were 5.62 (±2.0) and 5.96 (±1.7) in the randomized placebo and droxidopa groups, respectively. Mean OHQ item 1 scores were 6.2 (±2.4) and 6.5 (±2.1) in the randomized placebo and droxidopa groups, respectively.[7]

The primary endpoint of the study was amended to the change in OHQ composite score assessed at 1 week after a *post hoc* analysis of Study 302 showed positive results with this composite outcome measure as a secondary endpoint.[6] The original primary endpoint of Study 301 was the same Study 302, which failed to demonstrate a statistical significant difference from placebo in item 1 of the OHQ.[6,8]

After the protocol amendment, data demonstrated a statistically significant difference favoring droxidopa relative to placebo with respect to the mean change in the composite OHQ score from randomization to Day 7 (-0.93 vs. -1.83 units for placebo and droxidopa, respectively), with a mean difference of 0.9 units (95% CI, 0.30 to 1.48; p=0.003).[7] *Post hoc* analyses found an improvement of ≥3 units in the composite score in 27.2% of droxidopa patients versus 11.4% of placebo patients (p=0.016) and ≥4 units in the composite score in 17.3% of droxidopa patients versus 2.5% of placebo patients.[7] Pre-specified secondary outcomes showed mean symptom composite scores (first 6 items) improved by -1.68 units in droxidopa patients versus -0.95 units in patients receiving placebo, a statistically significant difference of 0.73 units (95% CI, 0.10 to 1.36 units; p=0.01).[7] Specific items that showed significant improvement include dizziness/lightheadedness (item 1), vision disturbance, weakness and fatigue. Mean change in the activity composite scores (last 4 items) improved by -1.98 units versus -0.92 units, favoring droxidopa by 1.06 units (95% CI, 0.41 to 1.71 units; p=0.003).[7] All activity items showed significant improvement with droxidopa. Hemodynamically, droxidopa had no effect on orthostatic decrease in SBP upon standing.[6] An increased SBP while standing and in the supine position was higher for droxidopa relative to placebo: a mean 7.3 mmHg difference in standing SBP (95% CI, 1.1 to 13.5 mmHg; p<0.001) and a mean 6.8 mmHg difference in SBP while supine (95% CI, 1.53 to 12.07; p<0.001).[7]

Interestingly, the FDA found irregular findings at 2 clinical sites. In particular, data from the largest enrolling site, located in the Ukraine, had highly irregular findings, with a difference of -3.6 units favoring droxidopa over placebo in the OHQ composite score. The FDA found concerning variability within all of the study endpoints at this site and deemed these data unreliable. The results from this study were no longer statistically significant when data from this site was omitted; a difference of -0.56 units relative to placebo for the primary endpoint (p=0.07) and a difference of only 4 mmHg SBP increase upon standing. Thus, the FDA required an additional positive, well-controlled trial for approval.[6]

In response, the applicant recruited patients previously enrolled in Studies 301 and 302 for Study 303 (n=75), including those that already had at least a 1-point improvement in item 1 of the OHQ during the open-label dose titration phase, but failed to achieve the requisite increase in SBP of at least 10 mmHg within 3 minutes of standing required for randomization.[6] Study 303 was a randomized withdrawal study that failed to achieve a significant difference in the composite OHQ score from randomization to the end of week 2.[6,9] Interestingly, composite OHQ scores actually worsened for the droxidopa group by +0.57 units and the placebo group by +0.90 units. However, a *post hoc* analysis of study 303 showed a better treatment effect with droxidopa on item 1 of the OHQ in patients of

western countries, including the U.S., Canada, Italy, Germany and Austria. In response, the applicant conducted Study 306 in PD patients only within the U.S., with the redesigned endpoint of item 1 of the OHQ; an outcome, as mentioned previously, considered more representative of the core symptoms associated with nOH.[6]

Study 306B

Study 306 was a poor quality phase 3, randomized, parallel-group, placebo-controlled, double-blind trial located in centers solely within the U.S evaluating symptomatic nOH patients with PD who experienced a decrease of at least 20 mmHg SBP or 10 mmHg DBP within 3 minutes of standing. Following randomization of patients 1:1 to droxidopa 100 mg TID or placebo TID, doses were titrated for up to 14 days to determine an optimal dose for each participant, which was followed by an 8-week treatment period. Doses were titrated until i) the patient became asymptomatic (i.e., score of 0 on item 1 of the OHQ) and had an improvement of standing SBP of at least 10 mmHg from baseline; ii) sustained SBP greater than 180 mmHg or DBP greater than 110 mmHg after 3 minutes standing, or 5 minutes sitting, or in the supine position; iii) unable to tolerate side effects; or iv) reached the maximum dose of 600 mg TID.[6]

The original primary endpoint of the study was change in OHQ composite score assessed at 8 weeks.[6] However, the trial was terminated early for futility after a pre-specified interim analysis found a conditional power less than 0.1 after data from 51 patients were reviewed.[6] Among 24 droxidopa patients and 27 placebo patients, mean OHQ composite score change at weeks 1, 2, 4 and 8 were not significantly different.[10] Indeed, at week 8 the mean OHQ composite score change was -2.2 units versus -2.1 units for droxidopa and placebo patients, respectively (p=0.98).[10] The mean change for item 1 of the OHQ (dizziness/lightheadedness) was -3.1 units for droxidopa versus -1.6 units for placebo after week 1 (p=0.24) and -2.3 versus -1.0 after week 2 (p=0.24), with the margin of difference narrowing later in the study.[10] Overall, similar numbers of patients reported falls with droxidopa (54%) as with placebo (59%).[10] However, interim data showed positive data for droxidopa on the total number of patient-reported falls and fall rate. The applicant opted to continue the study but split it into study 306A, which included the unblinded data of the first 51 patients, and study 306B.[6] The primary endpoint for study 306B was changed from the OHQ composite score to patient-reported falls assessed at 8 weeks.[6] Patients from study 306A (n=51) were not included in the data analyses of study 306B (n=174).[6,11]

After the *post hoc* analysis of Study 303 was reviewed, the applicant changed the primary endpoint of study 306B to change in item 1 of the OHQ from baseline to Day 7. Secondary endpoints included change in item 1 of the OHQ at Week 2, Week 4 and Week 8, change in composite OHQ score from baseline at week 8, rate of patient-reported falls, and change in lowest SBP within 3 minutes upon standing from baseline to Day 7.[6]

At 7 days, 147/174 patients were assessed and included in the analysis of the primary endpoint. There were 3-times more patients in the droxidopa group (n=20, 22%) that did not have week 1 data as in the placebo group (n=7, 8%).[11] The primary reasons for the high attrition rate in the droxidopa group were adverse events (n=6), treatment failure (n=4), withdrawal of consent (n=3), and investigator decision (n=2). In contrast, 4/7 patients in the placebo group who dropped out during week 1 withdrew because of adverse effects.[6] None of the patients in the placebo group dropped out due to treatment failure.[6]

Thus, only 69 patients in the droxidopa group and 78 patients in the placebo group were analyzed. Two-thirds of the patients studied were male; 96% were white; and mean age was 72 years.[11] Baseline characteristics were similar between the two groups with the exception of fludricortisone use at baseline, which was more common in the droxidopa group relative to placebo (34% vs. 20%, respectively).[6] Mean item 1 scores of the OHQ were similar at baseline.[6]

The mean difference in item 1 score of the OHQ was statistically significant in favor of droxidopa compared to placebo at -0.94 units (95% CI, -1.78 to -0.10 units; p=0.028) using FDA analyses of the data.[6] The statistical significance found at Day 7 vanished in subsequent weeks, with p-values of 0.77, 0.26 and 0.19 for

Weeks 2, 4, and 8, respectively.[6] Interestingly, the FDA found an unblinded statistical team had access to the treatment codes for all study 306 patients after the study was split into 306A and 306B but had difficulty determining if study integrity was compromised. Similar to study 301, one site disproportionately recruited more participants in the study and had a much larger mean treatment difference of -2.6 units. Excluding data from this particular site changed the results to a non-significant difference of -0.68 units (p=0.13). However, the FDA inspected the site and found no apparent study violations.[6]

Clinical Safety:

The study periods for safety evaluation were brief. In addition, safety assessment is difficult because there were no single serious adverse events reported in the placebo-controlled groups in any of the studies. In Study 306, 5 participants on droxidopa reported a total of 9 serious adverse events, and 4 participants receiving placebo reported a total of 5 serious adverse events. No serious adverse event was reported more than once.[6]

Most of the safety data is from the uncontrolled portions of the studies, which overestimates risk of the drug since all reported adverse events must be attributed to the drug. Noting these limitations, 105/402 patients (25%) reported 224 serious adverse events, of which 20% led to study drug discontinuation and 12% resulted in death. The most commonly reported serious adverse events in the uncontrolled data were syncope (n=14, 3%), pneumonia (n=9, 2%), dehydration (n=8, 2%), hip fracture (n=6, 1%), falls (n=5, 1%), and urinary tract infection (n=5, 1%). According to the FDA, one cannot determine the extent to which droxidopa was causally related to these adverse events.[6]

The most frequently reported common adverse events in the placebo-controlled study phases were hypertension (7% and 1% in the droxidopa and placebo groups, respectively), headache, nausea and dizziness.[6]

Safety data from the open-label, extension studies are detailed in **Appendix 1**.

Comparative Clinical Efficacy:

Relevant Endpoints:
1) Symptom relief
2) Long-term quality-of-life and functional capacity
3) Patient fall rate

Primary Study Endpoints:
1) Short-term (7 days) change in composite score of the OHQ containing 10 items; 6 items address symptoms of orthostatic hypotension and 4 items affect activities of daily living
2) Short-term (7 days) change in item 1 of OHQ, which specifically addresses dizziness/lightheadedness

Ref. / Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Outcomes	ARR/ NNT	Safety Outcomes	ARR/ NNT	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
Study 301[6,7] R, DB, PC, PG, MC Europe U.S. Canada Aug 2008 – Jul 2010	OL dose titration phase followed by 7 d washout (n=263) Only 168/263 patients considered "responders" after OL dose titration phase randomized: ▪ ≥1 unit on OHQ item 1 and; ▪ ≥ 10 mmHg standing SBP and; ▪ tolerated droxidopa 1.Droxidopa 100-600 mg TID for 7 d (D) (n=82) Mean 430 mg 2.Placebo TID for 7 d (P) (n=80)	Demographics: (P, D) ▪ Age 55.7, 57.4 y ▪ Males 52.5%, 51.2% ▪ White 93.8%, 100% ▪ PD 38.8%, 42.7% ▪ PAF 35.0%, 31.7% ▪ OHQ item 1 score 6.2, 6.5 ▪ Standing SBP 90.7 mmHg, 90.8 mmHg ▪ Supine SBP 122.4 mmHg, 127.6 mmHg Inclusion Criteria: ▪ Age ≥18 y ▪ Clinical dx of nOH due to PD, PAF, MSA, NDAN or DBH deficiency ▪ ≥20 mmHg SBP or ≥10 mmHg DBP upon standing ≤3 min Exclusion Criteria: ▪ Use of vasoconstrictor agent ≤2 d before baseline ▪ Use of long-acting antihypertensives or norepinephrine reuptake inhibitors ▪ Sustained, severe supine HTN ▪ Significant systemic, hepatic, cardiac or renal disease	ITT: Not applied PP: D: n=82 P: n=77 Attrition: D: 0/82 P: 3/80 (LOCF)	**Primary Outcome:** Mean Δ composite OHQ* score (SD) from randomization to Day 7: D: -1.83 (2.07) units P: -0.93 (1.69) units Mean difference 0.90 units (95% CI, 0.30 to 1.48; p=0.003) **Secondary Outcomes:** Mean Δ composite symptoms OHQ score from randomization to Day 7: D: -1.68 (2.13) units P: -0.95 (1.90) units Mean difference 0.73 units (95% CI, 0.1 to 1.36; p=0.01) Droxidopa vs. placebo on individual items: • Dizziness/lightheadedness -1.3 units (p<0.001) • Vision disturbance -0.8 unit (p<0.05) • Weakness -1.0 unit (p<0.01) • Fatigue -0.7 unit (p<0.05) • Trouble concentrating 0.0 unit (p=NS) • Head/neck discomfort -0.2 unit (p=NS) Mean Δ composite activity OHQ score from randomization to Day 7: D: -1.98 (2.31) units P: -0.92 (1.82) units	N/A	OL Dose Titration Phase: Total AE: 38% D/C due to AE: 4.9% DB Phase: Syncope: D: 2.5% P: 1.2% Falls: D: 0% P: 3.7 % No reported SAEs No D/C due to AE	N/A	**Quality Rating: Poor** **Internal Validity:** Selection: only droxidopa "responders" (168/263) randomized to study; unclear exclusion criteria with undefined terms; adequate randomization and concealment of allocation with centralized, computerized schedule; baseline characteristics vary between groups with unknown clinical significance. Performance: method of double-blinding with matching placebo not adequately described. Detection: Unclear if data acquisition and interpretation was blinded. Attrition: 6/168 were randomized in error and not treated; all 82 assigned to D completed study; 77/80 assigned to P completed study. **Applicability:** Recruitment: MC study recruited patients in Canada, Europe and the United States Patient Characteristics: Adults patients, nearly all white with PD or PAF. Setting: outpatient clinics Outcomes: unclear how composite OHQ predicts sx of nOH as only item 1 measures dizziness/lightheadedness. Clinical significance of a decreased average composite score of 0.9 units out of 10 units is unclear. Long-term efficacy for management of sx unknown. **Analysis:** Study sponsored by the manufacturer of droxidopa. Lead author and PI serves on scientific advisory board for manufacturer and was involved in study

				Mean difference 1.06 units (95% CI, 0.41 to 1.71; p=0.03) Droxidopa vs. placebo on individual items: • Standing a short time -1.06 units (p<0.01) • Standing a long time -1.1 units (p<0.01) • Walking a short time -1.0 unit (p<0.01) • Walking a long time -0.7 unit (p<0.01)				design, data acquisition and interpretation, and revisions of all manuscripts. Study limited to previous responders who tolerated D. Largest recruiting site had highly irregular results; excluding data made primary efficacy endpoint non-significant. Durability of treatment effect unknown.
Study 306B (unpublished)[6] R, DB, PC, PG, MC U.S. Nov 2012 - ?	DB PC dose titration phase until: ▪ asymptomatic ▪ intolerable AE ▪ ↑ supine SBP or DBP to 180/110 mmHg ▪ dose titrated to 600 mg TID 1. Droxidopa 100-600 mg TID for 8 weeks 2. Placebo TID for 8 weeks	Demographics ▪ 65% Male ▪ 97% white ▪ Mean age 72 y ▪ Fludricortisone use (D=34% vs. P=20%) ▪ Item 1 OHQ score 5.1 in both groups Inclusion Criteria: ▪ Symptomatic nOH associated with PD ▪ Composite OHQ >3 ▪ Clinician CGI-S >3 ▪ ≥20 mmHg SBP or ≥10 mmHg DBP upon standing ≤3 min Exclusion Criteria: Not reported	ITT: Not applied PP: D: n=69 P: n=78 Attrition: D: 26/89 (22%) P: 17/85 (8%)	**<u>Primary Outcome:</u>** Mean Δ item 1 OHQ score (SD) from randomization to Day 7: D: -2.3 (2.95) units P: -1.3 (3.16) units Mean difference 0.94 unit (95% CI, 0.10 to 1.78 units; p=0.028) **<u>Secondary Outcomes:</u>** Mean Δ item 1 OHQ score from randomization to Week 2: D: -1.9 (±2.86) units P: -1.6 (±2.97) units Mean difference, p=NS Mean Δ item 1 OHQ score from randomization to Week 4: D: -2.0 (±3.08) units P: -1.5 (±2.74) units Mean difference, p=NS Mean Δ item 1 OHQ score from randomization to Week 8: D: -2.1 (±3.03) units P: -1.5 (±2.92) units	N/A	Droxidopa attrition rate due to: ▪ AE (n=6; n=3 due to HTN) ▪ Tx failure (n=4) ▪ Withdrew consent (n=3) ▪ Investigator decision (n=2) ▪ Not reported (n=5) Placebo attrition rate due to: ▪ AE (n=4) ▪ Tx failure (n=0) ▪ Not reported (n=3)	N/A	**Quality Rating: Poor** **Internal Validity:** <u>Selection</u>: unclear exclusion criteria; unclear method of randomization and concealment of allocation; baseline fludricortisone use different between groups with unknown clinical significance. <u>Performance</u>: method of double-blinding with matching placebo not adequately described. <u>Detection</u>: Data unblinded to statistics team. Difficult to determine significance. <u>Attrition</u>: Unequally distributed between D and P. 20% of D not evaluated for primary endpoint. **Applicability:** <u>Recruitment</u>: multicenter study recruited patients in the United States <u>Patient Characteristics</u>: Adults patients, nearly all white with PD. <u>Setting</u>: outpatient clinics <u>Outcomes</u>: Primary endpoint predicts symptoms of nOH but clinical significance of decreased item 1 OHQ score (described in key) of -0.94 units on a scale from 0-10 at 7 days is unclear. Long-term efficacy beyond 1 week similar to placebo.

				Mean difference, p=NS Mean Δ composite OHQ score from randomization to Week 8: D: -2.2 (±2.29) units P: -2.0 (±2.18) units p-value not reported Mean Δ lowest standing SBP within 3 min from randomization to Day 7: D: 6.4 (±18.85) mmHg P: 0.7 (± 20.18) mmHg p-value not reported Rate of pt-reported falls from baseline to week 10: D: 0.4 (±0.84) falls/week P: 2.0 (±12.95) falls/week p-value not reported				**Analysis:** Study conducted and sponsored by the manufacturer of droxidopa. Protocol amendments concerning for detection bias. Baseline fludricortisone use differences concerning. Differences in attrition also very concerning while using per protocol analysis. LOCF analysis makes primary endpoint non-significant. The largest site had a much higher treatment effect of -2.6 units. Drug lacks durable treatment effect.

Key: AE = adverse effects; ARR = absolute risk reduction; d = day(s); CGI-S = Clinical Global Impression-Severity scale; D = droxidopa; DB = double blind; DBH = dopamine-β-hydroxylase; DBP = diastolic blood pressure; D/C = discontinuations; dx = diagnosis; HTN = hypertension; ITT = intention to treat analysis; LOCF = last observation carried forward; MC = multi-centered; mg = milligrams; min = minutes; MSA = multiple system atrophy; n = number of patients; N/A = not applicable; NDAN = nondiabetic autonomic neuropathy; NNT = number needed to treat; nOH = neurogenic orthostatic hypotension; NS = non-significant; OHQ = Orthostatic Hypotension Questionnaire; OL = open-labeled; P = placebo; PAF = pure autonomic failure; PC = placebo-controlled; PD = Parkinson's disease; PG = parallel group; PI = Principal Investigator; PP = per protocol analysis; pt = patient; R = randomized; SAE = serious adverse event; SBP = systolic blood pressure; SD = standard deviation; sx = symptoms; TID = three times daily; tx = treatment; y = years

*OHQ is a 10-item questionnaire that addresses the previous weeks' perception of orthostatic hypotension: 6 items address symptoms of orthostatic hypotension and 4 items address activities of daily living. Item 1 specifically asks about "dizziness, lightheadedness, feeling faint, or feeling like you might black out". Each item is scored on a Likert scale from 0 (not bothered/no interference) to 10 (worst possible/complete interference). The composite score is an average of the 10 items not rated 0 at baseline.

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Author: A. Gibler, Pharm.D. Date: January 2015

Appendix 1: Specific Drug Information

Clinical Pharmacology:
Droxidopa is an orally administered synthetic amino acid catecholamine prodrug that is converted both peripherally and centrally into norepinephrine through the catecholaminergic metabolism system, specifically by L-aromatic-amino-acid decarboxylase (DOPA decarboxylase). DOPA decarboxylase is a widely expressed enzyme, even in situations where postganglionic sympathetic neurons are not intact.[12]

Norepinephrine binds to alpha adrenergic receptors in the vascular smooth muscle of arterioles causing vasoconstriction and consequent elevation in blood pressure. By elevating blood pressure, norepinephrine theoretically promotes maintenance of cerebral blood flow, thereby lessening symptoms of orthostatic hypotension such as dizziness, lightheadedness or syncope.[12]

Droxidopa crosses the blood brain barrier and may therefore exert both central and peripheral effects of norepinephrine production.[12]

Pharmacokinetics:[12]

Parameter	Result
Oral Bioavailability	Not reported but 90% in animal data
Time to Maximum Concentration	2 hours
Protein Binding	Concentration-dependent: 75% at 0.1 mcg/mL; 26% at 10 mcg/mL
Elimination	70% of droxidopa and its metabolites excreted in urine (animal model)
Half-Life	2.5 hours
Metabolism	Non-CYP mediated pathways via catecholamine systems

Dose & Availability:[1]

Formulations	Route	Dosage	Renal or Hepatic Dose Adjustments	Elderly Dose Adjustments	Pediatric Dose	Other Dosing Considerations
100 mg 200 mg 300 mg	Oral	Initiate at 100 mg three times daily, 4 hours apart and titrate dose up to 600 mg three times daily, 4 hours apart.	No dose adjustments recommended	No dose adjustments recommended	Not studied	Administer upon arising in the morning, at midday, and in the late afternoon at least 3 hours prior to bedtime to reduce supine hypertension during sleep.

Drug Safety:

*Pregnancy/*Lactation:[12]

Pregnancy Category C: There are no adequate and well controlled trials in pregnant women. In animal studies, high doses of droxidopa increased incidences of lower body weight and occurrence of undulant rib in fetuses, which spontaneously reverse after birth. Shortening of the gestation period was also observed. Low incidence of renal lesions (cysts, indentations or renal pelvic dilation) was observed in female rats during the period of fetal organogenesis.

Lactation: Droxidopa is excreted in breast milk. When droxidopa was administered to nursing animal models during the period of lactation, reduced weight gain and reduced survival were observed in the offspring.

Serious (REMS, Black Box Warnings, Contraindications):[1]

REMS: N/A

Black Box Warning:

WARNING: 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.

Contraindications: None reported at this time.

Warnings and Precautions:[1]

Supine Hypertension: droxidopa may cause or exacerbate supine hypertension in patients with nOH. Patients should be advised to elevate the head of the bed when resting or sleeping. Monitor blood pressure, both in the supine position and in the recommended head-elevated sleeping position. Reduce or discontinue droxidopa if supine hypertension persists. If supine hypertension is not well managed, droxidopa may increase the risk of cardiovascular events.

Hyperpyrexia and Confusion: Postmarketing cases of a symptom complex resembling neuroleptic malignant syndrome has been reported with droxidopa use during postmarketing surveillance in Japan. Observe patients carefully when the dosage of droxidopa is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Ischemic Heart Disease, Arrhythmias and Congestive Heart Failure: Droxidopa may exacerbate existing heart disease, arrhythmias and congestive heart failure.

Allergic Reactions: Northera™ contains FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. This particular sensitivity is frequently seen in patients who also have aspirin sensitivity.

Unanswered Safety Questions:

Clinical trials reviewed by the FDA are limited in duration so long-term safety data, such as morbidity and mortality data, are limited at this time. Adverse reaction rates observed in short-term clinical trials cannot predict adverse reaction rates seen in clinical practice.

Look-alike/Sound-alike Error Risk Potential:

Not applicable at this time.

Adverse Reactions:[12]

Table: Common Treatment-emergent Adverse Events for Study 306.

Adverse Reaction (Study 306)	Droxidopa (n=114)	Placebo (n=108)
Headache	15 (13.2%)	8 (7.4%)
Dizziness	11 (9.6%)	5 (4.6%)
Nausea	10 (8.8%)	5 (4.6%)
Fatigue	6 (5.6%)	8 (7.0%)
Hypertension	8 (7.0%)	1 (0.9%)
Contusion	12 (11.1%)	6 (5.3%)
Excoriation	8 (7.4%)	6 (5.3%)
Peripheral Edema	6 (5.6%)	5 (4.4%)
Skin Laceration	10 (9.3%)	5 (4.4%)
Increased Blood Pressure	7 (6.5%)	4 (3.5%)
Diarrhea	8 (7.4%)	4 (3.5%)
Back Pain	6 (5.6%)	3 (2.6%)

In long-term, open-label trials with a mean exposure to droxidopa for 1 year (n=442; mean age 65 years), the most common reported adverse events were:[1]

Falls:	24%
Urinary Tract Infections:	15%
Headache:	13%
Syncope	13%
Dizziness:	10%

Allergies/Interactions:[1]

Allergic Reactions: Northera™ contains FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. This particular sensitivity is frequently seen in patients who also have aspirin sensitivity.

Interactions: Administering droxidopa with other drugs that increase blood pressure (e.g., midodrine, triptans, ephedrine) may increase supine hypertension. Concomitant use with dopa-decarboxylase inhibitors (e.g., carbidopa, methyldopa) may require dose adjustments for droxidopa.

Appendix 2: Suggested PA Criteria

Droxidopa (Northera™)

Goal(s):

- To optimize appropriate pharmacological management of symptomatic neurogenic orthostatic hypotension.

Length of Authorization:

Initial: 14 days
Renewal: 3 months

Requires PA:

- Northera™

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the treated diagnosis an OHP funded condition?	Yes: GO TO #3	No: PASS TO RPH; deny
3. Does the patient have a diagnosis of symptomatic orthostatic hypotension (ICD9 458.0) due to primary autonomic failure (Parkinson's disease, multiple system atrophy or pure autonomic failure), dopamine beta-hydroxylase deficiency, or nondiabetic autonomic neuropathy? (ICD9 332.0; 333.0; 270.0-270.8; 337.0-337.9)	Yes: GO TO #4	No: PASS TO RPH; deny (medical appropriateness)
4. Is the patient currently receiving antihypertensive medication?	Yes: PASS TO RPH; deny (medical appropriateness)	No: Go to #5

Approval Criteria		
5. Does the patient have a documented trial of appropriate therapy with both fludrocortisone and midodrine? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	Yes: Approve for up to 14 days	No: Inform provider fludrocortisone and midodrine are both covered alternatives. If justification provided for not trying alternatives (contraindications, concern for adverse effects, etc.), approve for up to 14 days.

Renewal Criteria		
1. Is this the first time the patient is requesting this renewal?	Yes: Go to #2	No: Approve for up to 3 months
2. Does the patient have documented response to therapy (e.g., improvement in dizziness/lightheadedness)?	Yes: Approve for up to 3 months	No: Pass to RPh; Deny (medical appropriateness)

P&T / DUR Action: 1/15 (AG)
Revision(s):
Initiated: 1/15

Author: A. Gibler, Pharm.D.

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