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RESEARCH**

*APPLICATION NUMBER:*

**203202Orig1s000**

**OTHER REVIEW(S)**

RHPM NDA Overview  
February 18, 2014

**NDA 203202**

**Sponsor:** Chelsea Therapeutics  
**Classification:** Class 2 Resubmission

**Indication:** 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 (NOH) caused by primary autonomic failure [Parkinson's disease (PD), 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 established. The continued effectiveness of NORTHERA should be assessed periodically.

**Date of Application:** August 13, 2013

**Goal Date:** February 18, 2014

**Background:**

Northera (droxidopa) is a synthetic catecholamine acid analogue that is metabolized by dopa decarboxylase to norepinephrine (NE), which is thought to increase blood pressure (BP) through binding and activation of adrenergic receptors. Droxidopa is indicated for the short-term 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 (D $\beta$ H) Deficiency, and Non-Diabetic Autonomic Neuropathy (NDAN).

The proposed starting dose is 100 mg three times daily during the day. Dose may be increased in increments of 100 mg three times daily, up to a maximum dose of 600 mg three times daily and to reduce the potential for supine hypertension during sleep, last dose should be taken at least 3-4 hours prior to bedtime

The original NDA was submitted on September 28, 2011 and the applicant submitted studies 301, 302, and 303 to support effectiveness but only study 301 met its primary endpoint. The NDA was presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting and the committee voted 7 to 4 in favor of approval.

On March 28, 2012, a Complete Response Letter was issued based on inadequate evidence of effectiveness and at least one additional adequate and well-controlled clinical trial would be needed to demonstrate efficacy prior to approval. A Formal Dispute Resolution Request was submitted by Chelsea on December 12, 2012 for FDA to reconsider the available clinical data, which supports the safety and efficacy of droxidopa, and grant accelerated approval with a requirement for a post-approval clinical trial to confirm clinical benefit in patients with NOH. A Formal Dispute Resolution Meeting was held with Chelsea on January 10, 2013 and on February 8, 2013, their request was denied.

On August 14, 2013, Chelsea's response to our Complete Response was received. The NDA was brought forth to the Cardiovascular and Renal Drugs Advisory Committee Meeting and the committee voted 16 to 1 in favor of approval.

In this resubmission, the applicant provided study 306B as an additional pivotal efficacy study. Study 306B began as an amendment to study 306 after an unblinded interim analysis; study 306 met criteria for futility, with an original primary endpoint of the change in OHQ from baseline to Week 8. Study 306 was amended to studies 306A and 306B; 306B retained the same study design and population as the original study 306, but amended the primary endpoint to patient-reported falls, and later amended the primary endpoint to OHS item-1 from baseline to Week 1 (thus, the primary endpoint for 306 was changed twice). Study 306B met its amended primary endpoint.

**Reviews:** *(Please note these are summaries and not complete reviews. Please refer to their complete reviews in DARRTS).*

**Office Director's Memo (February 18, 2014)**

**Reviewer:** Ellis F. Unger, M.D.

**Conclusion:** The NDA will be approved under Subpart H, where the short-term effect is construed as "reasonably likely" to predict the long-term effect that would be clinically meaningful.

**Summary:**

I believe that the appropriate action is accelerated approval, based on new evidence of short term effectiveness submitted August 13, 2013. Approval under Subpart H will be granted because it is critical to establish that the effect of droxidopa in NOH, a chronic illness, is maintained in at least a subset of the population treated.

The actual indication will be:

"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 (NOH) caused by primary autonomic failure [Parkinson's disease (PD), 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 established. The continued effectiveness of NORTHERA should be assessed periodically."

**Division Director's Memo (February 5, 2014)**

**Reviewer:** Norman Stockbridge, M.D., Ph.D.

**Conclusion:** No approval

**Summary:**

In sum, I do not believe droxidopa should be approved, because the evidence supporting any effect is poor, and the nominal effect seen is not clinically relevant. If one were to decide that the evidence of effectiveness needs not be good in the setting of an orphan disease and that it does not matter if the effects of treatment will be overwhelmed by waxing and waning of disease symptoms, the product should then be approved, not under Subpart H, with labeling that describes the observed effect size and durability.

**Cross-Discipline Team-Leader Memo (February 5, 2014)**

**Reviewer:** Shari Targum

**Conclusion:** No approval

**Summary:** Please refer to her review in DARRTS.

**Medical (December 5, 2013)**

**Reviewer:** Shari Targum, M.D.

**Conclusion:** No-approval

**Summary:** Please refer to her review in DARRTS.

**Statistical (December 3, 2013 & February 18, 2014)**

**Reviewer:** Jialu Zhang, Ph.D.

**Conclusion:** No-approval

**Summary:**

The droxidopa group had a statistically significant treatment effect over placebo group in the mean change in the OHSA Item 1 score from Baseline to Week 1. Other measurements at Week 1 were all trending in the right direction, though might not reach statistical significance.

However, the treatment effect on OHSA Item 1 at Week 1 seemed small when compared with intra-subject variability. It is also concerning to observe an imbalance of dropouts between treatment groups. The treatment effect of droxidopa did not seem to sustain through the 8-week treatment period. This made it questionable whether droxidopa has any long term treatment effect.

The credibility of the study was also undermined by a number of major changes on the study design and the discovery of inappropriate access to the treatment codes of all study patients enrolled until March 2011. Sensitivity analyses were performed to include only patients enrolled after certain time point to examine the consistency of the study results. The treatment effects in various measurements were all trending in the right direction but the magnitude of the treatment effect tended to be less for the patients who enrolled later during the trial.

Overall, Study 306B alone did not seem to provide strong and robust evidence to support the efficacy of droxidopa in treating NOH, especially for long-term treatment.

**Clinical Pharmacology Review (December 5, 2013)**

**Reviewer:** Sreedharan Sabarinath, Ph.D.

**Conclusion:** No-approval

**Labeling:** Please refer to his review in DARRTS.

**Summary:**

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology and

biopharmaceutics (CPB) information provided in the NDA 203-202 and our observations are listed below:

- NOH is an orphan indication with limited treatment options and one might find some clinical utility in approving droxidopa for short term symptom relief. But the pattern of symptom relief based on CGI-S was comparable for both droxidopa and placebo groups during the dose-titration phase. The observed intra-individual variability (~ 2.9 units) for OHSA Item-1 is much higher than the treatment effect of 1.0 unit favoring droxidopa and the treatment effect lost statistical significance after one week.

- The bioequivalence (BE) result from Study 104 is acceptable. However, the clinical and bioanalytical site inspection report from Office of Scientific Investigations (OSI) for this pivotal BE study is currently pending.

**Biopharmaceutics Review (December 24, 2013)**

**Reviewer:** Tien Mien (Albert) Chen, Ph.D.

**Conclusion:** Approval

**Summary:**

Since the Applicant accepted Biopharmaceutics' proposed revisions to the dissolution acceptance criterion, the original NDA was accepted and recommended for approval.

**Product Quality Review (December 4, 2013 and February 7 & 10, 2014)**

**Reviewer:** Lyudmila Soldatova, Ph.D.

**Conclusion:** Approval

**Labeling:** Please refer to her September 27, 2013 review in DARRTS.

**Summary:**

NDA 203-202 for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint pending the overall OC recommendation. The drug substance DMF (b)(4) remains adequate. Based on the drug product stability data, the following expiration dating period is recommended only for Northera capsules manufactured using droxidopa synthesized by (b)(4) method at (b)(4) facility: 48 months for Northera™ (droxidopa) Capsules, 100 mg and 200 mg, packaged in 90 counts/90 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles. The expiration date of 36 months for 100 mg and 200 mg Northera capsules packaged in aluminum foil blister packs was granted previously, and remains as such. The expiration period for 300 mg capsules packaged in 120 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles, (b)(4) is not granted due to the insufficient amount of stability data (regarding the size of these batches) for granting expiry. The overall OC recommendation for drug substance and drug product facilities is currently pending.

**Office of Scientific Investigation (January 8, 2014)**

**Reviewer:** Sharon Gershon, Pharm.D.

**Summary:**

Four domestic clinical investigator sites were inspected in support of the NDA 203202 resubmission. The FDA field investigator audited Protocol 306B at all four sites. No regulatory violations were found during the inspections at two clinical investigator sites: Dr. Isaacson and Dr. Prado. Minor regulatory violations were found during the inspection of Dr. Lisk, and a one observational Form FDA 483 was issued for failure to follow the investigational plan. Numerous regulatory violations were found during the inspection of Dr. Ramon Gil, and resulted in issuance of a 3-observational FDA-483 for failure to follow the investigational plan, failure to maintain accurate records with respect to observations and data pertinent to the investigation, and inaccurate drug disposition records. Because these many violations did not impact the primary efficacy data or subject safety for this study, OSI recommends the data from Dr. Gil's site be used in support of the study and the review division considers analyzing the data from this site using multiple imputations. The data from the other three sites may also be considered reliable based on available information.

**Office of Medication Error Prevention and Risk Management (December 13, 2013)**

**Reviewer:** Somya Dunn, M.D.

**Summary:** In conclusion, risk mitigation measures beyond professional labeling are not warranted for Northera, if approved. There were no new or unique safety concerns associated with Northera in the resubmission NDA.

**Division of Medical Policy Programs (February 11, 2014)**

**Reviewer:** Sharon Mills, BSN, RN., CCRP

**Summary:** Please refer to her review in DARRTS.

**Division of Medication Error and Prevention (February 2014)**

**Reviewer:** Jean Olumba, M.D., Pharm.D.

**Labeling:** Reviews have not been placed in DARRTS but per Dr. Neshiewat's email dated February 7, 2014, "*DMEPA reviewed the revised labels sent via e-mail on February 6, 2014 and have no additional comments*".

**Action:**

An Accelerated Approval Letter with Subpart H has been drafted and will be signed by Dr. Unger. The following clinical trial and timelines have been agreed upon with the applicant:

**PMR/PMC Description:** A clinical trial of patients with symptomatic neurogenic orthostatic hypotension to assess sustained effects of droxidopa therapy. The trial design consists of a 3 month open-label droxidopa treatment period, followed by a 4-week, randomized, double-blind, placebo-controlled, withdrawal period. The trial will enroll an adequate number of patients to give 80% power to rule out a treatment effect of 0.45 if the true effect is 0. The primary endpoint will be the mean change in ambulatory Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 from randomization to Week 4 of the randomized withdrawal period.

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PMR/PMC Schedule

Draft Protocol Submission:

28 March 2014

Milestones:	Final Protocol Submission:	30 May 2014
	Total 25% patients First Visit Complete:	30 December 2016
	Total 50% patients First Visit Complete:	29 December 2017
	Total 100% of Patients First Visit:	28 August 2020
	Complete Trial Completion:	31 December 2020
	Trial Completion:	31 December 2020
	Interim Report Submission (to include topline data of primary and secondary analyses):	26 February 2021
	Final Report (as a supplemental application) Submission:	30 April 2021

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Anna Park  
Senior Regulatory Management Officer  
February 18, 2014

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/s/  
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ANNA J PARK  
02/18/2014

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: February 10, 2014

To: Norman Stockbridge, MD, PhD  
Director  
**Division of Cardiovascular and Renal Products (DCRP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**  
Emily Baker, PharmD  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Close Out Memo

Drug Name (established name): NORTHERA (droxidopa)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 203-202

Applicant: Chelsea Therapeutics, Inc.

## **1 INTRODUCTION**

On August 14, 2013, Chelsea Therapeutics, Inc. re-submitted for the Agency's review (class 2 resubmission) their Original New Drug Application (NDA) 203-202 for NORTHERA (droxidopa) capsules. The Applicant received a Complete Response letter (dated March 28, 2013) during the first review cycle due to outstanding clinical/statistical, facility inspections, product quality, clinical pharmacology, and non-clinical deficiencies. The Applicant re-submitted their Original NDA on July 3, 2013, following denial of a dispute appeal on February 8, 2013; however, the submission was determined to be incomplete at that time.

On July 17, 2013 and on July 18, 2013, respectively, the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) review the Applicant's proposed Medication Guide (MG) for NORTHERA (droxidopa) capsules. On February 10, 2014, DCRP notified DMPP and OPDP that patient labeling is not needed for this product because section 17 (Patient Counseling Information) of the Prescribing Information (PI) is adequate to advise prescribers to convey the patient-centered issues related to NORTHERA (droxidopa) capsules.

## **2 CONCLUSIONS**

This memo serves to close out the DMPP and OPDP consult requests referenced above for NORTHERA (droxidopa) capsules.

Please let us know if you have any questions.

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/s/  
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SHARON R MILLS  
02/10/2014

EMILY K BAKER  
02/10/2014

BARBARA A FULLER  
02/10/2014

LASHAWN M GRIFFITHS  
02/11/2014

## **SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies**

<b>Product Title<sup>1</sup></b>	<b>NORTHERA (droxidopa) capsules, for oral use</b>
Applicant	Chelsea Therapeutics, Inc.
Application/Supplement Number	NDA 203202
Type of Application	Original
Indication(s)	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, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy
Office/Division	ODE I/DCRP
Division Project Manager	Anna Parks
Date FDA Received Application	August 14, 2013
Goal Date	February 14, 2014
Date PI Received by SEALD	February 10, 2014
SEALD Review Date	February 10, 2014
SEALD Labeling Reviewer	Elizabeth Donohoe
Acting SEALD Division Director	Sandra Kweder

<sup>1</sup> Product Title that appears in draft agreed-upon prescribing information (PI)

This Study Endpoints and Labeling Development (SEALD) Director sign-off review of the end-of-cycle, prescribing information (PI) for important format items reveals **outstanding format deficiencies** that should be corrected before taking an approval action. After these outstanding format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The Selected Requirements of Prescribing Information (SRPI) is a checklist of 42 important format PI items based on labeling regulations [21 CFR 201.56(d) and 201.57] and guidances. The word “must” denotes that the item is a regulatory requirement, while the word “should” denotes that the item is based on guidance. Each SRPI item is assigned with one of the following three responses:

- **NO:** The PI does not meet the requirement for this item (**deficiency**).
- **YES:** The PI meets the requirement for this item (**not a deficiency**).
- **N/A:** This item does not apply to the specific PI under review (**not applicable**).

# Selected Requirements of Prescribing Information

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## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:** *The top margin and left-side margin are greater than 1/2 inch. The space between the columns at the Boxed Warning is less than 1/2 inch.*

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

**Instructions to complete this item:** If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:** *The line between TOC and FPI is missing.*

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:** *Many headings are not centered (I&U, DFS, AR, DI, USP) and the horizontal lines do not extend the full width of the column (except in D&A).*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:** *There is a lot of white space in the right-sided column of HL. For improved readability, consider revising HL so that the two columns are of similar length, as shown in the sample in Appendix A.*

## Selected Requirements of Prescribing Information

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:** *The reference in the Boxed Warning is not the correct format; it should read: (5.1) at the end of the summarized topic without the brackets and "see Warnings and Precautions".*

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state "None.")
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

**Comment:**

#### Highlights Limitation Statement

- NO** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

**Comment:** *The established name "droxidopa" is included in the first sentence; this should be removed.*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

**Comment:**

## Selected Requirements of Prescribing Information

### Initial U.S. Approval in Highlights

- NO** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.  
***Comment:*** *The four-digit year is not complete; this should read: "2014".*

### Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.  
***Comment:***
- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
***Comment:***
- NO** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
***Comment:*** *The statement is not centered under the heading.*
- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
***Comment:***

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.  
***Comment:***
- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.  
***Comment:***
- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).  
***Comment:***

### Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.  
***Comment:***

## Selected Requirements of Prescribing Information

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

*Comment:*

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:*

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

*Comment:* The "1" is missing before the "855" toll-free number; recommend adding the "1" for completeness.

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:*

### Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:* The date is missing; it should read: “2/2014”. Also, the date is not bolded nor is it right-justified.

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- NO** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:* The colon ":" is missing after the word "INFORMATION".
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:* The TOC includes subsections 2.2, 7.3 and 14.2 which are not present in the FPI. The heading for subsection 13.1 is correct in the TOC "Carcinogenesis, Mutagenesis, Impairment of Fertility" where in the FPI the word "and" was added after "Mutagenesis". The heading for subsection 14.1 in the TOC (Study 301 and Study 306B) differs from the heading in the FPI (Studies in neurogenic orthostatic hypotension); if the heading from the FPI is retained, it should be in Title Case: Studies in Neurogenic Orthostatic Hypotension .
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:* The statement following the "\*" is in 6 point font; according to 21 CFR 201.57(d)(6) the .. type size for all labeling information... must be a minimum of 8 points.

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** Many numbers for the section headings have a period "." after the number; these should be removed and should also be removed from the TOC, where present. The heading for Section 3 should be "Dosage Forms and Strengths" and currently reads: "Dosage Form and Strengths". The heading for subsection 13.2 should be "Animal... and/or...." and currently reads: "Animal... and... ". The corresponding headings for Section 3 and subsection 13.2 in the TOC should also be corrected.

## Selected Requirements of Prescribing Information

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

**Comment:** *Although the format is correct, in Section 11, cross-reference is made to "Dosage Form and Strengths"; this should read: "Dosage Forms and Strengths".*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

**Comment:**

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is

## Selected Requirements of Prescribing Information

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

### **PATIENT COUNSELING INFORMATION Section in the FPI**

- NO** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** *The statement has been deleted from this version of the prescribing information and should be retained.*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

#### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

#### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

#### DOSAGE AND ADMINISTRATION

- [text]
- [text]

#### DOSAGE FORMS AND STRENGTHS

- [text]

#### CONTRAINDICATIONS

- [text]
- [text]

#### WARNINGS AND PRECAUTIONS

- [text]
- [text]

#### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

#### DRUG INTERACTIONS

- [text]
- [text]

#### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

#### 6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

#### 7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

ELIZABETH A DONOHOE  
02/10/2014

ERIC R BRODSKY  
02/10/2014

I agree. Eric Brodsky, SEALD labeling team leader, signing for Sandra Kweder, acting SEALD Division Director.

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

**Memorandum**

**Date:** January 30, 2014  
**To:** Anna Park, Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)  
**From:** Emily Baker, Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)  
**Subject:** **NDA 203202**  
**OPDP Labeling Comments for Northera (droxidopa) Capsules**

---

OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on July 18, 2013, for Northera (droxidopa) capsules (Northera). Our comments on the PI are based on the proposed labeling found in the eroom on January 29, 2014. Our comments on the carton and container labeling are based on the version submitted by the sponsor on July 3, 2013.

**Carton and Container Label**

OPDP has no comments on the proposed carton and container labeling at this time.

**Package Insert**

OPDP's comments are provided directly on the attached marked-up copy of the proposed PI.

Thank you for the opportunity to comment on the proposed material.

If you have any questions, please contact Emily Baker at 301.796.7524 or [emily.baker@fda.hhs.gov](mailto:emily.baker@fda.hhs.gov).

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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EMILY K BAKER  
01/30/2014

**REGULATORY PROJECT MANAGER  
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW  
OF THE PRESCRIBING INFORMATION**

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 203202

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Northera (droxidopa) oral capsules

**Applicant:** Chelsea Therapeutics

**Receipt Date:** August 14, 2013

**Goal Date:** February 14, 2014

### **1. Regulatory History and Applicant's Main Proposals**

Droxidopa is a new molecular entity that has been approved in Japan since 1989 for essentially the same indication now sought in the US. The drug was developed under Chelsea's IND 077248.

- 01/2007: Orphan drug designation granted for the NOH indication
- 03/2007: Pre-IND – FDA stated that a single study could support approval if the level of significance approximates that of two studies ( $p \sim 0.00125$ )
- 08/2007: End-of-Phase 2 Meeting
- 09/2007: IND opened
- 02/2008: Agreement on a Special Protocol Assessment for study 301
- 08/2008: Fast Track designation granted
- 12/2010: Pre-NDA meeting
- 09/28/2011: NDA submitted and studies 301, 302, and 303 were submitted to support effectiveness but only study 301 met its primary endpoint.
- 2/23/2012: NDA presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting. Vote: 7 to 4 in favor of approval.
- 03/28/2012: Complete Response issued based on inadequate evidence of effectiveness and at least one additional adequate and well-controlled clinical trial would be needed to demonstrate efficacy prior to approval
- 12/12/2012: Formal Dispute Resolution Request submitted by Chelsea for FDA to reconsider the available clinical data, which supports the safety and efficacy of droxidopa, and grant accelerated approval with a requirement for a post-approval clinical trial to confirm clinical benefit in patients with NOH.
- 01/10/2013: Formal Dispute Resolution Meeting held with Chelsea
- 02/08/2013: Formal Dispute Resolution Request Denied
- 08/14/2013: NDA resubmitted
- 01/14/2014: NDA presented at the Cardiovascular and Renal Drugs Advisory Committee Meeting. Vote: 16:1 in favor of approval

# Selected Requirements of Prescribing Information

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format. The resubmitted PI will be used for further labeling review.

---

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

---

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

**Comment:**

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select "YES" in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select "NO" because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

## Selected Requirements of Prescribing Information

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

**Comment:**

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

**Comment:**

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

**Comment:**

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

**Comment:**

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

**Comment:**

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• <b>Highlights Heading</b>	Required
• <b>Highlights Limitation Statement</b>	Required
• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:**

### HIGHLIGHTS DETAILS

#### Highlights Heading

## Selected Requirements of Prescribing Information

- NO** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.  
*Comment:* *Not bolded*

### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.  
*Comment:* *Not bolded*

### Product Title in Highlights

- NO** 10. Product title must be **bolded**.  
*Comment:* *Not bolded*

### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.  
*Comment:*

### Boxed Warning (BW) in Highlights

- NO** 12. All text in the BW must be **bolded**.  
*Comment:*

- YES** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.  
*Comment:*

- YES** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.  
*Comment:*

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).  
*Comment:*

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.  
*Comment:*

## Selected Requirements of Prescribing Information

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

**Comment:**

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:**

### Indications and Usage in Highlights

- N/A** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

**Comment:**

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:**

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

**Comment:**

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

**Comment:**

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- "See 17 for **PATIENT COUNSELING INFORMATION**"

If a product **has** FDA-approved patient labeling:

- "See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**"
- "See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**"

## Selected Requirements of Prescribing Information

*Comment:*

**Revision Date in Highlights**

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:* *Not bolded*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
*Comment:*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
*Comment:*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
*Comment:*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
*Comment:*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
*Comment:*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
*Comment:*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
<b>8.1 Pregnancy</b>
<b>8.2 Labor and Delivery</b>
<b>8.3 Nursing Mothers</b>
<b>8.4 Pediatric Use</b>
<b>8.5 Geriatric Use</b>
<b>9 DRUG ABUSE AND DEPENDENCE</b>
<b>9.1 Controlled Substance</b>
<b>9.2 Abuse</b>
<b>9.3 Dependence</b>
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
<b>12.1 Mechanism of Action</b>
<b>12.2 Pharmacodynamics</b>
<b>12.3 Pharmacokinetics</b>
<b>12.4 Microbiology (by guidance)</b>
<b>12.5 Pharmacogenomics (by guidance)</b>
<b>13 NONCLINICAL TOXICOLOGY</b>
<b>13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility</b>
<b>13.2 Animal Toxicology and/or Pharmacology</b>
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:**

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:**

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

*Comment:*

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

*Comment:*

#### BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

*Comment:*

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

*Comment:*

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

*Comment:*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

*Comment:*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

*Comment:*

#### PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

## Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

- [text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

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- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

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/s/  
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ANNA J PARK  
01/30/2014

MEMORANDUM  
SERVICES

DEPARTMENT OF HEALTH AND HUMAN  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND

RESEARCH

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**CLINICAL INSPECTION SUMMARY**

**DATE:** January 8, 2014

**TO:** Shari Targum, Medical Team Leader  
Anna Park, Regulatory Project Manager  
Division of Cardio-Renal Drug Products

**FROM:** Sharon K. Gershon, Pharm. D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Kassa Ayalew, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 203202 resubmission

**APPLICANT:** Chelsea Therapeutics, Inc.

**DRUG:** Northera™ (droxidopa)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority Review

**INDICATIONS:** treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with Parkinson's Disease (PD)

**Protocol: Study 306B** A Multi-Center, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Study to Assess the Clinical Effect of Droxidopa in the Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Patients with Parkinson's Disease

**CONSULTATION REQUEST DATE:** September 3, 2013

**INSPECTION SUMMARY GOAL DATE (revised):** January 9, 2014

**ADVISORY COMMITTEE MEETING:** January 14, 2014

**DIVISION ACTION GOAL DATE:** February 14, 2014

**PDUFA DATE:** February 14, 2014

## **I. BACKGROUND:**

Chelsea Therapeutics, Inc. (Chelsea) seeks marketing approval for NDA 203202 (droxidopa) in the U.S. for the proposed treatment of symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure (Parkinson's disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF), Dopamine Beta Hydroxylase (D  $\beta$  H) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

NOH is defined as a reduction in standing systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mm Hg within three minutes of standing. Symptomatic NOH can be a severely debilitating condition that can substantially reduce a patient's quality of life. Dizziness, which characteristically presents as lightheadedness, or pre-syncope, is the cardinal symptom of NOH.

The current submission is a resubmission of the original NDA, adding the data from Study 306B to support the short-term efficacy proposal. Study 306 (51 subjects in 306A and 171 subjects in Study 306B) took place at 80 centers in the United States, and was designed to evaluate the efficacy and safety of droxidopa versus placebo in patients with symptomatic NOH associated with Parkinson's Disease (PD). For Study 306B, the primary efficacy endpoint was the mean change in Orthostatic Hypotension Symptom Assessment (OHSA) Item 1, from Baseline to Visit 4 (Week 1).

### **Rationale for Site Selection**

Droxidopa is a NME with proposed indication in treatment of symptomatic neurogenic orthostatic hypotension (NOH). Four sites were chosen for inspections, based on the following criteria by the Review Division:

- Site 132 (Isaacson) enrolled the largest number of study subjects; excluding this site would alter the results leading to a failure to reject the null hypothesis.

-  (b) (6)

- Site 115 (Prado) appeared to have a large treatment difference (-4.4; where the mean effect was about -1.0). In addition, this site reported 8 patients with adverse events.
- Sites 132 (Isaacson) and 146 (Lisk) appeared to have 9 and 7 patients excluded from the per protocol analysis set; site 132 (Isaacson) reported 2 patients excluded from the full analysis set.

## II. RESULTS (by Site):

Name of CI/Location	Protocol #/Site #/# of Subjects	Inspection Dates	Final Classification
<b>Stuart Isaacson</b> Parkinson's Disease and Movement Disorder Center 951 NW 13th Street, Boca Raton, FL 33486	Protocol 306B Site No 132 25 subject	November 4 – 15, 2013	NAI
<b>Ramon Gil</b> Parkinson's Disease Treatment Center of Southwest Florida 4235 Kings Highway Port Charlotte, FL 33980	Protocol 306B Site No. 122 14 subjects	November 11 – 15, 2013	VAI
<b>Patricio Espinosa Prado</b> ECommunity Research, LLC 15770 Paul Vega MD Drive, Hammond, LA 70403	Protocol 306B Site No. 115 7 subjects	October 28 – 30, 2013	NAI
<b>Jerome Lisk</b> Neurosearch, Inc. 630 South Raymond Avenue, Suite 110 Pasadena, CA 91105	Protocol 306B Site No. 146 10 subjects	October 16- 28, 2013	VAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. Stuart Isaacson,  
Parkinson's Disease and Movement Disorder Center, 951 NW 13th Street, Building 5-E  
Boca Raton, FL 33486**

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. (b) (4)

The FDA field investigator reported that all observations from the previous inspection appeared to be corrected.

For this study, 33 subjects were screened, 25 subjects enrolled, and 23 subjects completed the study. Subjects #04 and #10 were terminated early due to a lack of drug efficacy. Neither subject had their Visit 4, and no primary endpoint was determined for these subjects. The inspection included review of regulatory binders, the monitor site visit log, Principal Investigator and IRB correspondence, Principal Investigator and Sponsor correspondence, team list and delegation log, drug accountability records, laboratory certifications (b) (4). The inspection also reviewed the Investigational Product (IP) reconciliation log with each subject's IP dispensation record. The FDA field investigator reviewed records for the 25 randomized subjects. The records contained a physical assessment, medical history information, inclusion and exclusion criteria, primary efficacy endpoints (change in OHSA Item #1 from Baseline to Week 1/Visit 4), adverse events, and protocol deviations.

**b. General observations/commentary:** There was only one discrepancy noted during data validation. While corroborating the source data with the data listings, the FDA field investigator noted in source records that Subject #26 reported headache during Visit 4, and this adverse event was not captured in the CRF or data listings. All primary endpoints were reported as verifiable and accurate. The FDA field investigator reported that protocol deviations consisted mostly of out-of-window visits, signature errors, or test article compliance issues. He reported that all protocol deviations were appropriately documented and reported to the sponsor. One Serious Adverse Event (SAE) occurred during the study, but was considered unrelated to study drug. Specifically, Subject #27 was hospitalized on (b) (6) due to a viral infection, and was released several days later.

**c. Assessment of data integrity:** In general, no regulatory violations were noted during this inspection and the study appears to have been conducted well at this site. OSI recommends the data as acceptable in support of the claimed indication.

**2. Ramon Gil, Parkinson's Disease Treatment Center of Southwest Florida  
4235 Kings Highway, Suite 102, Port Charlotte, FL 33980**

**a. What was inspected:** This inspection was conducted according to Compliance Program 7348.811. At this site, 17 subjects were screened, and 14 subjects randomized. Three subjects failed the initial screening because they did not meet the eligibility criteria. One subject had elevated systolic

blood pressure reading above 180 mm Hg, another subject was noncompliant with study drug, and the third subject cited personal reasons for withdrawal. The inspection included review of protocols and amendments, IRB approvals, IRB correspondence, randomization procedures, monitoring logs, a review of all 17 subjects' source documentation, electronic Case Report Forms captured in a Personal Health Technology database, subject evaluations captured in a Pharmaceutical Product Development database, test article dispensing records, medical records and laboratory data. The field investigator corroborated the primary and secondary efficacy endpoint data with the source records at the site. He observed and reported that the Orthostatic Hypotension (OH) scores were entered directly into a site tablet computer and that data was sent directly to the sponsor. The OH score data was not documented at the site.

- b. **General observations/commentary:** The FDA field investigator did not observe any discrepancies or underreporting of adverse events. At the conclusion of the inspection, he issued a three observation Form FDA- 483 for the following regulatory violations:
- 1) an investigation was not conducted according to the investigational plan;
  - 2) failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation;
  - 3) investigational drug disposition records not adequate with respect to quantity and use by subjects.

The observed findings appeared to fall under the following main categories:

1. late review of EKGs by the clinical investigator
2. performance of Orthostatic Standing Tests (OSTs) outside the window specified by the protocol; most OSTs were done too early.
3. The initials documented for certain procedures did not match the initials of the person who actually did the procedure in some cases;
4. investigation drug accountability issues for two subjects (described below).
5. miscellaneous issues, such as use of prohibited concomitant medications

Under Observation 1, the field investigator noted that EKGs and vital signs were often not reviewed by Dr. Gil in a timely manner. For example:

- For Subject 122010, the Visit 1 EKG tracing done on December 8, 2010 but was not signed by the Principal Investigator until June 20, 2011, about seven months later. This subject was randomized on December 20, 2010. Also for Subject 122010, the Visit 7 EKG tracing done on February 16, 2011 was not signed by Dr. Gil until July 22, 2011, about five months late.
- For subject 122012, the Visit 7 EKG tracing done on March 10,

2011 was not signed by Dr. Gil until June 20, 2011, two months later; and for Subject 122013, the Visit 6 EKG tracing done on February 25, 2011 was not signed until June 20, 2011, about four months later.

- For Subject 122013, the Visit 7 laboratory results of March 28, 2011 were not signed by Dr. Gil until June 13, 2011, almost three months later.

For Observation 1, the protocol required that the Orthostatic Standing Test (OST) evaluations be performed two to five hours following study drug administration, to evaluate the effect of droxidopa on standing blood pressure. The FDA field investigator found that for eight subjects, during multiple visits, the OST evaluations were done outside the protocol specified window. Most out-of-window OST evaluations occurred too soon. For example:

- For Subject 122002, the Visit 3a OST evaluation on August 25, 2010 was performed 317 minutes post-dose, or 17 minutes late;
- For Subject 122002, the Visit 3b OST evaluation done on August 26, 2010 was performed 68 minutes post-dose, approximately 52 minutes too soon;
- For Subject 122002, the Visit 3c OST evaluation performed on August 27, 2010 was done 73 minutes post-dosing, approximately 47 minutes too soon;
- For Subject 122002, the Visit 5 OST evaluation on September 15, 2010 was performed 59 minutes post-dosing, approximately 61 minutes too soon.

This observation was discussed with the Medical Officer, who stated that the significance might be that taking OST measurements outside the protocol defined timeframe could affect the measured effect of droxidopa on raising blood pressure. In general, she felt that the above findings trend more towards a general sloppiness in study conduct. Note that the primary efficacy endpoint was determined using symptoms from subject diaries, not the OST per se.

Under Observation 2, the field investigator found recordkeeping concerns for 5 of 16 subject records reviewed. For example:

- For Subject 122009, the OST test at Visit 2 was conducted by Coordinator (b) (6) but the form was signed by Coordinator (b) (6);
- For Subject 122007, vital signs and OST test at Visit 3b were performed by Study Coordinator (b) (6) and the pages signed by Study Coordinator (b) (6).
- For Subject 122016, screening eligibility was not reviewed by Dr.

Gil. His signature appears on the Verification of Eligibility page but the questions were not answered and signature is not dated.

Under Observation 3, the field investigator observed that Subject 122011 was rolled over into the 304 open-label study but was dispensed study drug from the 306 study. This observation was not reported in the Investigational Product Accountability Records for the 306 study. He also found that for Subject 122016 the study drug compliance at Visit 3a was listed as having been at least 80% by the Study Coordinator, whereas the Patient Investigational Product Accountability Record documented only 50% compliance.

Dr. Ramon Gil submitted a response to the Form FDA- 483 in a letter dated December 13, 2013. In his written response, he acknowledged most observations and noted that he implemented corrective action to prevent recurrence of similar violations.

- c. **Assessment of data integrity:** Many regulatory violations were found during the inspection of Dr. Gil that indicate poor overall good clinical practice. However, the findings do not appear to impact subject safety or primary efficacy outcome. Therefore, OSI recommends the data from this site may be used in support of the application and the review division considers analyzing the data from this site using multiple imputations.
3. **Patricio Espinosa Prado**  
**ECommunity Research, LLC**  
**15770 Paul Vega MD Drive,**  
**Hammond, LA 70403**

a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. (b) (4)

At this site, eight subjects were enrolled, and seven subjects completed the study. The first subject was consented and screened for this study on December 2, 2010. The first administration of the test article took place on December 16, 2010. The last follow-up for study Subject # 115010 was conducted on October 16, 2012.

The inspection included review of source documentation against data line listings provided for all eight randomized subjects (Subjects 115001, 115003, 115004, 115005, 115006, 115007, 115009 and 115010).

**b. General observations/commentary:** All enrolled subjects were reported to have met eligibility criteria; all subjects except Subject 115004 completed the study. Subject 115004 began the titrations but was discontinued after Visit 3b (within the window for Visit 4) for worsening hallucinations.

Records were noted to be complete, legible and organized. Original hard copy study visit worksheets were available for inspection. Printed copies of electronic medical records and hard copy records from outside sources were used to verify subject eligibility based on prior medical history. Study activities were generally conducted in compliance with the protocol, with all protocol deviations noted as indicated in the data line listings.

No significant protocol deviations were noted with respect to subject selection, number of subjects enrolled, randomization scheme, schedule of required procedures and evaluations, administration of the investigational product, or frequency of observations and testing prescribed for subject follow up. Protocol deviations which were noted in the records and line listings included failing to use the same arm for blood pressure readings at each visit and performing the orthostatic standing test (OST) before the C-CGI-S.

The primary efficacy endpoint (change in OHSA Item #1 from Baseline to Week 1/Visit 4) was verifiable. There was no evidence of under-reporting of adverse events. Informed consent was obtained from all subjects prior to the performance of any screening procedures and after approval by the institutional review board (IRB). No lapses in IRB approvals or failure to file required reports were noted. The consent forms appear to contain all of the necessary basic elements without exculpatory or overly technical language. The site appeared to be well-monitored with notes of clarification posted by the investigator to resolve potential compliance issues. The investigator maintained control and oversight of the study. No inappropriate delegations of study responsibilities were noted. No financial conflicts of interest were noted.

- c. **Assessment of data integrity:** In general, no regulatory violations were noted during this inspection and the study appears to have been conducted well at this site. OSI recommends the data as acceptable in support of the claimed indication.

4. **Jerome Lisk, MD**  
**Neurosearch, Inc.**  
**630 South Raymond Avenue, Suite 110**  
**Pasadena, CA 91105**

- a. **What was inspected:** This inspection was conducted according to Compliance Program 7348.811. (b) (4)  
[REDACTED]. At this site, thirteen subjects were screened for the study, and 11 subjects enrolled. A total of nine subjects completed the study. From source documents, the FDA field investigator observed that Subjects 146003 and 146009 were screen failures, and that Subject 146009 was rescreened and entered the study as Subject 146011. Two subjects did not complete the study: Subject 14006 had an

adverse event (syncopal episode) and excluded concomitant medication use, and Subject 146007 withdrew consent because of lack of effect.

The inspection took place over three days and covered the following records: protocols and protocol amendments; protocol deviation filings; IRB/Sponsor correspondence; informed consent documents; subject medical records, source documents, case report forms; drug accountability records; monitoring records; and training records. The FDA field investigator reviewed the screening, informed consent documents, and source documents for all subjects. Source documents consisted of the subject's medical records, visit information, and laboratory records. Medical records consisted of physical exams, clinician notes, treatment records, adverse events, concomitant medications, electrocardiograms, study drug administration, progress notes, questionnaires, and clinical assessments.

For all eleven enrolled subjects, FDA field investigator corroborated the data listings against source records for adverse events, concomitant medications, laboratory results, Clinical Global Impressions (CGI) rating, Orthostatic Hypotension Questionnaire (OHQ) scores, Orthostatic Hypotension Symptom Assessment (OHSA) scores, and Orthostatic Hypotension Daily Activity Scale (OHDAS) scores.

**b. General observations/commentary:** The field investigator did not note any discrepancies between the data entered into the source documents and the Case Report Forms (CRFs). He did not find any discrepancies between source documents and data listings in the symptom measurement scores (OHQ, OHSA, OHDAS). He did note that some values were missing or extreme in the review of the OHQ, OHSA and OHDAS, and this was presented as a discussion item (described below).

All laboratory results, adverse events, and concomitant medications were documented and reported. The field investigator reviewed test article records, and reported that the blind was maintained throughout the study.

At the close of the inspection a one observational FDA 438 was issued for not conducting the study in accordance with the investigational plan. Specifically,

**1) Subject 146013 was screened on June 26, 2012, with a history of diabetic neuropathy, an exclusion criteria (#15). Subject 146013 was enrolled on July 10, 2012 and completed the study on September 18, 2012.** The site submitted a protocol deviation form to the IRB on July 18, 2012. In his response letter dated November 12, 2013, Dr. Lisk stated that upon review of the subject's records, he did not believe the protocol had been violated, as this patient had diabetic **peripheral** neuropathy, and not diabetic **autonomic** neuropathy. Diabetic peripheral neuropathy was not an

exclusionary criterion for the study. Subsequent discussion with the sponsor on November 1, 2013 resulted in agreement that the protocol had not been violated.

***Medical Officer's Comment: Although Dr. Lisk presents a reasonable argument regarding the cause of the subject's lower extremity neuropathy, this is not a differentiation that can be definitely made at a single visit. In addition, Dr. Lisk queried the sponsor regarding the subject's eligibility, but subsequently enrolled the subject prior to receiving the sponsor's response that the subject should not be enrolled. When he asked the sponsor if he should be discontinued, they instructed Dr. Lisk that they would have preferred he had not been enrolled, but would continue and not be included in the per protocol analysis. This clearly represents a protocol violation, despite Dr. Lisk's statement that he discussed this issues with the sponsor on November 1, 2013, and they said that no protocol violation occurred.***

**2) Two subjects were screened and changed doses of concomitant medications during the titration period of the study, against exclusion criteria (#4).**

- Subjects 146012 began using fludrocortisone and pyridostigmine for treatment of NOH on February 22, 2012, and stopped taking these drugs on April 9, 2012. Subject 146012 had Visit 1 (screening visit) on March 22, 2012, Visit 2 (baseline visit) on April 4, 2012 and Visit 3d (dose titration) on April 10, 2012. Exclusion criteria #4 indicated “doses of concomitant medications should not be changed within two weeks of baseline visit”. The site submitted a protocol violation form to the IRB on July 16, 2012 – 3 months later. At that time, site staff was retrained on the inclusion and exclusion criteria for this study.
- Subject 146013 was randomized on July 10, 2012, and administered Sinemet CR on July 15, 2012. The site submitted a protocol deviation report to the IRB on August 30, 2012. Site staff was retrained at that time on the inclusion and exclusion criteria for this study.

In his November 12, 2013 response letter to the FDA 483, Dr. Lisk states that he interpreted the protocol exclusion criteria to mean that patients would be on a stable dose of concomitant medications with no change in drug treatment within two weeks ‘prior’ to the start of the study. He stated that he submitted protocol violation forms after identification from the interim monitor visits.

***Medical Officer's Comment: Although the protocol is somewhat unclear regarding which time period is encompassed by “no change in dose, frequency, or type of prescribed medication within two weeks of baseline visit...”, there should have been clarification with the sponsor. Administration of Sinemet is clearly a protocol violation. The protocol states that “All anti-parkinsonian***

*drugs will be permitted during the study, provided that patients have been taking a stable dose and there has been no change within 2 weeks of the start of study drug administration at baseline (Visit 2.)*

3) Subject 146011 was administered 200 mg of investigational study drug at Visit 3b (dose titration phase) on November 30, 2011, when the subject became asymptomatic. The subject's dose was increased to 300 mg during Visit 5 on December 12, 2011. The dosage was increased at the PI's discretion, "to determine if stronger dose will eliminate the patient's dizziness spells." A protocol deviation form was submitted to the CRO on February 1, 2012.

In his November 12, 2013 response letter Dr. Lisk states that at Visit 5 the subject reported increased dizziness, and he up-titrated the dosage from 200 mg to 300 mg to prevent worsening of the adverse event for the duration of the study.

*Medical Officer's Comment: The protocol allows only for down titration of study drug in the event of adverse events. The subject's symptoms are consistent with underlying disease, and would presumably be treated by upward titration, which is not a procedure allowed by the protocol.*

Several items were discussed with Dr. Lisk at the conclusion of the inspection. For several subjects, he observed missing values for the OHSA or OHDAS scores. For example, Subject 146004 had missing values for Visit 2 and 4, so the OHDAS values were reported as 6, blank, 5, blank, and the composite OHDAS score was 5.5. Similarly, for Subject 146010 the values were reported as 3, 0, 5, 3, 0, 3 and the composite score was 3.5. OSI defers to the review division to decide on the acceptability of these composite scores.

*Medical Officer's Comment: The site was not involved in manipulation or calculation of these scores. The data was entered directly by the subject, and the sponsor was responsible for score calculation.*

- c. **Assessment of data integrity:** Although regulatory violations were noted, they are minor and unlikely to affect the efficacy of the data. OSI recommends the data as acceptable in support of the claimed indication.

#### **IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS**

Four domestic clinical investigator sites were inspected in support of the NDA 203202 resubmission. The FDA field investigator audited Protocol 306B at all four sites. No regulatory violations were found during the inspections at two clinical investigator sites: Dr. Isaacson and Dr. Prado. Minor regulatory violations were found during the inspection of Dr. Lisk, and a one observational Form FDA 483 was issued for failure to follow the investigational plan. Numerous regulatory violations were found during the inspection of

Dr. Ramon Gil, and resulted in issuance of a 3-observational FDA-483 for failure to follow the investigational plan, failure to maintain accurate records with respect to observations and data pertinent to the investigation, and inaccurate drug disposition records. Because these many violations did not impact the primary efficacy data or subject safety for this study, OSI recommends the data from Dr. Gil's site be used in support of the study and the review division considers analyzing the data from this site using multiple imputations. The data from the other three sites may also be considered reliable based on available information.

*{See appended electronic signature page}*

Sharon Gershon, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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SHARON K GERSHON  
01/08/2014

SUSAN D THOMPSON  
01/08/2014

KASSA AYALEW  
01/08/2014

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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DATE: December 13, 2013

TO: Norman Stockbridge, M.D.  
Director  
Division of Cardiovascular & Renal Products  
Office of Drug Evaluation I

Mehul Mehta, Ph.D.  
Director  
Division of Clinical Pharmacology I  
Office of Clinical Pharmacology

FROM: Sripal Mada, Ph.D.  
TL (Acting), GLP Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

Gajendiran Mahadevan, Ph.D.  
GLP Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Charles Bonapace, Pharm.D.  
Chief (Acting), GLP Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

William H. Taylor, Ph.D.  
Director  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIR covering NDA 203-202 Droxidopa Capsules,  
300 mg sponsored by Chelsea Therapeutics, Inc., USA.

At the request of the Division of Cardiovascular & Renal  
Products (DCRP), the Division of Bioequivalence and GLP  
Compliance (DBGLPC) inspected the following study:

**Study 104:** "A randomized, open-label, two-period, two treatment crossover bioequivalence study of one 100 mg and one 200 mg capsule of droxidopa (reference) versus one 300 mg capsule of droxidopa (test) in healthy subjects"

**Clinical:**

The inspection of the clinical portion of the study was conducted by Larry K. Austin (ORA) during September 17-19, 2013 at **Covance Clinical Research, Evansville, IN**. No significant issues were observed and no Form FDA 483 was issued.

**Analytical:**

The inspection of the analytical portion of the study was conducted by Sripal R. Mada, Ph.D. (OSI), Gajendiran Mahadevan, Ph.D. (OSI), and Barbara Rusin (ORA) during [REDACTED] (b)(4) at [REDACTED] (b)(4)

Following the inspection, no Form FDA 483 was issued. However, [REDACTED] (b)(4) did not finalize the long-term stability data until the close-out of the inspection because the studies were on-going. [REDACTED] (b)(4) confirmed during the close-out that they would submit to the sponsor the final bioanalytical method validation report containing the long-term stability studies.

**Conclusions:**

The clinical and analytical data from the audited study were found to be reliable. Therefore, these reviewers recommend that the data be accepted for agency review provided the sponsor submits the final bioanalytical method validation report containing the long-term stability studies.

Sripal Mada, Ph.D.,  
Gajendiran Mahadevan, Ph.D.,  
GLP Branch, DBGLPC, OSI

**Final Classifications:**

**NAI - Covance Clinical Research, Evansville, IN**  
FEI: 333282

**NAI - [REDACTED] (b)(4)**  
FEI: [REDACTED] (b)(4)

cc:

OSI/DBGLPC/Taylor/Haidar/Bonapace/Mada/Mahadevan/Dejernett

OND/ODE1/DCRP/Stockbridge/Park

OCP/DCP1/Mehta/Sabarinath

ORA/DET-DO/Austin/Rusin

Draft: GM 12/05/2013

Edit: SRM 12/06/2013; CB 12/10/13; WHT 12/12/13

OSI: BE6481; O:\Bioequiv\EIRCover\203202.dro.che

**FACTS: 8689631**

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/s/  
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GAJENDIRAN MAHADEVAN  
12/13/2013

SRIPAL R MADA  
12/13/2013

CHARLES R BONAPACE  
12/13/2013

WILLIAM H TAYLOR  
12/13/2013

# OSI/DGCPC CONSULT: Request for Clinical Inspections

**Date:** September 3, 2013

**To:** Ann Meeker-O'Connell, Acting Division Director, DGCPC  
Constance Lewin, M.D., M.P.H, Branch Chief, GCPEB\*  
Susan Thompson, M.D., Acting Branch Chief, GCPAB  
Janice Pohlman, M.D., M.P.H., Team Leader GCPAB  
Susan Leibenhaut, M.D. Acting Team Leader, GCPAB  
CDER OSI PM Track  
Sharon Gershon, Pharm.D.  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** Shari Targum, M.D. Medical Team Leader, Division of Cardiovascular and Renal Products  
Norma Stockbridge, M.D., Ph.D., Division Director, Division of Cardiovascular and Renal Products

**From:** Anna Park, R.Ph., RAC, Regulatory Health Project Manager, Division of Cardiovascular and Renal Products

**Subject:** **Request for Clinical Site Inspections**

## I. General Information

Application#: **NDA 203202/ SDN 049**  
Applicant/ Applicant contact information (to include phone/email): **Chelsea Therapeutics, Inc.**  
**3530 Toringdon Way, Suite 200 Charlotte, NC 18177/ (704) 341-1516/ Fax: (704) 752-1479/**  
**POC: Loni da Silva** (b) (4), (b) (6)  
Drug Proprietary Name: **Northera**  
Generic Drug Name: **droxidopa**  
NME or Original BLA (Yes/No/Not Applicable\*): **NME**  
Review Priority (Standard or Priority or Not Applicable\*): **Resubmission**

Study Population includes < 17 years of age (Yes/No): **No**  
Is this for Pediatric Exclusivity (Yes/No/Not Applicable\*): **n/a**

*\*For inspection requests not connected to a PDUFA timeline (i.e., for-cause when marketing application is not pending for product)*

Proposed New Indication(s): **Treatment of symptomatic neurogenic orthostatic hypotension**

OSI/DGCPC Consult  
version: 01/16/2013

PDUFA: **February 14, 2014**

Action Goal Date: **February 14, 2014**

Inspection Summary Goal Date: **January 7, 2014**

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table (Note: ALL items listed are required, to process inspection request. Failure to provide complete information will result in delay of inspection process).*

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication/Primary endpoint and other endpoints for verification</b>
<b>132</b> Stuart Isaacson, MD Parkinson's Disease and Movement Disorder Center 951 NW 13 <sup>th</sup> Street, Building 5-E Boca Raton, FL 33486	306B	18	OHSA #1, also exclusions from full analysis and per protocol analysis, adverse events, early terminations.
<b>115</b> Patricio Espinosa Prado, MD ECommunity Research, LLC 15770 Paul Vega MD Drive, Suite 102 Hammond, LA 70403	306B	7	OHSA #1 (see below)
<b>122</b> Ramon Gil, MD Parkinson's Disease Treatment Center of Southwest Florida 4235 Kings Highway, Suite 102 Port Charlotte, FL 33980	306B	8	OHSA #1 (see below)
<b>146</b> Jerome Lisk, MD Neurosearch, Inc. 630 South Raymond Avenue, Suite 110 Pasadena, CA 91105	306B	10	OHSA #1 (see below)

### **III. Site Selection/Rationale**

*Summarize the reason for requesting OSI/DGCP consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection. For example:*

#### ***Rationale for OSI Audits***

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*
- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See\*\*\* at end of consult template for OSI's thoughts on things to consider in your decision making process*

#### **Rationale:**

- Site 132 enrolled the largest number of study subjects; excluding this site would alter the results leading to a failure to reject the null hypothesis.
-  (b) (4), (b) (6)
- Site 115 appeared to have a large treatment difference (-4.4; where the mean effect was about -1.0). In addition, this site reported 8 patients with adverse events.
- Sites 132 and 146 appeared to have 9 and 7 patients excluded from the per protocol analysis; site 132 reported 2 patients excluded from the full analysis set.

#### **Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

Should you require any additional information, please contact Anna Park, Regulatory Project Manager at 301-796-1129 or Shari Targum, Medical Officer at 301-796-1151.

#### **Concurrence: (as needed)**

\_\_\_\_\_x\_\_\_\_\_ Medical Team Leader  
\_\_\_\_\_ Medical Reviewer

\_\_\_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for OSI/DGCPC Audit\*\*\***

- *Notification by sponsor or applicant that they have identified GCP related concerns at site (such notifications may be submitted to IND or NDA/BLA).*
- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
-  (b) (4)
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Is the concern related to a study conducted under IND?*
- *Were the NDA studies conducted under an IND?*

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/s/  
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ANNA J PARK  
09/03/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: July 30, 2013

TO: Director, Investigations Branch  
Detroit District Office  
300 River Place, Suite 5900  
Detroit, MI 48207

FROM: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval  
Data Validation Inspection**, Bioresearch Monitoring,  
Human Drugs, CP 7348.001

RE: NDA 203202  
DRUG: Droxidopa Capsules, 300 mg  
SPONSOR: Chelsea Therapeutics, Inc.  
Charlotte, NC

This memo requests that you arrange for inspections of clinical and analytical portions of the following bioequivalence study. The **background material will be uploaded to ORA/ECMS. Following identification of the ORA investigator, please contact the DBGLPC point of contact (POC) for the link to ORA/ECMS for background material. A DBGLPC scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGLPC POC upon receipt of this assignment to arrange scheduling of the analytical inspection. Please complete the inspections prior to November 03, 2013.**

**Do not notify the sites of the application number, the study to be inspected, drug name, or the study investigators prior to the start of the inspection. The information will be provided to the site(s) at the inspection opening meeting. Please note that this inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).**

**At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the DBGLPC POC.**

**Study Number:** 104  
**Study Title:** "A randomized, open-label, two-period, two-treatment crossover bioequivalence study of one 100 mg and one 200 mg capsule of droxidopa (reference) versus one 300 mg capsule of droxidopa (test) in healthy subjects"

**Clinical Site:** Covance Clinical Research Unit, Inc.  
617 Oakley Street  
Evansville, Indiana 47710  
TEL: (812)474-5000; (812)-474-5017  
FAX: (812)469-5400

**Investigator:** Charles Crockett, M.D.

#### **SECTION A**

**RESERVE SAMPLES:** Because this is a bioequivalence study subject to 21 CFR 320.38 or 320.63, the site conducting the study (i.e., each investigator site) is responsible for randomly selecting and retaining reserve samples from each shipment of drug product (test and reference) provided by the sponsor for subject dosing.

Please note that the final rule for "Retention of Bioavailability and Bioequivalence Testing Samples" (Federal Register, Vol. 58, No. 80, pp. 25918-25928, April 28, 1993) specifically addresses the requirements for bioequivalence studies

(<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120265.htm>).

Please refer to CDER's "Guidance for Industry, Handling and Retention of BA and BE Testing Samples" (May 2004), which clarifies the requirements for reserve samples

(<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>).

Please follow the instructions below:

- Verify if reserve samples were retained according to regulations.
- If the reserve samples were stored at a third party site, please verify and collect an affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing

of the location. In an event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.

- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance [21 CFR 320.38(d, e, g)] on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be collected and shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

John Kauffman, Ph.D.  
Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis  
US Courthouse and Customhouse Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101  
TEL: (314) 539-2168

#### SECTION B

Please confirm the informed consent and records for 100% of subjects enrolled at the site. The study records in the NDA submission should be compared to the original documents at the site. Include a description of your findings in the EIR.

#### Data Audit Checklist:

- Evidence of under-reporting of AEs identified? \_\_\_\_\_
- Evidence of inaccuracy in electronic data capture? \_\_\_\_\_
- Presence of 100% of signed and dated informed consent forms: \_\_\_\_\_
- Reports for the subjects audited: \_\_\_\_\_
- Number of subject records reviewed during the inspection: \_\_\_\_\_
- Number of subjects screened at the site: \_\_\_\_\_
- Number of subjects enrolled at the site: \_\_\_\_\_
- Number of subjects completing the study: \_\_\_\_\_

- Verify from source documents that evaluations related to the primary endpoint were accurately reported in case report forms:\_\_\_\_\_
  - Confirm that clinical assessments were conducted in a consistent manner and in accordance with the protocol:\_\_\_\_\_
  - Confirm that SOPs were followed during study conduct:\_\_\_\_\_
  - Examine correspondence files for any sponsor- or monitor-requested changes to study data or reports:\_\_\_\_\_
  - Include a brief statement summarizing your findings (IRB approvals, study protocol and SOPs, protocol deviations, adverse events, concomitant medications, inclusion/exclusion criteria, adequacy of records, drug accountability documents, and case report forms for dosing of subjects, etc.)
  - Other Comments:
- 
- 

Collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

**ANALYTICAL:**

**Analytical Site:**



**Investigator:**



**Methodology:**

LC-MS/MS

**Please confirm the following during the inspection:**

- Examine all pertinent items related to the analytical methods used for the measurement of **droxidopa/L-Threo 3, 4-dihydroxyphenylserine concentrations in human plasma.**
- Compare the accuracy of the analytical data provided in the NDA submission by the applicant with the original documents at the site.
- Determine if the validated analytical method was employed for the subject sample analysis.
- Compare the assay parameters (such as variability between and within runs, accuracy and precision, etc.) observed during the

study sample analysis with those obtained during method validation.

- Confirm that the accuracy and precision in matrix were determined using standards and QCs prepared from separate stocks.
- Determine if the subject samples were analyzed within the validated stability period.
- **Confirm that freshly made calibrators and/or freshly made QCs were used for stability evaluations during method validation.**
- **Confirm that the precision and accuracy was demonstrated at least one time using QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject plasma samples, the reason for such repetitions, the SOP(s) for repeat assays, and if relevant stability criteria such as the number of freeze-thaw cycles sufficiently covered the stability of reanalyzed subject samples.**
- Examine correspondence files between the analytical site and the sponsor for their content.

**Additional instructions to ORA Investigator:**

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions, inspection-related questions or clarifications before the inspection, and also regarding data anomalies or questions noted during review of study records on site.

**Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the DBGLPC POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar (Fax: 1-301-847-8748 or Email: [sam.haidar@fda.hhs.gov](mailto:sam.haidar@fda.hhs.gov)) and DBGLPC POC. Please address the EIR to Dr. Haidar:**

Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance (DBGLPC)  
Office of Scientific Investigations (OSI)

Office of Compliance  
Bldg. 51 Rm. 5330  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

DBGLPC POC: Jyoti B. Patel, Ph.D.  
Email: jyoti.patel@fda.hhs.gov  
TEL: (301)796-4617  
FAX: (301)847-8748

cc:

CDER OSI PM TRACK

OSI/DBGLPC/Taylor/Haidar/Patel/Choi/Dasgupta/Dejernett/CF  
CDER/OND/ODE1/DCRP/Park, Anna J/Sabarinath, Sreedharan

Draft: JBP 07/24/2013

Edit: SHH 7/29/2013

OSI file #: BE6481; O:\BE\assigns\bio203202.doc

ECMS: Cabinets/CDER\_OC/OSI/Division of Bioequivalence & Good  
Laboratory Practice Compliance/Electronic Archive/BEB

**FACTS: 8689631**

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/s/  
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JYOTI B PATEL  
07/30/2013

SAM H HAIDAR  
07/30/2013

<b>OSI Consult Request for Biopharmaceutical Inspections</b>	
Date	July 21, 2013
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	William H. Taylor, PhD Director, Division of BE and GLP Compliance Office of Scientific Investigations william.taylor1@fda.hhs.gov
Consulting Office/Division	ODE1/DCRP
Project Manager	Anna Park
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	203202
Drug Product	Droxidopa
Sponsor Name	Chelsea Therapeutics, Inc.
Sponsor Address	3530 Toringdon Way, Suite 200, Charlotte, NC 28277
US Agent (if applicable)	
US Agent Address	
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA/BsUFA Due Date	January 3, 2014
Action Goal Date	January 3, 2014
OSI Review Requested By	Sreedharan Sabarinath, Ph.D.

<b>Inspection Request Detail</b> (All fields should be fill out completely)	
<b>Study #1</b>	
Study Number	104
Study Title	A randomized, open label, bioequivalence study of one 100 mg and one 200 mg capsule of droxidopa versus one 300 mg capsule of droxidopa in healthy subjects.
Study Type	<input type="checkbox"/> In vivo BE <input type="checkbox"/> In vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Others (specify)
<input checked="" type="checkbox"/> Inspection Request - <b>Clinical</b> Site	<input checked="" type="checkbox"/> Inspection Request - <b>Analytical</b> Site
Facility #1 Name: <b>Covance Clinical Research Unit, Inc.</b> Address: <b>617 Oakley Street Evansville, Indiana 47710</b> (Tel): (812)-474-5017 (Fax)	Facility #1 Name: [REDACTED] (b) (4) [REDACTED] [REDACTED] (Fax)
Clinical Investigator: <b>Charles Crocket, MD</b> (email)	Principal Analytical Investigator: (email)
Facility #2 Name: (if applicable)	Facility #2 Name: (if applicable)

Address: (Tel) (Fax)	Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input type="checkbox"/> Study Report: (location, eg., 5.3.1.2)	<input type="checkbox"/> Validation Report: (eg., 5.3.1.2) <input type="checkbox"/> Bioanalytical Report: (eg., 5.3.1.4)

<b>Study #2</b>				
Study Number				
Study Title				
Study Type	<input type="checkbox"/> In vivo BE	<input type="checkbox"/> In vitro BE	<input type="checkbox"/> Permeability	<input type="checkbox"/> Others (specify)
<input type="checkbox"/> Inspection Request - <b>Clinical</b> Site	<input type="checkbox"/> Inspection Request - <b>Analytical</b> Site			
Facility Name: (or indicate if same as above)	Facility Name: (or indicate if same as above)			
Address: (Tel) (Fax)	Address: (Tel) (Fax)			
Clinical Investigator: (email)	Principal Analytical Investigator: (email)			
Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input type="checkbox"/> Routine inspection <input type="checkbox"/> For cause			
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>				
<input type="checkbox"/> Study Report: (location, eg., 5.3.1.2)	<input type="checkbox"/> Validation Report: (eg., 5.3.1.2) <input type="checkbox"/> Bioanalytical Report: (eg., 5.3.1.4)			

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.**

## ***I. Appendix***

### **Specific Items To be Addressed During the Inspection**

The NDA 203202 droxidopa re-submission has a pivotal BE study (Study Number 104). Please conduct the biopharmaceutical inspection for this bioequivalence study site and its bioanalysis.

EDR Link to Study Report: <\\cdsesub1\evsprod\NDA203202\0044\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\noh104>

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/s/  
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ANNA J PARK  
07/22/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CONSULT REVIEW MEMO**

DATE: January 23, 2013

TO: Anna J. Park, R.Ph., RAC, Regulatory Project Managers  
Melanie Blank, M.D., Clinical Reviewer  
Division of Cardiovascular and Renal Products

FROM: Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance

THROUGH: Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

Ann Meeker-O'Connell  
Acting Division Director  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Recommendations concerning continued blinding of the 306B trial

NDA: 203202

APPLICANT: Chelsea Therapeutics, Inc

DRUG: Northera® (droxidopa) tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: treatment of symptomatic neurogenic orthostatic hypotension (NOH)

CONSULTATION REQUEST DATE: January 4, 2013

## I. BACKGROUND

Chelsea Therapeutics, Inc. (Sponsor) submitted an NDA for the indication of treatment of symptomatic neurogenic orthostatic hypotension (NOH), associated with several underlying diseases. A complete response letter was sent on March 28, 2012 requesting an additional clinical trial. At an End of Review meeting, Chelsea proposed that data from an ongoing study NOH306B (hereafter “306B”) could fulfill the request for an additional trial. An advice letter sent June 29, 2012 informed the sponsor of concerns with the potential for inappropriate unblinding of the 306B study to have influenced redesign of the study’s analytic plan. On December 12, 2012, Chelsea Therapeutics submitted a formal dispute resolution request, appealing the requirement to conduct an additional clinical trial for approval. Chelsea is requesting either accelerated approval or full approval with a PMR based on the clinical evidence in the NDA, which did not include efficacy data from 306B. Dr. Jenkins, through the Division of CardioRenal Products, requested that the Office of Scientific Investigations (OSI) “provide recommendations related to the continued blinding of the 306B trial and whether FDA should consider the efficacy data as part of its assessment of this application.”

This review is limited to the documents outlined below and to the issues concerning blinding and unblinding of study data in Protocol 306 and considering efficacy data generated during the trial .

- Addendum 2: “Study 306 - Overview of Blinding of Patients Enrolled in NOH306B” including nine appendices, submitted as Sequence 36 (37) to the NDA on May 31, 2013
- FDA Advice Letter to sponsor (June 29, 2012)
- Medical Officer review of Addendum 2 above (July 3, 2012)
- Chelsea public website announcement of study results on December 4, 2012 and 2012 SEC filings

This review does not address study design or issues of adequacy of sample size. It does not address the blinding issues with capsules as noted on Page 3 of Dr. Blank’s review

**Sponsor “Table 1. Enrollment Timeline” from Addendum 2, Page 8**

Date	Milestone	Total Enrollment	Patient Details
14 Dec 2010	Data Cut for Interim	94	51 safety and efficacy (306A) 41 masked safety only (306B) 2 not in interim (306B)
14 Jan 2011	Tables Sent to DMC	107	51 in 306A 56 in 306B
25 Jan 2011	DMC Held, Enrollment Halted	113	51 in 306A 62 in 306B
23 Feb 2011	Enrollment Resumes	114	51 in 306A 63 in 306B
2 Mar 2011	Unblinded Statistical Team Read-Access is Revoked	118	51 in 306A 67 in 306B
9 Mar 2011	Final Database Lock for 306A	119	51 in 306A 68 in 306B
10 May 2012	Current Enrollment	210	51 in 306A 159 in 306B

Note that this is the Sponsor’s timeline with milestones. These milestones are discussed in the review.

**Executive Summary:**

OSI has reviewed the information submitted by the sponsor related to the blinding of study 306B, and we did not find evidence that would conclusively support a recommendation to reject the entire 306B dataset.

While the PPD internal audit report (Attachment 15, PPD Targeted Process Audit) describes multiple internal process and documentation deficiencies in PPD’s management of their information systems, we have no evidence suggesting that the sponsor had access to the full randomization schedule or that they applied randomization codes to the clinical database. We note that the sponsor’s narrative in support of their assertion that bias was not introduced through telephone discussions and e-mails between the sponsor and unblinded PPD statisticians in January and February 2011 is plausible but cannot be definitively proven.

Further, the PPD internal audit did not conclusively demonstrate that access to unblinded data in the Biostatistics Technology Infrastructure (BTI) study area was granted inappropriately. Rather, the auditor identified deficiencies in the process for completing and maintaining study access request (SAR) forms for PPD staff identified as having access to blinded or unblinded 306 study areas. Because the information system itself did not maintain a historical log of user access rights, the SAR forms served as the historical documentation of PPD’s granting and revoking user access and for defining levels of access (e.g. read only). The audit report findings primarily related to missing documentation supporting the level of access granted to authorized BTI study areas rather than users with unauthorized access to the unblinded study files.

Additionally, we did not identify information that would disprove the sponsor's assertion that access to the unblinded database for the unblinded PPD DMC statisticians was revoked on March 2, 2011. However, as per the PPD audit, we have no absolute documentation that this did occur on the date stated, but the audit did confirm that the access to the unblinded study area was revoked as of June 27, 2011. We also note that there is no information in the material submitted as to when and how the procedures in Appendix 5, "General Information about PPD Environment" were implemented, when access to the blinded area was actually revoked, and what was viewed prior to the revoking of access.

Although we find the sponsor's explanation of the occurrences concerning the unblinding of Study 306A and the subsequent blinding process concerning Study 306B to be plausible based upon the documentation provided, we cannot definitively rule out the introduction of bias. As evidenced by the meeting minutes of February 17, 2011, there was a high risk of unblinding at the patient level prior to the splitting of teams for Studies A and B. Whether any unblinding at the patient level actually occurred, and what or how this could have introduced bias into the study design and analysis cannot be determined from the documents submitted. We agree with the PPD auditor's recommendation that the nine subjects in the overlapping block in the randomization table for 306B be included in the 306A analysis instead. Finally, our review also identified a separate issue related to the completeness and reliability of patient-reported data for falls and secondarily to sponsor oversight of study conduct. The decision as to whether the efficacy data should be considered in the assessment of this application must be made with these caveats in mind.

## **II. Review of documents provided:**

Protocol NOH 306 entitled, "A Multi-Center, Double-Blind, Randomized, Parallel-Group Placebo-Controlled Study to Assess the Clinical Effect of Droxidopa in the treatment of Symptomatic Neurogenic Orthostatic Hypotension in Patients with Parkinson Disease" was initiated to provide evidence of safety and efficacy for droxidopa in the treatment of orthostatic hypotension. Chelsea Inc., contracted with PPD to provide services including monitoring, database management, and biostatistics for the study. An independent data monitoring committee (DMC) was also formed by the sponsor to oversee the study. In November 2010, Chelsea submitted an amendment to the Study 306 protocol to include an interim analysis to review safety and perform an interim analysis of efficacy to decide whether to resize the study or potentially halt the study for futility (SN0096 to IND 77,248).

**Data flow:** According to the "Addendum 2:, Section 4.3 Pre-Defined DMC Interim Analysis Information Flow and Timeline", the efficacy measures and the patient reported outcomes were captured via a dedicated computer at the clinical sites (ePRO) or a handheld e-diary device given to patients (for patient reported falls). A vendor, PHT, managed by PPD, handed the ePRO and e-diary programming and data transfers. For analysis purposes, data was extracted from the PPD Oracle Clinical Database or was transferred as SAS datasets by PHT, into a Blinded Project Area on the Biostatistics Technology Infrastructure (BTI) system managed by PPD. Unblinded statistical team members use read-only access to gather data from the Blind Project Area and copy it into an Unblind Project Area. Randomization codes are

independently transferred to the unblind statistical team only, who uses them to unblind the data in the Unblind Project Area and generate tables, figures, and listings.

**Chronology Summary:** Unblinded efficacy data on 51 subjects and blinded safety data on 92 subjects were presented to the DMC according to specific work instructions dated January 24, 2011 (Appendix 3). On January 25, 2011, the DMC recommended stopping for futility. The sponsor requested unblinded data for the 51 subjects in order to conduct additional analyses and, on January 27, 2011, the unblinded data for the 51 subjects was provided to the sponsor. From January 27 to February 9, 2011, the unblinded team performed the interim analysis for the DMC meeting and subsequent requests from the sponsor for unblinded data and sample size calculations. During this time in which 113 subjects were enrolled in Study 306, discussions occurred between the sponsor and PPD via both e-mail and telephone. On February 9, 2011, the sponsor was informed that the PPD unblinded team had been granted access to randomization codes for all 306 subjects and discussions between the parties ceased.

*Reviewer comment:* There is concern that the unblinded PPD team may have inadvertently conveyed some information to the sponsor because the PPD statisticians had access to the randomization code for the entire study. However, it appears from the narrative that the code was only applied for the 51 subjects for which efficacy data was available on December 14, 2010.

On February 17, 2011 a “NOH306A/306B Kick-off” meeting (minutes in Appendix 4) was held between Chelsea and PPD to discuss the separation of the analysis of the subjects in NOH 301A and 306B and to agree on the affiliated activities/strategies to move forward. Action items included “follow-up with biostats regarding PPD’s Team Recommendation and “work with biostats to develop timelines for analyzing, modeling firewall, TLFs (tables, lists and figures).” An undated, unsigned document, Appendix 5 “PPD Document regarding Biostatistics Project Area and Establishment of Separate Work Areas and Teams to Maintain Blinding of 306B Study Data” describes the arrangements for the five discrete areas and four discrete teams to preserve the blind within PPD for complete unblinding and analysis of Study 306A while preserving the blinding of Study 306B.

According to the meeting minutes:

- “Further clarification occurred that the data that is moved to the secure area for analyses is a copy of what is in OC RDC. At the patient level, there is a high risk of unblinding if using the same team as everyone will be exposed to the randomization schedule at one point for both A and B. Further meetings will need to occur between PPD and Chelsea to discuss how to reduce further bias in part A and part B.”
- “Chelsea had expressed concerns about how PPD will maintain blind after extraction. PPD has added a variable to the database indicating “306A” or “306B”. PPD verified that randomization codes are stored separately and the randomization codes must be applied to be unblinded.”
- “Currently analysts are blinded because the randomization codes were not applied.”

From February 17 to March 9, 2011, PPD worked to validate clean and freeze data on subjects for Study 306A. On March 2, 2011, PPD confirmed that the unblinded statistical team did have

access to all 306 randomization codes. Access to the Blind Project Area was revoked on this day.

On March 9, 2011, the “Biostatistics Study Unblinding Request /Authorization Form (Appendix 6) was signed to authorize the unblinding of the 51 patients utilized in the interim efficacy analysis for a final analysis as described in the document.

*Reviewer comment: Although the plan for separation of the data and statistical review teams described in Appendix 5 seems adequate to ensure continued blinding, it is not clear from this narrative when the procedures described in Appendix 5 were implemented and why privileges to the blind project area for the unblinded DMC team were continued until March 2, 2011.*

**PPD Internal Audit:** From June 10 to 28, 2011, PPD conducted a targeted audit which included a retrospective and concurrent review of documentation and controls surrounding the interim analysis in January 2011, the database lock of 306A subjects in March 2011, current access status to the database and BTI study areas, and assessment of an internal firewall between data for 306A subjects and 306B subjects.

The audit concluded that PPD staff generally adhered to work instructions and SOPs, and that proper approvals were obtained before database lock and unblinding of a subset of 51 subjects. However three Major findings were noted with regard to system access controls and adequate identification of unblinded study subjects. These findings are summarized below:

1. One external user was granted unauthorized access to the blinded Oracle Clinical Remote Data Capture (OC RDC) database. Specifically, (b) (4) a Clinical Investigator not participating in the 306 study, had ‘browse’ (read-only) access to electronic case report form (eCRF) data for all investigator sites. Access was granted on June 25, 2010 and was revoked subsequent to the audit on June 16, 2011. In response to the audit, PPD confirmed that no data had been changed, but the system did not have the capability to verify if (b) (4) had read any data. Preventive actions were put in place to strengthen the access provisioning process for OC RDC and to strengthen account quality control.
2. There were concerns with the Biostatistics Technology Infrastructure (BTI) study area access because Study Access Request (SAR) Forms were not maintained in an orderly, traceable manner by Biostatistics, Programming, or IT. Because the system did not maintain an audit trail of access privileges, the SAR Forms are the primary documentation of granting access and removing privileges. Because the documentation was not complete at the time of audit, the auditor could not verify that all personnel had only the correct access at all times during the study.
3. Specifically, for the unblinded NOH306\_U study area, SARFs were not readily available for review. The auditor received a screen shot of user permissions to the unblinded area on June 27, 2011 and confirmed that no one currently had access to that area; however, they could not definitively determine when such access was revoked, and therefore, the auditors could not verify that separately secured computational server folder locations were maintained, accessible by the unblinded Biostatistics team members only.

*Reviewer comment: These findings raise general concerns about PPD's implementation of process controls for their information systems. They do not, in and of themselves, document that users did actually have access or view unblinded data.*

4. There was potential that the sponsor could be unblinded to the randomized study arm for nine blinded subjects in the 306B group. The treatment assignment for these nine subjects could be deduced from a combination of unblinded randomization stratification provided for the 51 subjects in 306A subjects and other study data such as order of entry into the study and demographics.

**PPD memo:** On May 2, 2012, Simon Pedder, Ph.D., President and CEO of PPD wrote a memorandum (Appendix 7) regarding Study 306B blinding, noting that the biostatistics teams within PPD were separated and Chelsea did not engage PPD to provide biostatistics services to 306B. Additional bullets were that PPD did not provide any randomization codes to Chelsea, and that it would be possible for someone to deduce the allocated treatment codes for nine patients in 306B based on the treatment that three of the four patients in the randomization blocks actually received as shown in the unblinded analysis.

**Meeting with FDA:** At the meeting held between FDA and the sponsor on January 10, 2013, the sponsor noted that Study 306B was terminated, the data analyzed, and that this was posted on the company website. This is confirmed by accessing the sponsor website public announcement of December 4, 2012:

<http://chtp.client.shareholder.com/releasedetail.cfm?ReleaseID=724894>

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The consult request to OSI is to “provide recommendations related to the continued blinding of the 306B trial and whether FDA should consider the efficacy data as part of its assessment of this application.” This review is limited to the documents listed in the “Background Section I” above. It does not address issues of study design or adequacy of sample size. It does not address the blinding issues with capsules as noted on Page 3 of Dr. Blank’s review. OSI has reviewed the information submitted by the sponsor related to the blinding of study 306B, and we did not find evidence that would conclusively support a recommendation to reject the entire 306B dataset.

While the PPD internal audit report (Attachment 15, PPD Targeted Process Audit) describes multiple internal process and documentation deficiencies in PPD’s management of their information systems, we have no evidence suggesting that the sponsor had access to the full randomization schedule or that they applied randomization codes to the clinical database. We note that the sponsor’s narrative in support of their assertion that bias was not introduced through telephone discussions and e-mails between the sponsor and unblinded PPD statisticians in January and February 2011 is plausible but cannot be definitively proven.

Further, while we have no evidence to contradict the sponsor narrative concerning the revocation of privileges for the unblinded PPD statisticians, there is no information in the material submitted as to when and how the procedures in Appendix 5 “PPD Document regarding Biostatistics Project Area and Establishment of Separate Work Areas and Teams to Maintain Blinding of 306B Study Data” were implemented. As evidenced by the meeting minutes of February 17, 2011, there would have been a high risk of unblinding at the patient level prior to the splitting of teams for Studies 306A and 306B.

Whether any unblinding actually occurred and what or how this could have introduced bias into the study design and analysis cannot be definitively determined from the documents submitted. Submission and review of additional documents such as the standard operating procedures (SOPs) related to Appendix 5 and documentation of implementation of these procedures as well as on-site inspection, may lower the level of uncertainty concerning this issue, but cannot provide definitive assurance. In addition to the above, there is no information concerning what occurred with the data after the June 2011 audit. In the May 2, 2012 memo from Simon Pedder, Ph.D., wrote “Chelsea did not engage PPD to provide biostatistics services to 306B.” A statistical analysis plan for 306B prepared by the Chelsea Therapeutics, dated and signed May 12, 2011, was submitted as Appendix 8. Because no information was submitted concerning the data transfer and storage procedures, we cannot comment definitively on what occurred once the data was transferred from PPD to the sponsor or CRO for further analysis, except to state that there would be no obvious concerns because of the statement in this memo that “PPD did not provide any randomization codes pertinent to NOH 306B”.

#### **Other Issues Relevant in Consideration of Efficacy Data for Study 306B**

During review of the sponsor’s submission related to study blinding, we identified an ancillary study conduct issue that may be relevant to the review of data for study 306B and may warrant evaluation during on-site inspections. This issue, in combination with the major findings from the PPD internal audit, raises concern about whether the sponsor provided adequate oversight for study conduct. Appendix 4 (Chelsea and PDD February 17, 2011 Meeting Minutes) of Chelsea’s “Study 306-Overview of Blinding of Patients Enrolled in NOH306B” states that: “Fall patient data: 37 of 51 patients have missed data equaling a total of 199 days of missed data.” This “voluminous amount of missing data” is ascribed to an error on the part of the patient report outcomes (PRO) vendor, PHT; the vendor did not “implement a change in the way the question was asked.” Per the meeting minutes, the error was discovered on February 17, 2011.

The sponsor and CRO planned to address the missing PRO data through contacting each clinical investigator and “determining which sites have source data to document the missed data.” If source documentation exists, then a Data Clarification Form was to be generated and initialed and dated by the patient. The minutes do not discuss the extent to which data may be missing for the 62 subjects randomized to study 306B as of the date of the meeting, the rationale for changing the PRO tool mid-study or any implications for the validity of falls data for study 306(B).

While it is unclear what primary endpoint the sponsor might submit for this study, the review division may wish to consider the impact and nature of missing falls data on analyses related to this endpoint. Further, the review division may wish to consider the implications of having patient-entered data comingled with data collected secondarily from site source documents that may be subject to recall bias as well as the impact of changes made to the PRO tool during the study.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
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Ann Meeker-O'Connell  
Acting Division Director  
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Office of Scientific Investigations

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/s/  
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SUSAN LEIBENHAUT  
01/24/2013

WINIFRED M MEEKER - O'CONNELL  
01/24/2013

SUSAN D THOMPSON  
01/24/2013

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Promotion  
Division of Direct-to-Consumer Promotion**

## Memorandum

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**Date:** April 2, 2012

**To:** Anna Park, Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Emily Baker, Regulatory Review Officer  
Division of Professional Promotion (DPP)  
Office of Prescription Drug Promotion (OPDP)

Zarna Patel, Regulatory Review Officer  
Division of Direct-to-Consumer Promotion (DDTCP)  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 203202 Northera (droxidopa)  
OPDP Labeling Consult Response

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**\*\*\*\* Pre-decisional Agency Information\*\*\*\***

We acknowledge receipt of your October 13, 2011, consult request for the proposed Package Insert, Patient Package Insert, Carton/Container Labeling and Medication Guide for Northera (droxidopa), NDA 203202. OPDP was notified by DCRP on March 19, 2012, that the Review Division plans to issue a Complete Response and will not be providing labeling comments. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DCRP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials. If you have any question on the Package Insert or Carton/Container Labeling, please contact Emily Baker at 301.796.7524 or [Emily.Baker@fda.hhs.gov](mailto:Emily.Baker@fda.hhs.gov). If you have any questions concerning the Patient Package Insert or Medication Guide, please contact Zarna Patel at 301.796.3822 or [Zarna.Patel@fda.hhs.gov](mailto:Zarna.Patel@fda.hhs.gov).

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/s/  
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EMILY K BAKER  
04/02/2012

ZARNA PATEL  
04/02/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**REVIEW DEFERRAL MEMO**

**Date:** March 28, 2012

**To:** Norman Stockbridge, MD, PhD, Director  
**Division of Cardiovascular and Renal Products (DCRP)**

**Through:** LaShawn Griffiths, MSHS-PH BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling Team  
**Division of Medical Policy Programs**

**From:** Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs**

**Subject:** Review Deferred: Medication Guide

**Drug Name(s):** NORTHERA (droxidopa) Capsules

**Application Type/Number:** NDA 203-202

**Applicant/Sponsor:** Chelsea Therapeutics, Inc.

**OSE RCM #:** 2011-3686

This memorandum documents the deferral of our review of the Applicant's proposed Medication Guide (MG) for Northera (droxidopa). On October 13, 2011, the Division of Cardiovascular and Renal Products requested that OSE review the proposed MG for Northera (droxidopa).

Due to outstanding Clinical/Statistical, Facility Inspections, Product Quality, Clinical Pharmacology, and Non-Clinical deficiencies, the Division of Cardiovascular and Renal Products plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's Medication Guide at this time. A complete review will be performed after the Applicant submits a Complete Response to the Complete Response letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/  
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SHARON R MILLS  
03/28/2012

BARBARA A FULLER  
03/28/2012

LASHAWN M GRIFFITHS  
03/28/2012

RHPM NDA Overview  
March 22, 2012

**NDA 203202** Droxidopa oral capsules

**Sponsor:** Chelsea Therapeutics, Inc.

**Classification:** 1/P

**Indication:** Treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson’s Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta hydroxylase (D $\beta$ H) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN)

**Date of Application:** September 23, 2011

**Goal Date:** March 28, 2012

**Background:**

Chelsea Therapeutics, Inc. submitted a 505(b)(1) NDA for Droxidopa, an orally administered, synthetic catecholamine acid pro-drug that is converted to norepinephrine (NE). The proposed indication for Droxidopa is for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson’s Disease [PD], Multiple System Atrophy [MSA] and Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (D $\beta$ H) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Droxidopa was granted Orphan Designation on January 17, 2007 and Fast-Track Designation on August 7, 2008 for the treatment of symptomatic NOH.

On November 16, 2011, the sponsor was notified they would receive a Priority review. The sponsor submitted a Special Protocol Assessment Request on October 12, 2007 for their clinical protocol entitled, “A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Induction-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension” and an agreement was reached on November 28, 2007.

The sponsor's clinical development program included 3 studies, Study 301, 302 and 303, to assess the efficacy of Droxidopa. Study 301 was a pivotal, Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose-titration period (up to 14 days) prior to a 7-day washout period, followed by a 7-day double-blind randomized treatment period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo. Study 301 is the pivotal efficacy trial in the droxidopa development program, and the efficacy results from this study are the predominant focus of this NDA.

Study 302 was a supportive, Phase 3, multi-center, double-blind, randomized, placebo controlled, parallel-group, withdrawal-design study that included an initial open-label dose-titration period (up to 14 days), a 7-day open-label treatment period, and a 14-day randomized-withdrawal period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo. Study 302 failed to meet its primary endpoint and, as a result, the efficacy data from this trial are supportive in nature. Of note, the Division met with the sponsor on November 18, 2009 in light of the results of the failed study and the sponsor was allowed to modify the primary outcome variable in Study 301.

Study 303 was a Phase 3, multi-center, long-term extension study to evaluate the long-term safety and efficacy of droxidopa in patients with NOH. All patients entered this study from a prior study with droxidopa (Studies 301 or 302).

A Pre-NDA meeting was held on December 1, 2010. Since the primary endpoint was changed after 124 subjects had been enrolled and 165 subjects have been randomized, Dr. Stockbridge recommended the sponsor be as thorough as possible in providing the full documentation for the basis of that decision in their complete study report. The sponsor agreed and would provide the documentation to show that they remained blinded to the study results at the time.

On November 3, 2011, the sponsor was notified of the Division's decision to take Droxidopa to the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on February 23, 2012.

On February 23, 2012, both FDA and Chelsea Therapeutics, Inc. presented at the Advisory Committee meeting and the committee members voted to approve Droxidopa.

**Filing Meeting:** October 27, 2011

**Office Director's Memo**

Dr. Unger's recommends a Complete Response based on inadequate evidence of effectiveness.

**Summary:**

Depending on the determination of reliability of the data from site 507 (study 301), I view the evidence of efficacy in this dossier to be either 3 negative studies, or 1 positive study (301) where 1 site is disproportionately responsible for the favorable effect, such that it alone does not provide a sufficient basis for approval. The concern about site 507 arose late in the review cycle, and additional actions will be needed to address the data integrity questions.

He strongly agree with the majority of the review team that a demonstration of efficacy over a period of only 1 week is not adequate, given that patients with NOH have chronic disorders, such that this drug would likely be used on a chronic basis.

Additional studies, if undertaken, should assess the efficacy of droxidopa for much longer than 1 week. Recognizing the arbitrary nature of this advice, I would say that 6 weeks would be minimally adequate.

The need to address, prior to marketing, concerns regarding potential neurotoxicity of DOPAL and DOPEGAL depend on the overall benefit-risk analysis. If the benefit ultimately shown seems either quantitatively or qualitatively small, then I would favor completion of the non-clinical studies prior to marketing. If, on the other hand, important efficacy is shown, then such study(ies) could be deferred until after approval.

#### **Division Director's Memo**

If the outstanding CMC issues get resolved, Dr. Stockbridge recommends approval for the intermittent use with labeling that says long-term effectiveness with continuous use is not recommended. Unless one can construe this as a safety issue, Dr. Stockbridge did not think the long-term study was a candidate for a PMR.

#### **Reviews (date)**

##### **CDTL Review (March 8, 2012)**

**Reviewer:** Shari Targum

**Conclusion:** No approval

**Labeling:** None

#### **Summary:**

Dr. Targum recommends a complete response, with the need for an additional efficacy trial and additional controlled safety data.

- **Risk Benefit Assessment**

Droxidopa was studied in a heterogeneous population of patients with symptomatic NOH. From a selected population of responders who tolerated the drug, droxidopa increased SBP and met its primary endpoint in study 301, with

consistency in most of the OHQ components; however, these results were not substantiated in the other two studies.

There is uncertainty as to validity of the primary endpoint instrument or how clinically meaningful the result. The global scales (included to support the OHQ interpretation) but did not show statistically significant improvement.

According to the SEALD reviewer, concordance between the OHSa Item 1 and the patient-reported global assessment was poor. The SEALD could not state with confidence a minimal clinically meaningful inpatient change in OHSa item 1.

The medical and statistical reviewers did not recommend approval. The medical reviewer felt that study 301 showed a treatment effect; however, the application showed no evidence of durability in a chronic condition, and the safety review showed signals of concern. The statistical reviewer concluded that an additional trial was needed to confirm the results of study 301. I concur with both reviewers; however, I find the safety results to be difficult to interpret without a concurrent placebo group of some duration longer than one week.

Without demonstration of durability of benefit, one can potentially label droxidopa for “one week of benefit” with uncertainty beyond a week. But how should a health care provider prescribe droxidopa? Does the patient need to take the medication three times daily, or is compliance related to occurrence of symptoms and need for medication (like “PRN” pain medications)?

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

The sponsor submitted a proposed Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide, communication plan, and timetable for submission of assessments. The Division of Risk Management concluded that the risk of supine hypertension can be managed through labeling and a REMS is not warranted. However, if droxidopa were to be approved, the sponsor may voluntarily implement a DHCP letter and additional voluntary measures (e.g.,

<sup>(b) (4)</sup> The Medication Guide should be included in labeling, with language informing patients to elevate the head of their bed to minimize risk of supine hypertension. If the supine hypertension risk associated with Droxidopa is comparable to that of midodrine, a boxed warning should be considered. The Division of Epidemiology should be consulted to obtain input and evaluate feasibility regarding the proposed Phase IV registry. Dr. Targum concurs.

- Recommended Comments to Applicant

1. Need for additional efficacy data, perhaps in a subset with the largest effect (such as PAF population);
2. Need for additional safety data, including but not limited to study 306.

**Medical (January 27, 2012)**

**Reviewer:** Melanie Blank, M.D.

**Conclusion:** No approval

**Labeling:** None

**Summary:**

Dr. Blank does not recommend approval due to a lack of sufficient evidence of efficacy. There is only one successful trial and it is well known that random factors can cause erroneous clinical trial outcomes. Patients with symptomatic neurogenic orthostatic hypotension are vulnerable and it is important to ensure their safety by protecting them from exposure to drugs that may not be effective, particularly drugs that have a theoretical basis for causing cardiovascular safety issues, as this drug has. Additionally the lack of evidence of durability is particularly concerning. Patients should not be exposed to a drug chronically unless benefit is established over a reasonable amount of time – at least three months. It is possible that there is a down regulation of NE receptors in the peripheral circulation after prolonged exposure to Droxidopa. If this is the case, one might consider approval but would need to label the product differ than what is being currently proposed (long-term use). Durability of effect should be studied further so that proper instructions for use can be crafted. Finally, the safety of droxidopa is still poorly characterized and another properly designed trial should be conducted to evaluate it. This development program was not properly designed to evaluate safety because of three factors: 1) the absence of a pure placebo group, 2) most of the safety data were collected in open-label trials and 3) blood pressure was collected with the head of the bed tilted at 30 degrees. Vasoconstriction is the mechanism of action of droxidopa. Therefore, without a control group, it is logical to assume that the cardiovascular adverse events, and there were many, were cause droxidopa. There is also the concern of neuroleptic malignant syndrome. Since there were some Japanese postmarketing cases that were not explicable on the basis of other drugs known to cause the syndrome, one needs to be concerned that Droxidopa may cause this sometimes fatal condition.

**Statistical (January 23, 2012)**

**Reviewer:** Jialu Zhang, Ph.D.

**Conclusion:** No approval

**Labeling:** None

**Summary:**

The Chelsea-sponsored droxidopa clinical development program includes two randomized, placebo-controlled, double-blind studies (Studies 301 and 302). Only one study showed the efficacy of droxidopa. Additional study is needed to confirm the finding. Dr. Zhang did not recommend approval.

**Pharmacology (February 3, 2012)**

**Reviewer:** Donald Jensen, Ph.D.

**Conclusion:** Approval

**Labeling:** Dr. Jensen included labeling recommendations in his review.

**Summary:**

Because of the severe renal tubular toxicity observed in rats and, with lesser severity, in mice, Dr. Jensen recommends that the ongoing clinical study in renal-impaired patients be completed and evaluated before final approval is considered.

Similarly, due to the myocardial necrosis and scarring observed in both rats and mice, it is important the sponsor provide adequate clinical cardiac safety data, including the clinical cardiac troponin measurements requested during the December 1, 2010, pre-NDA meeting.

Prior to approval, the sponsor should provide data sufficient to define human serum metabolites and to define serum levels of each of these metabolites in humans and in the toxicology species. This data is particularly important for evaluating the adequacy of the reproductive toxicity studies and of the rodent carcinogenicity assays. As noted above, of four human metabolites of droxidopa evaluated by the CDER Computational Toxicology Group, each was predicted to be positive in more than one genotoxicity assay, two were predicted to be positive in 3-year rodent carcinogenicity assays, and a third has been previously shown to produce tumors in rats. One human metabolite was predicted to be teratogenic in rabbits, but it is not known whether rabbits produce that metabolite.

**Secondary Review (February 21, 2012)**

**Reviewer:** Thomas Papoian, Ph.D.

**Conclusion:** Approval

**Labeling:** None

**Summary:**

Dr. Papoian recommends approval given that droxidopa is a prodrug of an endogenous catecholamine (norepinephrine) with known pharmacological properties, both peripherally and centrally, it has been approved in Japan since 1989, and no significant adverse toxicities were seen in dogs or monkeys at large multiples of the human dose, there are no major safety issues for use in the indicated human patients.

However, even with the absence of clear clinical signals, the potential neurotoxicity of one of its metabolites DOPEGAL has not been adequately assessed, because the specific

adrenergic neurons known to be vulnerable to DOPEGAL toxicity were never specifically examined. An animal study to help clarify this issue is feasible, relatively easy to perform, and may be considered, particularly given the serious nature of potential drug-induced neurotoxicity in this, or any other, patient population.

**Pharmacology - Toxicological assessment of impurities in drug substance,**

**(b) (4) method (March 6, 2012)**

**Reviewer:** Donald Jensen, Ph.D.

**Summary:**

(b) (4) - Proposed limit of (b) (4) ppm is acceptable.

(b) (4) - Proposed limit of (b) (4) ppm is not acceptable.

(b) (4) - The proposed limit of (b) (4) is not acceptable.

(b) (4) - Proposed limit of (b) (4) ppm is acceptable.

(b) (4) Control of these impurities at (b) (4) in the drug substance specification is acceptable.

(b) (4) - Control of this impurity at (b) (4) in the drug substance specification is acceptable, if it has the chemical structure that was submitted to the CDER Computational Toxicology group as “(b) (4) or if it is (b) (4)

(b) (4) - Additional information is required from the Sponsor.

(b) (4) - Control of this starting material at (b) (4) in the drug substance specification is acceptable.

**Pharmacology - Toxicological assessment of** (b) (4)

**(March 15, 2012)**

**Reviewer:** Donald Jensen, Ph.D.

**Summary:**

The sponsor’s replies are sufficient to address these concerns, with the qualification that the (b) (4) impurity should be controlled to (b) (4) not only in the drug substance but also in the drug product.

**Clinical Pharmacology (January 26, 2012)**

**Reviewer:** Sreedharan Sabarinath, Ph.D.

**Conclusion:** Approval

**Labeling:** Dr. Sabarinath included labeling recommendations in his review.

**Summary:**

Dr. Sabarinath feels the Clinical Pharmacology and Biopharmaceutics information provided is adequate to provide labeling recommendations for droxidopa. The NDA submission can be approved for NOH indication from a clinical pharmacology perspective, provided the available toxicology information on DOPAL is adequate and the observed effect size in orthostatic hypotension questionnaire (OHQ) composite scores in the Phase III trials are considered clinically meaningful.

The Office has the following specific recommendation:

The Office of Scientific Investigations (OSI), which performed clinical and bioanalytical site inspections for pivotal bioequivalence (BE) study 101, concludes that the bioanalytical part of the pivotal BE evaluation between 3 x 100 mg capsules (phase III formulation) and 1 x 300 mg capsules (proposed new formulation) is not reliable (Ref. Memorandum to file by Dr. Jangik I Lee, DARRTS date 24-January 2012). Therefore, the BE results from this study is not acceptable and the new 300 mg capsule formulation cannot be approved based on the above BE study.

**Post Marketing Requirements/Commitments**

Since droxidopa and its metabolites are predominantly renally cleared, a dedicated renal impairment study to assess their exposure in renal impairment (mild, moderate, severe and ESRD) relative to subjects with normal renal function should be required. (Note: The sponsor is currently conducting this study and expects to submit the report post-approval)

**Product Quality (March 22, 2012)**

**Reviewer:** Lyudmila Soldatova, Ph.D.

**Conclusion:** Approval

**Labeling:** Dr. Soldatova included labeling recommendations in her review.

**Summary:**

Dr. Soldatova recommends approval from a Chemistry, Manufacturing and Controls standpoint with pending overall OC recommendation. The drug substance DMF (b)(4) deficiencies, and NDA deficiencies have been resolved; the droxidopa DMF (b)(4) is found adequate. Based on the drug product stability data, the following expiration dating period is recommended: 36 months for Northera™ (droxidopa) Capsules, 100 mg and

200 mg, packaged in [REDACTED] (b) (6)  
[REDACTED] 9-count blister packs. The expiration period for 300 mg capsules packaged in 120 cc HDPE bottles, 21 counts/60 cc bottles and 9 count/40 cc bottles, [REDACTED] (b) (4) is not granted since this dosage strength is not approved by Clin/Pharm reviewer. The overall OC recommendation for drug substance and drug product facilities is currently pending.

**Product Quality Division Director Memo (March 22, 2012)**

**Reviewer:** Ramesh Sood, Ph.D.

**Conclusion:** Approval

**Summary:**

Dr. Sood recommends for approval pending an overall acceptable recommendation from the Office of Compliance.

**Study Endpoints and Labeling Development (SEALD)**

**Reviewer:** Elektra Papadopoulos, M.D., Ph.D.

**Labeling:** Dr. Papadopoulos included labeling recommendations in her review.

**Conclusion: (March 2, 2012)**

Dr. Papadopoulos recommends that if this product is approved based on the current submission, that product labeling should include a cumulative distribution function of only the OHSA Item 1 in order to show patients' responses by treatment group across the entire range of changes (i.e., worsening to improvement). We do not recommend describing OHQ, OHSA or OHDAS scores in product labeling.

On January 13, 2012, the Agency requested additional information regarding interpretation of study results based on the OHSA item 1 (dizziness, lightheadedness) using a responder definition. In response, the sponsor provided a series of tables for interpretation of study results using anchor-based methods for Studies 301 and 302.

The review concludes that the evidence submitted is inadequate to develop confidence in a single best responder definition for OHSA Item 1 in either study. Concordance between the OHSA Item 1 and the patient-reported global assessment is poor. Possible reasons include the fact that (a) the global measure of disease is likely is too general a concept to be used as an anchor for the more specific measure of dizziness/lightheadedness, (b) global measures have inherent concerns with content validity and interpretation, and (c) there were differences in recall period between the two measures. Additionally, the order of assessments was such that patients and investigators first responded to the global assessments, then the orthostatic blood pressure readings were done and finally patients responded to the OHQ. While the clinical protocol included a statement that investigators

were not to inform subjects of their orthostatic blood pressure measurement during the study, this may have been difficult if blood pressure readings were collected using an electronic device or if patients experienced orthostatic symptoms during the procedure.

The challenges related to interpretation of a clinically meaningful benefit highlight the need for well-developed content valid measures for future trials for this indication as well as appropriate study procedures. Patients should respond to the PRO assessments before other study procedures are completed so that these procedures do not influence patients' responses.

A measure that provides a good understanding of how symptoms are related to activities future studies in this disease is needed. The OHQ does not measure symptoms in the context of activities. Instead, symptoms are measured on a simple 11-point scale anchored at each end by none and worst possible while activities are assessed in a separate scale, the OHDAS. As described in our earlier SEALD endpoint review, it is preferable to ask the patients to rate their symptoms (e.g., dizziness or lightheadedness) in the context of typical daily activities that represent different difficulty levels for the disease of interest.

(January 23, 2012)

The qualitative research does not support the content validity of the OHQ score nor its subscales (OHSA and OHDAS).

If droxidopa is approved, we do not advise including a reference to the assessment used to support treatment benefit in the *Indications* section of labeling. Statements that name the OHQ overall score or its subscales (OHSA and OHDAS) should be avoided in all sections of labeling. (b) (4)

Generally, we discourage claims expressed in terms of domain or instrument titles because they often do not represent the concept measured and, in this particular case, we do not have demonstration of the content validity of the overall instrument or its subscales to measure the targeted concepts.

Instead, we recommend that the concept contained in item 1 of the OHSA (Dizziness, lightheadedness, feeling faint, or feeling like you might black out) should be described in the *Clinical Studies* section of product labeling, if droxidopa is approved. We suggest this approach because (a) the symptoms described in item #1 represent core symptoms of NOH; (b) the symptoms described in some of the other items are not documented to be core disease-defining symptoms of OH and present particular difficulties with undocumented validity and interpretation of result; and (c) not all of the symptoms measured were affected by treatment and some symptoms such as imbalance and falling were not measured so a general claim that NOH symptoms were improved is

unsubstantiated. Please also see section 1.2 (Sponsor's Proposed Labeling) for other comments with regard to the description of the OHQ results in labeling.

**CSS (March 2, 2012)**

**Reviewer:** Jovita Randall-Thompson, Ph.D.

**Conclusion:**

Dr. Randall-Thompson did not recommend that NORTHERA (droxidopa, L-threo-3,4-dihydroxyphenylserine, L-Threo-DOPS) be scheduled under the Controlled Substances Act (CSA). As shown, there were no abuse-related signals detected among the adverse event reports collected during Phase I and Phase III placebo-controlled experimental phases.

**REMS Review (February 22, 2012)**

**Reviewer:** Gita A. Toyserkani, Pharm.D., MBA

**Conclusion:**

Dr. Toyserkani recommends a REMS for droxidopa is not warranted at this time and that the risk of supine hypertension can be addressed through labeling. If droxidopa were to be approved, DRISK recommends the following:

- Inform the sponsor that we have determined that, at this time, a REMS is not necessary for droxidopa to ensure that its benefits outweigh its risks. However, the sponsor may voluntarily implement a DHCP letter and additional voluntary measures as proposed (i.e., [REDACTED] (b) (4) [REDACTED]).
- Include the Medication Guide as part of labeling and consider including language to inform patients to elevate the head of their bed to minimize the risk of supine hypertension, as was done in the clinical trials.
- If the risk of supine hypertension associated with droxidopa is comparable to that associated with midodrine, consider maximizing the labeling by prominently displaying the risk in a boxed warning.
- Consider consulting the Division of Epidemiology (DEPI) in OSE to obtain input on the proposed Phase IV study protocol and to evaluate the feasibility of the study.

**Office of Scientific Investigation (February 16, 2012)**

**Reviewer:** Sharon Gershon, Pharm.D.

**Conclusion:**

Dr. Gershon noted the inspections demonstrated that the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Five clinical investigator sites were inspected in support of this application. The sponsor site (Chelsea) was also inspected. The inspectional findings

identified at the 3 sites in Ukraine (#505, #507, #513) were minor, and concerned sporadic instances of failure to follow the protocol, and failure to maintain records with respect to data pertinent to the study. OSI does not consider these violations likely to influence data integrity, study outcome or subject safety. The inspectional items found during inspections at Site #105 (Jancovic, Houston, TX) were minor and isolated and will not importantly influence study or data outcome. There were no regulatory violations identified at Site #103 (Driver-Dunckley, Scottsdale, AZ) or at the Sponsor site (Chelsea). OSI recommends that the data submitted by Chelsea Therapeutics, Inc. may be used in support of the indication.

**OT-IRT (February 16, 2012)**

**Reviewer:** Qianyu Dang, Ph.D.

**Labeling:** Dr. Dang included labeling recommendations in his review.

**Conclusion:**

Dr. Dang noted no significant QTc prolongation effect of droxidopa (600 mg and 2000 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between droxidopa (600 mg and 2000 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4 (please refer to the review) , indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 52 healthy subjects received droxidopa 600 mg, droxidopa 2000 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Droxidopa (600 mg and 2000 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Droxidopa 600 mg	12	3.6	(1.8, 5.3)
Droxidopa 2000 mg	24	3.4	(1.4, 5.5)
Moxifloxacin 400 mg*	3	13.4	(9.9, 16.9)

\*The largest lower bound shows Bonferroni adjustment for 3 timepoints.

The supratherapeutic dose (2000 mg) produces mean  $C_{\text{max}}$  values which are 2-fold the mean  $C_{\text{max}}$  for the therapeutic dose (600 mg). Dose of 2000 mg represents the maximum single dose tested in humans. There is minimal accumulation of the drug upon t.i.d dosing and the steady state  $C_{\text{max}}$  is similar to a single dose  $C_{\text{max}}$  (Appendix 6.1). Studies to assess the effect of intrinsic (hepatic and renal impairment) and extrinsic (drug-drug interaction studies) factors have not yet been conducted. It is likely that renal impairment

may increase drug exposures because based on animal studies, the drug is primarily eliminated renally. The sponsor has submitted a clinical trial protocol to study the PK of droxidopa in renal impairment. This study will include patients with mild, moderate, severe renal impairment and ESRD. At this time with the limited information submitted so far, it is unclear if the suprathreshold dose would cover the exposures expected in patients with renal impairment, though the sponsor mentions that dosing would be adjusted to lower doses and less than t.i.d. in patients with renal failure. It is important to note that no dose adjustments are recommended for mild and moderate renal impaired patients since droxidopa is to be titrated to individualized doses as studied in pivotal trials, which included mild/moderate renally impaired patients.

**Statistical Review of Carcinogenicity (January 24, 2012)**

**Reviewer:** Steve Thomson, Ph.D.

**Conclusion:**

Dr. Thomson reviewed reports from a rat and a mouse studies. The original studies were conducted by (b) (4), at their research center in (b) (4) in 1987-1989 and 1988-1989, respectively. Reports for both studies were completed in 1991. The original rat report states that the object of this study “was to assess the potential carcinogenicity potential of the test material, SM-5688, [when administered] to rats by continuous dietary administration.” (page 13 of 1991 rat report) The mouse report uses the same expression for mice (page 12 of 1991 mouse report). Both studies were reanalyzed for Chelsea in 2011. Results from these reanalyses were summarized in further reports, both completed in 2011.

For both species, treatment was administered by dietary admixture, so assessing actual dose may be difficult. Note, as discussed in Section 1.3.1.1 below, rats were multiply housed together. This may cause problems in interpreting results.

**ONDOA Biopharmaceutics Review (January 13, 2012)**

**Reviewer:** Tien-Mien Chen, Ph.D.

**Conclusion:**

1. The stability batches manufactured were pilot batches, but were >1/10 of the full production ones. The ONDQA (Office of New Drug Quality Assessment) considers that this is acceptable.
2. The above dissolution data showed comparable *in vitro* dissolution results among the drug product using the drug substance manufactured by three different methods. It is also true among three strengths.
3. The sponsor should have evaluated discriminatory ability of the method further to make future changes.

An information request to (b) (4) the dissolution acceptance criterion was sent to the applicant on 12/22/11. On 01/05/12, the applicant agreed with the Agency's proposal and submitted the revised dissolution acceptance criterion of Q= (b) (4) at 20 minutes to update the Module 32P51 specifications.

**Executive CAC Report (January 10, 2012)**

The Committee concurred that the rat study was acceptable and that there were no drug-related neoplasms in rats. For the mouse, the Committee concurred that the study was acceptable, despite the suboptimal duration and concurred that there were no drug-related neoplasms.

**DMEPA**

**Reviewer:** Ray Ford, R.Ph.

In a review dated *January 23, 2012*, DMEPA reviewed the proposed package insert and offered recommendations to the Professional Sample Container Label, Trade Container Label, Blister Pack Outer Carton, Blister Pack Front and Back Label, and to the Highlights or Prescribing Information and Dosage and Administration.

In a review dated *January 4, 2012*, DMEPA reviewed the proposed proprietary name and concluded it is acceptable from both a promotional and safety perspective.

**Action:**

A Complete Response Letter will be drafted and signed by Dr. Unger.

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Anna Park  
Senior Regulatory Management Officer  
March 28, 2012



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** March 2, 2012

**To:** Norman Stockbridge, M.D., Director  
Division of Cardiovascular and Renal Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

Silvia Calderon, Ph.D., Team Leader  
Controlled Substance Staff

**From:** Jovita Randall-Thompson, Ph.D., Pharmacologist  
Controlled Substance Staff

**Subject:** NORTERA and NDA 203202  
**Indication:** Symptomatic neurogenic orthostatic hypotension  
**Dosages:** Capsules 100 mg, 200 mg, and 300mg.  
**Sponsor:** Chelsea Therapeutics, Inc.

**Materials reviewed:** NDA 203202

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**I. Summary**

A. Background

The Division of Cardiovascular and Renal Products (DCRP) consulted the Controlled Substance Staff (CSS) to review NDA 203202, NORTERA (immediate release tablets). The principle active pharmaceutical ingredient of NORTERA is droxidopa, also known as L-Threo-3,4-Dihydroxyphenylserine (L-Threo-DOPS), a new molecular entity (NME).

The recommended starting dose of NORTHERA is 100 mg, administered three times per day (TID) orally. The dose may be increased in increments of 100 mg TID up to a maximum dose of 600 mg TID (i.e., a maximum total daily dose of 1800 mg) at the prescriber's discretion.

The proposed indication of droxidopa is for the chronic treatment of symptomatic neurogenic orthostatic hypotension (NOH), in patients with primary autonomic failure, Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF), Dopamine Beta Hydroxylase (DβH) Deficiency, and Non-Diabetic Autonomic Neuropathy (NDAN). Different standard maintenance doses of droxidopa, which range from 300 mg to 600 mg daily, are recommended for each of these diseases, with doses not to exceed 1800 mg/day. Symptomatic neurogenic orthostatic hypotension is a rare, and often disabling condition that results in symptoms of dizziness, weakness, syncope, and falls. Treatment of NOH is categorized as an orphan indication.

Droxidopa has been marketed in Japan since 1989, for the treatment of orthostatic hypotension (OH), syncope, and dizziness on standing-up accompanied with familial amyloid polyneuropathy (FAP), and MSA, and for the treatment of freezing phenomenon and dizziness on standing-up in PD. In 2000, it was further approved for the alleviation of vertigo, staggering, dizziness on standing-up, lassitude, and weakness in hemodialysis patients with OH.

Droxidopa is an orally active synthetic amino acid that is a precursor for norepinephrine (NE). It is directly converted and metabolized to NE in a single step by DOPA-decarboxylase. The conversion of droxidopa to NE can occur peripherally, and centrally. The manufacturing process includes (b) (4)

The Sponsor submitted data on abuse potential of droxidopa in the NDA that comprises the following. The Sponsor discusses the overall findings, and safety information of several Phase 1 and Phase 3 studies, and several preclinical in vivo, behavioral and toxicology animal studies. Clinical studies included one double-blind, single-center, randomized, cross-over Phase I study (101); two double-blind, multi-center, randomized, open-label, and placebo-controlled Phase 3 studies (primary Study 301, and a supportive Study 302); and two long-term Phase 3 studies, one open-labeled and placebo-controlled (Studies 303) and the other open-labeled only (Study 304). Preclinical investigations included three in vivo studies (Documents C-1-5, C-1-6 and D-2), three behavioral studies (Documents C-1-24, C-1-19 and IB-1), and two toxicological studies (Report B-3-01 and Report B-3-03) that examined the general pharmacologic, general behavioral, and physical dependence effects induced by droxidopa.

## B. Conclusions:

1. The Sponsor did not provide primary data or detailed protocols for each preclinical study. Instead, the Sponsor submitted study report summaries translated from Japanese.
2. The abuse potential assessment of droxidopa relies mainly on the analysis of adverse events reported in Phase I and III clinical trials, consistent with the draft Guidance for Industry – Assessment of Abuse Potential of Drugs, January 2010, <http://www.fda>.

gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

3. We conducted a review of the adverse events reported during Clinical Study 101, and Studies 301 and 302. Clinical Study 101 included a 7-day treatment period, and Studies 301 and 302 included a short-term exposure period (4 - 5 consecutive weeks, a wash-out period then an additional duration of 1 - 3 consecutive weeks) of droxidopa treatment. In reviewing the adverse events reported during these studies no abuse-related adverse events were found during the placebo-controlled experimental phases.
4. Clinical Study 303 included an exposure period to droxidopa treatment that was longer in duration (12 consecutive weeks followed by a 2 week withdrawal phase and a long-term/follow-up open-label phase). The adverse events reported during this study were evaluated for any signal of abuse as well as dependence and withdrawal-related symptoms. No abuse-related signal as well as no dependence and withdrawal-related symptoms were detected during the placebo-controlled/withdrawal experimental phase.
5. We therefore conclude that there is no significant abuse potential associated with the use of droxidopa.

#### C. Recommendations:

1. We do not recommend that NORTHERA (droxidopa, L-threo-3,4-dihydroxyphenylserine, L-Threo-DOPS) be scheduled under the Controlled Substances Act (CSA). As shown, there were no abuse-related signals detected among the adverse event reports collected during Phase I and Phase III placebo-controlled experimental phases.

## II. Discussion

The Discussion section expands on the relevant studies that are the basis for the above conclusions.

#### A. Pharmacology of drug substance and active metabolites

The Sponsor submitted the summaries and findings of preclinical studies that were translated from Japanese. CSS's review of this information is provided below.

##### 1. In vitro studies

The Sponsor submitted summaries of each preclinical in vivo study (Documents C-1-5<sup>1</sup>, C-1-6<sup>2</sup> and D-2<sup>3</sup>) that included brief descriptions each study's purpose and methodology, however primary data and statistical analysis information was not

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<sup>1</sup> "Penetration of L-threo-DOPS, a precursor of norepinephrine, into the brain in various experimental animals" (Translated from Japanese)

<sup>2</sup> "Effects of L-threo-DOPS on catecholamine release in striatum – intracerebral dialysis study" (Translated from Japanese)

<sup>3</sup> Metabolism of L-DOPS in Animals (Translated from Japanese)

included. These studies were designed to elucidate the properties of droxidopa as an NE precursor in the central nervous system. The findings of these studies indicate that the intraperitoneal (IP) administration of droxidopa leads to its distribution to various areas of the brain, and is associated with a central increase in NE and DA levels.

Two of the three in vivo studies were designed to investigate the penetration of droxidopa into the brain by administering (IV or PO) radioactive <sup>14</sup>C-L-Threo-DOPS (10 or 100 mg/kg) into various species of animals (i.e., mice, rats, cats, dogs, and monkeys; Document C-1-5). The third study (Document C-1-6) involved investigating the amount of NE and DA that is released, and distributed in the brain after an injection of droxidopa (IP). Specifically, following injection, droxidopa was found to be slightly higher in the cerebral cortex, and slightly lower in the striatum, and hippocampus, areas of the brain associated with reward. Eighty minutes following injection of droxidopa, NE levels increased 20% to 60%, and for DA, at 100 minutes following an injection of droxidopa, its levels increased 30% to 60%. DA metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) also increased.

The results of these studies indicate that droxidopa after being orally administered is distributed to areas of the brain, and affects neurotransmitter activity that is associated with reward or liking. It is important to point out that the Sponsor did not evaluate the direct effects of droxidopa on all commonly known receptors associated with abuse or addiction, and so pharmacologically, the direct effects of droxidopa on mechanisms known to be directly involved in reward are still not fully understood. Clinical reports, however, do not show a significant pattern of abuse-related adverse events (AEs) correlated with the use of droxidopa. Clinical AE observations provide additional information, and demonstrate that even if it is the case that droxidopa can potentially modulate areas associated with abuse, such as the release of dopamine, the impact of these effects is not high or substantial enough, at the current doses tested, to induce significant abuse-related symptoms linked with abuse, and addiction. In the end, this supports the view that droxidopa has no significant abuse potential.

## 2. General behavioral responses

The Sponsor submitted Document C-1-24<sup>4</sup> that included a review of a series of pharmacological preclinical studies. Included in this series of studies were 11 behavioral studies. The Sponsor provides a summary of each behavioral study that briefly described the methodology, and findings of each study, yet here also, no primary data and statistical analysis were included. Of these studies, there were several behavioral assessments designed to explore the pharmacological effects of droxidopa on inducing or modulating CNS behavior. Some of these behavioral assessments, such as droxidopa-induced effects on general animal reactions, locomotor activity, motor coordination, muscle relaxation, and analgesia provide evidence to characterize the overall effects of droxidopa in the CNS.

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<sup>4</sup> General Pharmacology of (-) – (2S,#R) -2- Amino -3- hydrooxy-3-(3,4-Dihydroxyphenyl) propionic acid (L-Threo-DOPS) (Translated from Japanese)

The Sponsor reported that no substantial effects were noted in rats or mice when given droxidopa or the metabolite of droxidopa, 3-methoxy-4-hydroxy-phenylserine (3-OM-DOPS). Specifically, using an Irwin assessment, which evaluates the effects of a substance on general behaviors, the Sponsor reported that there were no changes in gross behavior. Using other studies, the Sponsor also reports no changes in locomotor activity, and no effects on both motor coordination, and muscle relaxation. The Sponsor claims that no effect on a model of analgesia (writhing test) was observed, however, no data was provided to support this finding.

Considering the limited amount of information provided by the Sponsor, the behavioral findings are considered at face value, and provide a general description of the overall central nervous system pharmacology of the drug.

### 3. Animal behavioral studies

The Sponsor submitted two separate summaries (Documents C-1-19<sup>5</sup> and IB-1<sup>6</sup>) on two separate preclinical behavioral studies designed to explore the pharmacological effects of droxidopa on operant or learning behavior. Each summary was translated from Japanese, and briefly described the methodology, and overall findings of each operant behavioral study. Primary data and statistical analysis were not provided.

One of the studies refers to a lever-press operant experiment with a food pellet as a positive reinforcement, and examined the effects of droxidopa in fixed-rate (FR-20), fixed-interval (FI-60 sec), and differential-reinforcement-of-low-rate (DRL-20 sec) schedules in comparison with tricyclic antidepressants imipramine (Document IB-1), which has an inhibitory action of NE uptake. The Sponsor also compared droxidopa's operant effects to L-DOPA (Document IB-1) using the same paradigm.

Findings reported in each of the food operant studies indicated that droxidopa is similar to imipramine, an SSRI, and not as similar to L-DOPA, a DA agonist.

As described above, the two operant studies submitted by the Sponsor do not directly assess the reinforcing effects of droxidopa. A self-administration study directly examining the reinforcing effects of a drug involves animals bar pressing to receive an injection of the test drug. In this case, animals were trained to bar press for food. Specifically, the operant studies submitted by the Sponsor are second-order scheduling or chained scheduling paradigms. By testing and comparing a drug with an unknown mechanism (NME, i.e., droxidopa) to a drug with a known mechanism examined extensively (i.e., imipramine) within a second-order schedule, results from such a study inform as to whether the test drug is similar in mechanism to a known drug.

The findings from the two operant studies provided by the Sponsor show that the effects of droxidopa are more similar to the effects mediated by imipramine, which is a drug that has a low abuse potential, and is not scheduled rather than L-DOPA, a

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<sup>5</sup> Effects on Operant Behavior, Rat/Sprague Dawley, Sumitomo Pharmaceutical Co., Ltd. (Translated from Japanese)

<sup>6</sup> Effects Of L-Threo-3,4-Dihydroxyphenylserine (L-Threo-DOPS), A NE Precursor, On Operant Behavior In Rats, Rat/Sprague Dawley, Sumitomo Pharmaceutical Co., Ltd. (Translated from Japanese)

drug known to increase dopamine. This is evidence that supports our view that the acute use of droxidopa has a very low or no abuse potential.

#### 4. Physical dependence study

In their Abuse Potential Assessment document, the Sponsor provided a brief summary of toxicological findings collected after the discontinuation of droxidopa. The Sponsor discusses findings from these two toxicological studies (Report B-3-01<sup>7</sup> and Report B-3-03<sup>8</sup>) as a means to evaluate physical dependence. Both studies were not specifically designed to assess the physical dependence of droxidopa. Rather, the studies are designed to evaluate the toxic effects of droxidopa at various doses, not only after its discontinuation, but mainly when the drug is at peak levels in the blood. In the Abuse Potential Assessment document, the Sponsor makes the case that since there were no reported toxic effects that signaled dependence, and withdrawal during the drug discontinuation phase of each study, these findings support the view that there is no physical dependence linked to droxidopa use.

CSS reviewed each study report to verify the Sponsor's claims. The toxicological assessment involved a total of 100 Sprague-Dawley rats initially given 0, 10, 30, and 100 mg/kg/day of droxidopa (Report B-3-01), and a total of 30 dogs initially exposed to 0 and 2000 mg/kg/day of droxidopa (Report B-3-03). Droxidopa was given orally. Animals were observed daily for signs of toxic effects during the discontinuation (treatment-free or reversibility phase) of droxidopa. A match placebo control group was utilized in both studies. As previously discussed, a drug exposure phase was conducted as well, but these findings were not included in this assessment. No significant or relevant signs of abuse-related toxic effects were found during droxidopa administration or its discontinuation with rats or dogs.

Thus, as indicated by the Sponsor there were no signs of physical dependence or withdrawal upon the cessation of chronic dosing in rats and dogs.

Overall, preclinical information shows that the administration of droxidopa is not associated with abuse, tolerance or physical dependence and withdrawal.

### B. Clinical Studies

1. An evaluation of droxidopa's adverse events collected during Phase 1 and 3 clinical trials (no Phase 2 studies were performed) showed no significant pattern of AEs that are associated with abuse potential.

Three studies were included in our analysis. These studies are placebo controlled safety, and efficacy Study 301<sup>9</sup>, and Study 302<sup>10</sup>, and Pharmacokinetic Study 101<sup>11</sup>.

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<sup>7</sup> SM-5688: 52-week toxicity and 12-week reversibility study in oral administration to CD rats, final report (Translated from Japanese)

<sup>8</sup> Chronic toxicity study in dogs Sm-5688, final report (Translated from Japanese)

<sup>9</sup> A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Induction-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

<sup>10</sup> A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Withdrawal-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension: Pharmacodynamic Analysis

Studies 301 and 302 included 444 patients with PD, MSA and PAF, DBH Deficiency or NDAN. Studies 301, and 302 included an open-label phase (4 to 5 weeks; N = 444), and a double-blind placebo control phase (2 weeks; N = 261). Study 101 included 23 healthy volunteers and included a double-blind placebo control phase only. Across these studies, patients received doses of droxidopa ranging from 100 mg to 2000 mg/day. During the placebo-control phase of the clinical studies (101, 301, and 302) a total of 154 patients were given 1 to 2 weeks of droxidopa treatment. Dizziness was the most commonly reported AE, which is an expected adverse event in the studied population. There were 3 hallucination events, two visual (1.1%, N = 2 out of 181 subjects), and one auditory (0.6%, N = 1 out of 181 subjects) in nature, reported during open-label testing in Study 302 (also see, NDA 203202, Melanie J, Clinical Review, DARRTS, 01/27/2012, pg 138). All three hallucinations were documented as mild in severity. There were no abuse related events reported during the placebo control phases of Study 301 and 302.

In addition, the Sponsor submitted AE reports collected from postmarketing surveys conducted between January 1989 through January 1995 (Module 5, Japanese Post-Marketing Report, R1-Overview). From the droxidopa postmarketing experience, a total of 131 (7.2%) out of 1819 patients surveyed reported a total of 194 AEs. One of the most frequently reported AEs collected during the first 6 years of the post-marketing survey (N=1819) was hallucination with 14 (<1%) out of the 194 events being reported. Hallucinations were reported as being mild (N = 6), moderate (N = 6) or severe (N = 2), and occurring in a range of 3 to 351 days after treatment initiation (Module 5, Japanese Post-Marketing Report, R1-Overview, Table III-1-23). Patients ranged in age between 60 and 86 all having a primary diagnoses of PD, however, it was not specified whether or not each patient experienced more than one hallucinatory event. The hallucinations were possibly related to droxidopa treatment or to other concomitant medications. Certain concomitant medications, used by this population, such as levodopa and carbidopa, are associated with hallucination adverse-related symptoms (see NDA 203202, Melanie J, Clinical Review, DARRTS, 01/27/2012). The Sponsor however, does specify, in the Abuse Potential Assessment document in the NDA that all postmarketing findings were forwarded to them in “abbreviated reports with no individual patient data listings, limited summary tables, no coding of AEs to a standard medical dictionary, and no electronic data or analyses files (pg 43)”. In addition, the doses of droxidopa used by patients in these surveys were lower (i.e., 200 to 900 mg/day) than the highest dose (1800 mg/day) recommended in the currently proposed NDA application for droxidopa. As a result, the postmarketing findings do not provide any relevant information on droxidopa’s abuse-related effects or risks.

Overall, there was a lack of abuse-related adverse events reported with the use of droxidopa.

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<sup>11</sup>A Randomized, Open-Label, Three-Period, Three-Sequence, Single-Dose Crossover and Separate Three-Daily-Dose Treatment Period Study Comparing the Pharmacokinetic Profiles Following Oral Dosing of 300 mg of Droxidopa in the Fed versus Fasted State, the Bioequivalence of Three 100 mg capsules of Droxidopa versus a Single 300 mg Capsule of Droxidopa, and 300 mg of Droxidopa Administered Three Times at Four Hour Intervals in Healthy, Elderly Subjects.

2. The Sponsor submitted their own separate analysis of AEs collected during two long-term extension clinical trials, Studies 303<sup>12</sup>, and 304.<sup>13</sup> AE findings of Study 303 and 304 (see Abuse Potential Assessment document, pg 12) were combined. The study design differences between these two studies, however, weaken the validity of the analysis. Mainly, Study 304 does not include a placebo-control phase. Study 303 was reviewed separately from Study 304. In addition, the list of AEs collected for each phase of Study 303 was evaluated separately.

Experimental phases of Study 303 (N = 102) included the open-label (12 weeks), placebo-control withdrawal (2 weeks) and long-term/follow-up open-label phase (12 weeks). All patients entered this study from a prior droxidopa study (Study 301 or Study 302). During the placebo-control phase of Study 303, a total of 38 patients were given 2 weeks of droxidopa treatment.

When separating out those AEs collected during the placebo-control withdrawal phase, there weren't any AEs that signaled droxidopa physical dependence due to its continued use. While, as for the open-label and long-term open-label phase, there were AEs reported that signaled a possible low risk of abuse with the long term use of droxidopa.

For Study 303, the most commonly reported individual AEs that possibly signaled abuse were somnolence (4.9%, 5 patients out of N = 102), and hallucination (2.9%, 3 patients out of N = 102), and visual hallucination (1%, 1 patients out of N = 102) (Study 303, End of Study Analysis, Table 26.1.1). However, these AEs were reported during the three-month open-label phase of Study 303, and these events can't be attributed to droxidopa. The Sponsor indicates that in the long-term extension studies (303 and 304), 54 of 301 (17.9%) patients reported 104 SAEs (Section 2.7.4 Table 2-9 and ISS Table 2.2.3). Of the SAEs altered state of consciousness, agitation, anxiety, confusional state, hallucination, hallucination visual, and mental status changes, (all occurring in one patient, 0.3%) were SAEs that under different circumstances, such as a drug with an overt central nervous system activity, could potentially be interpreted as an abuse signal.

Overall, there was a lack of abuse-related adverse events reported with the use of droxidopa.

### 3. Overdose Prevalence

The Sponsor indicated no overdoses in their clinical studies with droxidopa. A further review by CSS of studies 101, 301, 302, and 303, studies that included a placebo control treatment, and Study 304, also indicated no reports of overdose at any droxidopa dose tested. There was one case of overdose reported postmarketing in Japan. The Sponsor does report one incidence of overdose by a patient that ingested 7700 mg of droxidopa, and experienced a hypertensive crisis that resolved promptly

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<sup>12</sup> A Multi-Center, Open-Label Study With a Two-Week Randomized, Placebo-Controlled Withdrawal Period to Assess the Long-term Safety and Clinical Benefit of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

<sup>13</sup> A Multi-Center, Open-Label Study To Assess the Long Term Safety of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

with treatment. This incident occurred, and was initially reported during post-marketing.

4. Evidence of misuse and diversion in clinical trials

In the clinical trial databases, there were no statistical or programmatic tests or algorithms specified to track if a patient reported “lost” bottles of drug or if a patient requested drug early after “running out”. The Sponsor conducted a post hoc review of the dataset, including a complete review of the listings for study medications. There are no known cases of diversion or tampering identified in the droxidopa clinical trials. An examination of patients who took more than the expected amounts of drug across all clinical trials revealed that there were 17 patients of 476 (3.6%) who were calculated to have taken more or unaccounted for, than 120% of their expected doses. An examination of drug accountability and dosing records for these patients did not reveal any evidence of drug hoarding or drug abuse behavior.

Adverse events that lead to study drug discontinuation by patients were reported in Study 303 and 304. For Study 304, one AE leading to study discontinuation reported for Study 303 included 2 AEs, visual hallucination (one patient, moderate severity), hallucination (unspecified, 1 patient, moderate severity). Additional cases (38 AEs) were reported by the Sponsor (Abuse Potential Assessment, pg 30). Given that patients were given concomitant medications during testing, the additional AEs reported could be due to the effects of another medication.

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/s/  
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JOVITA F RANDALL-THOMPSON  
03/02/2012

SILVIA N CALDERON  
03/02/2012

LORI A LOVE on behalf of MICHAEL KLEIN  
03/02/2012

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2011-118 (addendum)
APPLICATION NUMBER	NDA 203202
LETTER DATE/SUBMISSION NUMBER	Sequence 0022; February 6, 2012
PDUFA GOAL DATE	March 28, 2012
DATE OF CONSULT REQUEST	October 17, 2011
REVIEW DIVISION	DCARP
MEDICAL REVIEWER	<b>Melanie Blank</b>
REVIEW DIVISION PM	Anna Park
SEALD REVIEWER(S)	<b>Elektra J. Papadopoulos</b>
REVIEW COMPLETION DATE	<b>January 23, 2012</b>
DATE OF ADDENDUM	<b>February 28, 2012</b>
ESTABLISHED NAME	Droxidopa
TRADE NAME	Northera
APPLICANT	Chelsea Therapeutics, Inc.
ENDPOINT(S) CONCEPT(S)	Symptoms and symptom impacts associated with neurogenic orthostatic hypotension (NOH)
MEASURE(S)	Orthostatic Hypotension Questionnaire (OHQ)
CLINICAL OUTCOME ASSESSMENT TYPE	<b>PRO</b>
INDICATION/INTENDED POPULATION(S)	Symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure (Parkinson's disease, multiple symptom atrophy, and pure autonomic failure), dopamine beta hydroxylase deficiency, or non-diabetic autonomic neuropathy

## SEALD Review

Elektra J. Papadopoulos, MD, MPH

NDA 203202

Droxidopa

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### A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as an addendum to a previous SEALD review regarding NDA 203202 dated January 23, 2012 on the Orthostatic Hypotension Questionnaire (OHQ), which is comprised of the Orthostatic Hypotension Symptoms Assessment (OHSA) and Orthostatic Hypotension Daily Activity Scale (OHDAS). As previously stated, we recommend that if this product is approved based on the current submission, that product labeling should include a cumulative distribution function of only the OHSA Item 1 in order to show patients' responses by treatment group across the entire range of changes (i.e., worsening to improvement). We do not recommend describing OHQ, OHSA or OHDAS scores in product labeling.

On January 13, 2012, the Agency requested additional information regarding interpretation of study results based on the OHSA item 1 (dizziness, lightheadedness) using a responder definition. In response, the sponsor provided a series of tables for interpretation of study results using anchor-based methods for Studies 301 and 302.

The review concludes that the evidence submitted is inadequate to develop confidence in a single best responder definition for OHSA Item 1 in either study. Concordance between the OHSA Item 1 and the patient-reported global assessment is poor. Possible reasons include the fact that (a) the global measure of disease is likely is too general a concept to be used as an anchor for the more specific measure of dizziness/lightheadedness, (b) global measures have inherent concerns with content validity and interpretation, and (c) there were differences in recall period between the two measures. Additionally, the order of assessments was such that patients and investigators first responded to the global assessments, then the orthostatic blood pressure readings were done and finally patients responded to the OHQ. While the clinical protocol included a statement that investigators were not to inform subjects of their orthostatic blood pressure measurement during the study, this may have been difficult if blood pressure readings were collected using an electronic device or if patients experienced orthostatic symptoms during the procedure.

The challenges related to interpretation of a clinically meaningful benefit highlight the need for well-development content valid measures for future trials for this indication as well as appropriate study procedures. Patients should respond to the PRO assessments before other study procedures are completed so that these procedures do not influence patients' responses.

A measure that provides a good understanding of how symptoms are related to activities future studies in this disease is needed. The OHQ does not measure symptoms in the context of activities. Instead, symptoms are measured on a simple 11-point scale anchored at each end by none and worst possible while activities are assessed in a separate scale, the OHDAS. As described in our earlier SEALD endpoint review, it is preferable to ask the patients to rate their symptoms (e.g., dizziness or lightheadedness) in the context of typical daily activities that represent different difficulty levels for the disease of interest.

## SEALD Review

Elektra J. Papadopoulos, MD, MPH

NDA 203202

Droxidopa

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## B. REVIEW OF RELATIONSHIP BETWEEN PATIENT-REPORTED CGI-S AND THE OHQ ITEM #1 (DIZZINESS)

### Study 301:

In Study 301, a total of 162 patients were treated in an open-label titration phase lasting up to 14 days, washed out for a period of 7 days, and then randomized (1:1) at Visit 4 to either droxidopa or placebo for the double-blind treatment phase of the study lasting 7 days. Visit 5 was the end-of-study visit and Visit 2 was the baseline visit prior to the open-label dose titration.

**Table 1 Mean OHSA Item #1 change scores (Visit 5-Visit 2) by changes in Patient-reported CGI-S\* (Study 301)**

CGI-S	N	Mean OHSA Item #1 Change (SD)	95% CI
Improve $\geq$ 2 grade	55	-4.29 (2.33)	( -4.92, -3.66 )
Improve 1 grade	45	-2.49 (2.18)	( -3.14, -1.83 )
No change	45	-1.93 (2.93)	( -2.81, -1.05 )
Worse 1 grade	11	0.09 (2.30)	( -1.45, 1.64 )
Worse $\geq$ 2 grade	4	-0.25 (4.27)	( -7.05, 6.55 )

\***Patient CGI-S:** How severe is your orthostatic hypotension (OH) at this time?

1 (normal, no OH); 2 (borderline OH); 3 (mild OH); 4 (moderate OH);

5 (marked OH); 6 (severe OH); 7 (most extremely ill with OH)

At Visit 5, the mean OHSA Item 1 response improved by nearly 2 points among those patients whose patient-reported CGI-S showed no change. Patients were to respond to the OHSA Item 1 using whole numbers from 0-10.

*Reviewer's comments: The reasons for this discordance between CGI-S and OHSA Item 1 are unclear. The two instruments have several differences that could have led to the observed discordance. The CGI-S is asking a more general question than is the OHQ-Item 1 and the recall period for the CGI-S is "at this time" whereas the recall period for the OHSA Item 1 is over the previous week. Additionally, the order of assessments was such that patients and investigators first responded to the global assessments, then the orthostatic blood pressure readings were done and finally patients responded to the OHQ. While the clinical protocol included a statement that investigators were not to inform subjects of their orthostatic blood pressure measurement during the study, this may have been difficult if blood pressure readings were collected using an electronic device or if patients experienced orthostatic symptoms during the procedure.*

## SEALD Review

Elektra J. Papadopoulos, MD, MPH

NDA 203202

Droxidopa

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### Study 302:

In Study 302, which used a randomized withdrawal design, all patients were treated with open-label droxidopa following Visit 2 (Study Baseline). This included a 2-week titration period followed by a 1 week treatment period. At Visit 4, a total of 101 patients were randomized (1:1) to either to either continue droxidopa or to switch to placebo in a double-blind phase and were reassessed at the end-of-study visit (Visit 5). Patients randomized to placebo were hypothesized to experience worsening on the OHQ items and scales in comparison with patients randomized to continue droxidopa. In the following table, mean values for OHSA Item 1 are described for the entire study population (both groups combined); Visit 5 (end of study visit) is compared with Visit 2 (baseline).

**Table 2 Mean OHSA Item #1 change scores (Visit 5-Visit 2) by changes in Patient-reported CGI-S\* (Study 302)**

CGI-S	N	Mean OHSA Item #1 Change (SD)	95% CI
Improve $\geq$ 2 grade	49	-4.41 (2.80)	( -5.21, -3.60 )
Improve 1 grade	24	-2.54 (2.36)	( -3.54, -1.55 )
No change	15	-1.00 (2.30)	( -2.27, 0.27 )
Worse 1 grade	5	0.8 (1.79)	( -1.42, 3.02 )
Worse $\geq$ 2 grade	7	2.29 (2.87)	( -0.37, 4.94 )

\*Patient CGI-S: How severe is your orthostatic hypotension (OH) at this time?

1 (normal, no OH); 2 (borderline OH); 3 (mild OH); 4 (moderate OH);

5 (marked OH); 6 (severe OH); 7 (most extremely ill with OH)

In Study 302, the OHSA Item 1 shows improvement (Visit 5-Visit 2), on average, by 1 point, among those patients who did not show any change on the patient-reported CGI-S and the 95% confidence intervals for mean change in OHSA Item 1 overlap with those patients who showed a change of 1 unit on the CGI-S.

*Reviewer's comment: We cannot state with confidence what a minimal clinically meaningful difference is on the OHSA Item 1. We recommend that if this product is approved, that product labeling includes a cumulative distribution function of the OHSA Item 1 in order to shows the cumulative proportion of patient response by treatment group across the entire range of patient response (i.e., worsening to improvement).*

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ELEKTRA J PAPADOPOULOS  
03/02/2012

LAURIE B BURKE  
03/02/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL INSPECTION SUMMARY

DATE:

TO: Anna Park, Regulatory Health Project Manager  
Melanie Blank, M.D., Medical Officer  
Division of Cardio-Renal Drug Products

FROM: Sharon K. Gershon, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Thompson, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203202

APPLICANT: Chelsea Therapeutics, Inc

DRUG: Northera<sup>®</sup> (droxidopa) tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

PROTOCOL: **Study 301**: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Induction-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic

## Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

INDICATION: treatment of symptomatic neurogenic orthostatic hypotension (NOH)

CONSULTATION REQUEST DATE: October 12, 2011

INSPECTION SUMMARY GOAL DATE: February 15, 2012

DIVISION ACTION GOAL DATE: March 28, 2012

PDUFA DATE: March 28, 2012

**I. BACKGROUND:**

Chelsea Therapeutics, Inc. (Sponsor) obtained the right to develop and seeks marketing approval for NDA 203202 (droxidopa) in the U.S. for treatment of symptomatic neurogenic orthostatic hypotension (NOH), associated with several diseases (see below).

Droxidopa is an orally administered, synthetic catecholamine acid that is converted to norepinephrine (NE) through a single step of decarboxylation. Missing or low levels of NE are believed to be an important factor in the development of NOH.

NOH is a major manifestation of several diseases that are associated with chronic primary autonomic failure (CAF), which includes conditions such as pure autonomic failure, multiple system atrophy, and Parkinson's disease. In patients who suffer from NOH, the signs and symptoms of the condition can be severely disabling. In addition to symptoms of central nervous system (CNS) hypoperfusion such as dizziness, blurred vision, and impaired cognition, many patients experience recurrent falls. In aggregate, the symptomatic consequences of NOH can substantially reduce patients' quality of life. Due to lack of safe and clinically effective options for the treatment of NOH, there is a significant unmet need for pharmacotherapies that provide clinical benefits and have a favorable side effect profile.

Current pharmacological treatment options for symptoms of NOH include midodrine, fludrocortisone, pyridostigmine, methylphenidate, ephedrine, indomethacin, and dihydroergotamine. Of these agents, only midodrine is approved for the treatment of NOH in the U.S., and in some countries in the European Union (EU). However, the use of midodrine is associated with issues regarding clinical benefits. The initial approval of midodrine was only based on the drug's ability to increase standing systolic BP rather than on a demonstration of its clinical benefits in regards to either improving the symptoms of NOH or positively affecting patients' ability to perform daily activities. Although new studies are being developed, the FDA proposed to withdraw approval of midodrine in 2010, because required post-market studies to verify clinical benefit were not completed. Midodrine is also limited by an unfavorable safety profile that includes a black box warning for supine hypertension.

The clinical development program for NDA 203202 consists of two Phase III studies: one pivotal (**Study 301**) and one supportive (**Study 302**), in addition to 2 ongoing, long-term safety studies (Studies 303 and 304), and a completed, 24-hour ambulatory blood pressure study (Study 305).

To measure clinical benefit and assess improvement in the symptoms of NOH, the Sponsor used the Orthostatic Hypotension Questionnaire (OHQ), which consisted of two components: an OH System Assessment (OHSA) and an OH Daily Activity Scale (OHDAS). The Sponsor used the individual and composite scores of the OHSA and OHDAS to assess improvements in both symptoms and function, and these were considered as acceptable endpoints by FDA.

#### **STUDY 301:**

Study 301 was a multi-center, multi-national, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose titration prior to a 7-day washout period, followed by a 7-day double-blind randomized treatment period. A total of 263 patients were titrated to determine responders, and 168 patients were randomized. The full analysis set consisted of 162 subjects (80 placebo, 82 droxidopa).

#### **Study Objectives:**

The primary objective of Study 301 was to evaluate the efficacy of droxidopa in patients with symptomatic NOH as measured by the relative mean change in the composite of OHQ score 7 days following randomization. The secondary objectives included: symptom and activity measurements using the composite scores of the OHSA and OHDAS; clinician and patient-recorded Clinical Global Impression (CGI) Severity and Improvement Scales – (CGI-S and CGI-I); changes in systolic blood pressure and diastolic blood pressure measurements 3 minutes post-standing; and safety.

#### **Results:**

The change in the OHQ composite score from randomization to the end of the study showed statistically significant benefits favoring droxidopa. At the end of the study, droxidopa patients had a mean decrease of 1.83 points in the OHQ composite score compared with a 0.93 point decrease in the placebo patients, resulting in an approximate treatment difference of -0.90 points favoring droxidopa. Droxidopa also showed significant improvement over placebo in four individual items of the OHSA: dizziness, vision, weakness, and fatigue. Significant differences were not observed for the items of concentration and head/neck discomfort.

#### **DOSAGE ADMINISTRATION:**

The recommended starting dose of droxidopa is to be 100 mg three times per day (TID), titrated to the desired degree of symptom relief in increments of 100 mg, up to a maximum dose of 600 mg TID (maximum total daily dose of 1800 mg). The dosage may be adjusted daily according to the patient's symptoms. Both supine and standing blood pressures should be monitored at regular intervals during titration, and dose escalation should be discontinued if blood pressure rises excessively.

**RESULTS (by Site):** For GCP inspections, two U.S. sites and three non-U.S. sites were selected. As this was an NME, OSI completed a Sponsor inspection. Site selection was based on a combination of the review division's analysis of efficacy and risk assessment using the Risk-Based Site Selection Tool. Specific reasons for inspection included: better treatment effect (Eastern European sites 505, 507, 513), high number of protocol violations at U.S. Site #105 (Houston) and better treatment effect in the placebo arm at Site #103 (Arizona).

<b>Name of CI or Sponsor</b>	<b>Protocol # and # of Subjects enrolled</b>	<b>Inspection Date</b>	<b>Final Classification</b>
<b>Site 505</b> Dr. Volodymyr Lebedynets Kharkiv, 61018, Ukraine	Study 301 12 subjects	01/16/2012 – 01/18/2012	Preliminary VAI
<b>Site 507</b> Prof. Lyudmyla Dzyak Dnipropetrovsk, Ukraine	Study 301 19 subjects	01/20/2012 – 01/25/2012	Preliminary VAI
<b>Site 513</b> Prof. Valeryi Bitensky Odessa 65006 Ukraine	Study 301 7 subjects	1/27/2012 – 1/30/2012	Preliminary VAI
<b>Site 105</b> Joseph Jankovic, MD Baylor College of Medicine Houston, TX 77030	Study 301 8 subjects	1/24/2012 – 1/30/2012	Preliminary VAI
<b>Site 103</b> Erika D. Driver-Dunckley, MD Mayo Clinic Arizona Scottsdale, AZ 85259	Study 301 7 subjects	01/11/2012 – 01/18/2012	Preliminary NAI
<b>Chelsea Therapeutics, Inc.</b> 3530 Torringdon Way Charlotte, NC 28277	Study 301 Sponsor	01/18/2012- 01/19/2012	Preliminary NAI

#### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

#### 1. **Dr. Volodymyr Lebedynets**

State Treatment and Prophylactic Institution

Central Clinical Hospital Ukrzaliznytsi, Neurology Department No. 15, Balakireva provulok, Kharkiv, 61018, Ukraine

**a. What was inspected:** The inspection was conducted in accordance with Compliance Program (CP) 7348.811. There were 12 subjects enrolled at this site. The field investigator did a 100% data audit of all 12 subjects enrolled at this site, including review of inclusion and exclusion criteria, efficacy assessments, electronic case report forms (eCRFs), source documents, drug accountability records and AE reporting.

**b. General observations/commentary:** A two-observational item, Form FDA 483 was issued for the following regulatory violations: a) 21 CFR 312.60: investigation not conducted in accordance with the investigational plan; and b) 21 CFR 312.62(b): failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

With respect to Observational Item 1 (21 CFR 312.60), the following were noted:

1. According to the protocol, randomization will take place at Visit #4 (following the 7-day washout period). For Patient #1, the Progress Notes document that the patient was randomized and assigned randomization number 0037 at Visit #2 (prior to titration and washout).

**OSI Reviewer Comments:** Not having a full seven day washout period might affect the results of the OHQ composite score, showing a more favorable treatment effect for droxidopa. However, only a single subject had a shortened washout period reported, therefore this isolated finding is unlikely to significantly impact study outcome.

2. According to the protocol, patients were expected to begin the double-blind randomized treatment following a washout period of seven days. The inspection found that 2 of 12 patients could not be randomized and begin the blinded treatment after the 7 day washout period because there was an inadequate supply of study medication. For example:
  - i) Patient #6 completed the washout period and randomization was attempted on July 16, 2009. The Progress Notes document that the IVR system informed the site that randomization could not be performed due to lack of study medication. Randomization was subsequently performed on July 21, 2009 (5 days later).
  - ii) Patient #11 completed the washout period and randomization was attempted on August 31, 2009. The Progress Notes document that the IVRS informed the site that randomization could not be performed due to lack of study medication. Randomization was performed on September 4, 2009 (5 days later).
3. According to the protocol, patients must not take antihistamines during the study. Progress Notes document that Patient #11 took a medication containing

chlorpheniramine during the study (frequency and dosage unknown at this time).

4. According to the protocol, screening procedures should be conducted within 7 days of the start of dose titration (Visit #3). Source documents documented that the Screening Visit for Patient #1 was on May 12 2009, and Visit 3a occurred on May 22, 2009 (10 days later).

With respect to Observational Item 2 [(21 CFR 312.62(b))], the field investigator noted minor inconsistencies between Progress Notes and Case Report Forms.

For example:

1. Progress Notes document that Patient #1 was administered the morning dose of study medication at 9:30 am on May 22, 2009, whereas the CRF states the dose was administered at 9:20 am.
2. The Visit 4 Orthostatic Standing Test, the Orthostatic Hypotension Questionnaire and the Clinician-recorded and Patient-recorded CGI for Patient #6 are dated July 21, 2009. According to the corresponding CRF, these items were done on July 16, 2009.
3. The Visit 4 Orthostatic Standing Test, the Orthostatic Hypotension Questionnaire and the Clinician-recorded and Patient-recorded CG Impressions for Patient #11 are dated September 4, 2009. According to the corresponding CRF, these items were done on August 31, 2009.

Dr. Lebedynets provided a written response to the Form FDA 483, Inspectional Items in a letter dated February 7, 2012. As per his response, Dr. Lebedynets acknowledged the deficiencies and promised corrective action. OSI considers his response acceptable.

**c. Assessment of data integrity:** Although regulatory violations were noted during the inspection; the findings are unlikely to significantly impact data integrity. The findings appear limited and sporadic in nature and there is no evidence to suggest that errors occurred in a systemic manner. In general, the inspectional findings notwithstanding, the study appears to have been conducted adequately, and, the data generated by this site may be used in support of the respective indication.

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

**2. Prof. Lyudmyla Dzyak**

Dnipropetrovs'k State Medical Academy,  
Chair of Nervous Disease and Neurosurgery of the Faculty of Post-Diploma Education  
(FPE)  
9, Dzerzhynskogo Str., Dnipropetrovsk, 49044, Ukraine

**a. What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The site enrolled 19 subjects into the study. The field investigator reviewed the following records for all 19 subjects at this site: source data verification; inclusion and exclusion criteria; adverse events; review of CRFs, and questionnaires, and corroboration with CRFs and data listings; and drug accountability records.

**b. General observations/commentary:** A 2-observational Form FDA-483 was issued at the end of the inspection for the following regulatory findings: a) 21 CFR 312.60: investigation not conducted in accordance with the investigation plan; and b) 21 CFR 312.62(b): failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

With respect to Observational Item 1 (21 CFR 312.60), the inspection noted the following:

1. The protocol required patients to begin the double-blind randomized treatment after a washout period of seven days. The inspection found that 3 of 16 patients could not begin the blinded treatment after the 7 day washout period because there was an inadequate supply of study drug on site. For example:
  - i) Patient #13 completed the washout period and randomization was attempted on June 11, 2009. As per the IVRS, randomization could not be performed due to lack of study drug on site. Randomization was performed on June 24, 2009 (20 days later).
  - ii) Patient #14 completed the washout period and randomization was attempted on June 15, 2009. As per the IVRS, randomization could not be performed due to lack of study drug on site. Randomization was performed on June 30<sup>th</sup>, 2009 (23 days following the washout period).
  - iii) Patient #15 completed the washout period and randomization was attempted on June 15, 2009. The IVRS informed the site that randomization could not be performed due to lack of study medication on site. Randomization was performed on July 3, 2009 (a washout period of 26 days).
2. The protocol required that BP be measured immediately *prior* to standing during the orthostatic standing test. The medical records for Patient #1 document the BP was measured immediately *after* standing during the orthostatic standing test at Visit #1 and Visit #2.

With respect to Observational Item 2 (21 CFR 312.62(b)), the inspection noted the following:

1. In the documentations of the orthostatic standing test, the times associated with the blood pressures and heart rates were prospectively entered in at least 3 instances: for Patient #7 at Visits #3b and 3c; and for Patient #15 at Visit #1.
2. For Patient #8, the CRF documents that she began taking Valeriana on May 26, 2009 to treat the adverse event of anxiety and tremor in the hands and that treatment was ongoing; whereas medical records document that the patient was *advised* to take Valeriana, but there was no documentation that the patient began taking the drug.
3. The drug storage records failed to include the initials of the person recording daily measurements of temperature between September 17, 2009 and October 2, 2009.

**c. Assessment of data integrity:** Regulatory violations were noted during the inspection; however, these are unlikely to significantly impact data reliability. The findings observed during the inspection appear limited and sporadic in nature, and there is no evidence to suggest that errors occurred in a systemic manner. With the exception of items noted above, the study appears to have been conducted adequately, and, the data generated by this site may be used in support of the respective indication.

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

### 3. Prof. Valeryi Bitensky

Odessa Regional Clinical Psychiatric  
Hospital #1  
Males and Females Departments  
Odessa State Medical University  
Cathedral of Psychiatry  
9, Ac. Vorobyeva Str.  
Odessa 65006 Ukraine

**a. What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The site enrolled seven subjects into the study. The inspection did a 100% data audit of all 7 patients screened at this site. Only one patient completed here - due to the sponsor stopping enrollment in Ukraine as per protocol. According to the field investigator, "The medical monitor decided Patient #1 did not complete the study because the patient refused to do the final ECG."

**b. General observations/commentary:** The field investigator issued a 1-observational FDA-483 for failure to prepare or maintain adequate case histories with respect to data

pertinent to the investigation (21 CFR 312.62(b)).

Specifically, the following items were noted:

1. The study temperature log did not identify the thermometers used to record the storage temperature of the study drug. The maximum daily temperatures recorded from April 9, 2009 thru June 30, 2009, were retrospectively entered on the log (transcribed from an unidentified log used in another study).

**OSI Reviewer Comments:** Droxidopa is formulated as a capsule and stored at room temperature. According to stability storage conditions, droxidopa capsules maintain stability between 25° to 60° C [REDACTED] (b) (4) It is unlikely that the site experienced wide fluctuations in temperature that may have caused a loss in stability or potency of study drug given that the drug was stored at room temperature.

2. The time of Patient #4's BP at 8 minutes post-standing on September 1, 2009 was corrected in the medical records on September 1, 2009 from 11:38 to 11:48, (which is approximately 18 minutes post-standing). The corresponding CRF indicates the reading was done at 11:38.

The field investigator addressed the questions in the assignment memo as follows:

1. Please interview staff and verify the accuracy of the PRO measurement tool in terms of the efficacy endpoint

**Response:** The field investigator verified the entries in the questionnaire had been accurately transcribed to the case reports. The field investigator reviewed the original entries in all of the questionnaires and found no reason to suspect the questionnaire was not administered appropriately. It was also noted that the comments in the progress notes correlated to the answers in the questionnaires.

2. Please find out if "borderline" performers were or were not randomized, or if there was a pattern for such decisions.

**Response:** Enrollment in Ukraine was stopped by the sponsor on Sept 7th 2009, as per protocol amendment in September 2009.

3. Please find out how data values were determined and entered if patients provided answers to questions on the OHQ that were between different integers.

**Response:** There were no patients in Odessa (or anywhere else in Ukraine that were reviewed) that chose a non-whole number. The questionnaire was not set up for a response "between integers", and as far as the field investigator saw - it did not occur to any patients to choose multiple responses to a question in the questionnaire. (This is true for Kharkiv & Dnepropetrovsk as well).

4. Please find out if investigators elicited adverse events before or after the questionnaires were administered, or did it vary?

**Response:** The clinicians always asked how the patients were doing first.

5. Please find out if investigators took blood pressure readings before or after the questionnaires were administered, or did that vary?

**Response:** They performed vitals first (as per protocol).

6. Were the number and time of blood pressure measurements documented?

**Response:** Yes, this information was documented.

7. How close to the 3 hour mark after drug was administered were the questionnaire forms completed?

**Response:** For Patient #1: approximately 2.5 hours after the dose on the titration visits & approximately 3.5 hours after the dose on visit #5. Patient #2: approx 2.3 hours after the dose on the titration visits & approx 3.3 hours after the dose on visit #5. (b) (4) (sub-investigator) said both patients had tight schedules & were requested to take their study medications as early as possible.

8. Were concomitant medications captured and documented at each visit?

**Response:** Yes, from what could be determined from the medical records, concomitant medications were elicited, reported and documented at each visit.

**c. Assessment of data integrity:** The field investigator observed minor regulatory deficiencies at this site, which are sporadic in nature and are not likely to impact data outcomes or integrity. In addition, the field investigator stated that only one subject completed the study at this site as per the protocol requirement to stop enrollment after a certain date. The study appears to have been conducted adequately, and, the data generated by this site may be used in support of the respective indication.

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

4. **Joseph Jankovic, MD**  
Baylor College of Medicine  
6550 Fannin, Suite 1801

Houston, TX 77030

a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. The site screened 11 subjects, and enrolled 8; there were 3 screen failures. The inspection reviewed the following for each subject: signed and dated Informed Consent Documents (ICD); completed OHSA and OHDAS and CGI assessments for both Subject and Investigator; administration times for morning dose of study medication; the randomization scheme; all adverse events and serious adverse events; compliance with the protocol.

b. **General observations/commentary:** The field investigator reported that each subject had a signed and dated IRB approved, ICD. And that each subject had a completed OHSA/OHDAS and the CGIs for both subject and Investigator. The inspection reported that each subject was administered the morning dose of medication within 3 hours +/- 30 minutes. The field investigator did not observe any under reporting of adverse events; there were no SAEs at this site. Overall, the site appeared in compliance with the protocol and GCPs.

No Form FDA-483 was issued. However, the following items were discussed: The CGIs conducted by the Investigator(s) were not signed. It was simply a form that contained circled responses. There were no Physician Notes, or patient chart entries that indicated who performed the CGI-I. The Investigator stated adamantly the CGI would never be performed by anyone other than a qualified Neurologist/Physician. Additionally, there was no Master Drug accountability record. However, there were individual subject drug accountability records that verified accurate drug dispensation..

c. **Assessment of data integrity** At this site, there were no significant regulatory deficiencies, and no Form FDA-483 was issued. At the end of the inspection, the field investigator discussed several items with Dr. Jancovic, including his lack of signature and date on the CGI-I form and the lack of a master drug accountability records. These items are unlikely to impact data integrity, and the OSI recommends the data generated at this site may be used to support the NDA

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

5. Brent Goodman, MD

Replaced by:

**Erika D. Driver-Dunckley, MD**

Mayo Clinic Arizona

Department of Neurology

13400 East Shea Boulevard

Scottsdale, AZ 85259

a. **What was inspected:** The inspection was conducted in accordance with Compliance Program 7348.811. There were nine subjects screened, seven subjects enrolled, and six completed the study. There was one screen failure and one treatment failure during the titration phase (subject did not show response to study drug). The field investigator reviewed the following records for all subjects enrolled into the study at this site: 100 % informed consent documents (ICD) for all subjects screened for enrollment into the Open Label Period; inclusion and exclusion criteria; efficacy assessments; electronic case report forms (eCRF); source documents; drug accountability records; and SAE/adverse event reporting. The field investigator corroborated the source records (questionnaire data, progress notes) with the e-CRFs and data listings provided with the assignment. This corroboration applied to: the primary efficacy endpoints (relative change in mean score of the composite Orthostatic Hypotension Questionnaire (OHQ)); secondary efficacy endpoint (systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements 3 minutes post standing; assessment evaluations using CGI-I, CGI-S; and OHSA and OHDAS (the subcomponents of the OHQ) data

c. **General observations/commentary:** According to the field investigator, Dr. Driver-Dunkely took over the study on January 30th, 2009. She was previously a Sub-Investigator for the study. She stated that Dr. Goodman was transferred to other studies within the Mayo Clinic at the time she became Principal Investigator. The field investigator collected copies of the Form FDA 1572s for all Investigators, and stated all that all forms appeared to be appropriately completed.

The records were very well organized for each subject and easy to follow. The drug accountability records were accurate. The field investigator reported that there was a change in CRO monitoring mid-way through the study, and that the format for drug accountability was sometimes difficult to reconcile between the old and the new. However, the field investigator went over these records with the Study Coordinator, and found all records to be correct.

The study had an 80% drug adherence for drug administration (subjects taking the correct amount at the correct time) during the titration and randomized portions of the study. These were all easy to follow from one study to the next. One item was discussed during the close-out - that the Site was missing the last return shipment of drug to the supplier. Study drug was properly accounted for in the packing slip but was not documented in the master drug accountability log. This did not appear to importantly affect integrity of any data at the site.

The field investigator addressed the questions in the assignment memo as follows:

1. There are concerns about the study conduct in Study 301, as it employed a patient reported outcome (PRO) measurement tool as the primary efficacy endpoint. It is important to be reassured that the PRO measurement tool was appropriately administered and the results were correctly documented. Please-Interview staff and verify the accuracy of the PRO measurement tool in terms of the efficacy endpoint.

#### **Response**

The primary efficacy endpoint was based on the relative mean change in score of the composite Orthostatic Hypotension Questionnaire (OHQ) 7 days following

randomization. There were two questionnaires that made up the OHQ, OHSA (Orthostatic Hypotension Symptom Assessment) and OHDAS (OH Daily Activity Scale). These tests were given to subjects at the proper time, right after the standing test. Subjects were informed of the questions on these questionnaires, which they had addressed previously. They wrote their answers (based on their feelings) while the 3 minutes post standing test was conducted. Questionnaires for the visits were fully filled out (Visits 2, 4 and 5), and were filled out while subject was seated. During dose titration visits (all 3 visits) the patients were asked the one required question and could usually perform this during the 3 minutes post standing test.

2. A high proportion of patients were screened but not randomized in Study 301 (95/259). Please find out if "borderline" performers were or were not randomized, or if there was a pattern for such decisions. A "borderline" performer might be someone who scores 0.8 unit improvement (versus 1 unit) on the OHSA-1, or have a SBP improvement of only 8 mm Hg at 3 minutes post-standing (versus 10 mm Hg).

**Response:**

There were 3 subjects screened that were not randomized. There were no "borderline" performers at this site. The following 3 subjects were not randomized:

Subject 103003 – Screen Fail. No standing SBP drop on baseline visit. As per the protocol, "if the patient's standing SBP is 20% greater than the screening value, and if in the investigator's opinion, this is considered to be an atypical measurement that is uncharacteristically high and inconsistent with the patient's condition and history, the remaining visit procedures should not be conducted, and the patient should be brought back on a subsequent day to repeat. In this case the subsequent visits did not show the standing SBP to improve. Screening SBP was 151/96 and baseline was 145/96, with no drop from supine; this didn't meet protocol requirement of 20% increase to fulfill the inclusion criterion. This was not typical of NOH patients. Therefore the subject was a screen fail.

Subject 103008 – Treatment Fail. This subject did not show response to treatment drug during the open label titration visits. During the titration visits, the subject's standing SBP was being monitored until there was at least a 10 mm Hg improvement from baseline. Subject 103008 did not show any improvement from baseline, therefore the subject was a treatment fail.

Subject 103009 – Standing SBP was too high at Visit 4, randomization, so the subject did not continue with the study.

3. Please find out how data values were determined and entered if patients provided answers to questions on the OHQ that were between different integers.

**Response:**

Questionnaires were developed using all whole integers. The patients were given questions and told to rate on a scale of 0 to 10, zero being none or no feeling and 10 being high.

4. Please find out if investigators elicited adverse events before or after the questionnaires were administered, or did it vary?

**Response:**

Adverse events were acquired by following the order of the protocol. For Titration (Visit 3) visits AEs were elicited before the questionnaires were administered. During the randomization (Visit 4) visit, AE was elicited after the CGI-s & CGI-I and before the OHQ. For the evaluation (Visit 5) visit, AE was elicited in the same way as V4. The protocol states to follow the order of the checklist at the start of each visit, and the bolded procedures must be done in order indicated.

5. Please find out if investigators took blood pressure readings before or after the questionnaires were administered, or did that vary?

**Response**

During the titration visit the BP was taken during the questionnaire due to there only being one question for this visit. During the randomization visit the BP was taken right before the questionnaires were administered due to the subject's ability to stand and write on the questionnaire (or circle the proper number). During the evaluation visit, the same course of events occurred as in the randomization visit. BP was taken then the questionnaire was completed.

6. Were the number and time of blood pressure measurements documented?

**Response**

Yes, during this test the time and measurement of BP and heart rate were recorded on the source documents. There were no discrepancies noted while reviewing these source documents.

7. How close to the 3 hour mark after drug was administered were the questionnaire forms completed?

**Response**

The worst case that was noted when reviewing source documents was approximately 3 hours and 50 minutes after drug was administered. The protocol states that all assessments must be conducted in the morning after breakfast, but before lunch, 3 hours after their first dose of the day. It also states that each assessment must be documented on the CRF, which the questionnaires and CRFs have no bases of time, only that they were completed right after the standing test. The 3 hours and 50 minute timeframe was based on the timeframe it took to complete the BP and HR measurements.

8. Were concomitant medications captured and documented at each visit?

**Response**

Yes, concomitant medications were questioned at each visit and documented on source documents and in CRFs.

At the close-out of the inspection, there were no observations and no FDA-483 was issued.

**c. Assessment of data integrity:** No regulatory observations were noted during the inspection of Site #103. The study appears to have been conducted adequately, and, the data generated by the Sponsor site may be used in support of the respective indication.

**PLEASE NOTE: The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the field investigator, and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

**6. Chelsea Therapeutics, Inc.**

3530 Torringdon Way  
Charlotte, NC 28277

- a. **What was inspected:** The inspection of Chelsea Therapeutics, Inc. was conducted January 18–19, 2012, and was conducted in accordance with Compliance Program 7348.810, for Sponsors, Monitors and CROs. The field investigator reported that Chelsea Therapeutics, Inc. is *office space only*, with no manufacturing done onsite. The field investigator observed that the Sponsor delegated numerous responsibilities to various CROs. According to the list collected during the inspection, the primary CRO vendors were:

<b>CRO</b>	<b>Responsibilities</b>
(b) (4)	Manufacture of study drug and packaging
	Drug supply management and labeling
	IVRS (randomization and drug supply management)
	Provided ECG machines and central evaluation of ECGs
	Planning, monitoring, clinical supply management, data management, pharmacovigilance, medical monitoring, regulatory management, statistical analysis
	Planning, monitoring clinical supply management at North American sites
	Lab sample analysis

The Trial Master Files (TMF) were not available for review at the Sponsor site. The physical location where all study documents were maintained for the studies was [REDACTED] (b) (4). Documents located at [REDACTED] (b) (4) included source records, monitoring reports, drug accountability files, and AE files.

During the inspection, the copies of the following documents were collected:

- Organizational Chart
- List of all Vendors
- Location of Study 301 study documentation
- Vendor Management procedure
- Master Service Agreements with [REDACTED] (b) (4) for Study 301
- Master Service Agreement w/ [REDACTED] (b) (4)
- [REDACTED] (b) (4) list of CRAs
- [REDACTED] (b) (4) list of CRAs
- List of Clinical Investigator Sites
- [REDACTED] (b) (4) Clinical Monitoring Plan (Version 1.0 - July 9, 2009)
- [REDACTED] (b) (4) Clinical Monitoring Plan
- List of IRBs
- Type C Guidance Meeting Briefing Document (dated 18 Nov 2009)
- Type C Guidance FDA Meeting Preliminary Responses (dated December 11, 2009)
- Confirmation of Blinding of Study 301 at the time of Primary Endpoint Change – includes signed statements by Chelsea staff that they did not possess, view or request any unblinded data for Study 301 as of March 15, 2010, the date of the change in primary endpoint.
- [REDACTED] (b) (4) Study Visit Procedure Guidelines
- List of individuals at closing meeting

**b. General observations/commentary:** When asked by OSI, the field investigator stated she did not see anything at the Sponsor site that might necessitate the inspection of [REDACTED] (b) (4) unless the clinical sites inspections revealed data integrity issues or other problems that might warrant an inspection of records at the CRO sites. The field investigator reported that monitoring plan of clinical investigator sites appeared adequate, and that the CRO had detailed instructions for monitoring all clinical sites for this study. The field investigator reported that there were no non-compliant sites that required site closure during the trial; and there were no serious adverse events that qualified for expedited reporting.

Although no Form FDA-483 was issued at the conclusion of the inspection, the field investigator discussed the following issues and concerns:

The first patient was screened and enrolled on August 22, 2008. The last patient completed the study on July 23, 2010. The field investigator found that there were no formal SOPs for selection and oversight of vendor CROs before the study began enrolling subjects. Formal SOPs describing these procedures were developed in April, 2011, after the end of the study. In addition, there was no formal clinical trial monitoring plan in place until July 2009, a year after the study began.

**OSI Reviewer Comments:** As per Contract Amendment #2 (dated February 1, 2010) (b)(4) and Chelsea Therapeutics, Inc. entered into a Master Services Agreement effective March 16, 2007 that included a Scope of Work and Transfer of Obligations to contract for Services to be provided by (b)(4) to Chelsea in connection with the 301 Study. Contract Amendment #2 discussed the ongoing monitoring of the centers, the frequency of interim monitoring visits (2 per site depending on site enrollment), and the length of these interim monitoring visit (1-2 days). This Amendment 2 also discusses how monitoring visit reports will be provided in electronic format to Chelsea within 15 days of the visit. It is believed that the arrangement worked out between Chelsea and (b)(4) provided for ample monitoring at sites, beginning with site initiation visits. Therefore, despite no formal SOPs being gathered during the inspection of the Sponsor Chelsea, it appears that monitoring was most likely stipulated in the Master Services Agreement of March 16, 2007, that included the Scope of Work and Transfer of Obligations to (b)(4) and that Amendment #2 referenced back to the details of those monitoring obligations and that no significant concerns regarding adequacy of monitoring were raised.

d. **Assessment of data integrity** The inspection revealed no significant objectionable conditions and no critical issues that would suggest unreliability of the data submitted at the sponsor site. Data is considered reliable in support of the application.

#### IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the inspections demonstrated that the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. Five clinical investigator sites were inspected in support of this application. The sponsor site (Chelsea) was also inspected. The inspectional findings identified at the 3 sites in Ukraine (#505, #507, #513) were minor, and concerned sporadic instances of failure to follow the protocol, and failure to maintain records with respect to data pertinent to the study. OSI does not consider these violations likely to influence data integrity, study outcome or subject safety. The inspectional items found during inspections at Site #105 (Jancovic, Houston, TX) were minor and isolated and will not importantly influence study or data outcome. There were no regulatory violations identified at Site #103 (Driver-Dunckley, Scottsdale, AZ) or at the Sponsor site (Chelsea). OSI recommends that the data submitted by Chelsea Therapeutics, Inc. may be used in support of the indication.

{See appended electronic signature page}

Sharon Gershon, Pharm.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

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/s/  
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SHARON K GERSHON  
02/16/2012

SUSAN D THOMPSON  
02/16/2012

TEJASHRI S PUROHIT-SHETH  
02/16/2012

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	203202
<b>Generic Name</b>	Droxidopa (L-DOPS)
<b>Sponsor</b>	Chelsea Therapeutics, Inc.
<b>Indication</b>	Primary autonomic failure- dopamine Beta Hydroxylase deficiency or non-diabetic neuropathy and symptomatic neurogenic orthostatic hypertension
<b>Dosage Form</b>	Oral Capsules
<b>Drug Class</b>	Norepinephrine (NE) supplement
<b>Therapeutic Dosing Regimen</b>	Titrated from 100 to 600 mg t.i.d.
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Maximum dose tested: single-2000 mg Multiple- 600 mg t.i.d
<b>Submission Number and Date</b>	SDN 016 23 Dec 2011
<b>Review Division</b>	DCRP

**1 SUMMARY**

**1.1 OVERALL SUMMARY OF FINDINGS**

No significant QTc prolongation effect of droxidopa (600 mg and 2000 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between droxidopa (600 mg and 2000 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcI}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, blinded, four-period crossover study, 52 healthy subjects received droxidopa 600 mg, droxidopa 2000 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Droxidopa (600 mg and 2000 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time (hour)	$\Delta\Delta QTcI$ (ms)	90% CI (ms)
Droxidopa 600 mg	12	3.6	(1.8, 5.3)
Droxidopa 2000 mg	24	3.4	(1.4, 5.5)
Moxifloxacin 400 mg*	3	13.4	(9.9, 16.9)

\*The largest lower bound shows Bonferroni adjustment for 3 timepoints.

The suprathereapeutic dose (2000 mg) produces mean  $C_{max}$  values which are 2-fold the mean  $C_{max}$  for the therapeutic dose (600 mg). Dose of 2000 mg represents the maximum single dose tested in humans. There is minimal accumulation of the drug upon t.i.d dosing and the steady state  $C_{max}$  is similar to a single dose  $C_{max}$  (Appendix 6.1). Studies to assess the effect of intrinsic (hepatic and renal impairment) and extrinsic (drug-drug interaction studies) factors have not yet been conducted. It is likely that renal impairment may increase drug exposures because based on animal studies, the drug is primarily eliminated renally. The sponsor has submitted a clinical trial protocol to study the PK of droxidopa in renal impairment. This study will include patients with mild, moderate, severe renal impairment and ESRD. At this time with the limited information submitted so far, it is unclear if the suprathereapeutic dose would cover the exposures expected in patients with renal impairment, though the sponsor mentions that dosing would be adjusted to lower doses and less than t.i.d. in patients with renal failure. It is important to note that no dose adjustments are recommended for mild and moderate renal impaired patients since droxidopa is to be titrated to individualized doses as studied in pivotal trials, which included mild/moderate renally impaired patients.

## 2 PROPOSED LABEL

### 2.1 SPONSOR PROPOSED LABEL

Sponsor proposed the following text in the label:

#### 12.2 Pharmacodynamics

Cardiac Electrophysiology - No prolongation of the QTc interval was observed with droxidopa when administered as single doses up to 2000 mg, as shown in a dedicated thorough ECG study.

### 2.2 QT-IRT RECOMMENDED LABEL

*We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.*

#### 12.2 Pharmacodynamics

##### Cardiac Electrophysiology -

The effect of single oral dose of droxidopa 600 mg and 2000 mg on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400

mg) four-period crossover thorough QT study in 52 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern.

### **3 BACKGROUND**

#### **3.1 PRODUCT INFORMATION**

Droxidopa (L-threo-3,4-dihydroxyphenylserine, L-DOPS) is an orally administered synthetic catecholamine acid that is converted to the sympathetic neurotransmitter norepinephrine (NE) through a single step of decarboxylation by the endogenous enzyme 3,4-dihydrophenylalanine (DOPA) decarboxylase.

#### **3.2 MARKET APPROVAL STATUS**

Droxidopa was approved in Japan in 1989. No droxidopa marketing applications have been submitted or approved in any other country.

#### **3.3 PRECLINICAL INFORMATION**

From eCTD 2.6.2

“Tested in vitro at concentrations of 10, 30, and 90 µg/mL, droxidopa did not inhibit hERG tail current.

“Intravenously administered droxidopa did not affect HR, ECGs, or respiration rate at doses up to 10 mg/kg, although weak hypertensive effects were noted at doses  $\geq 1$  mg/kg in anesthetized cats.

“The effect of droxidopa treatment was also assessed in conscious dogs in three repeat-dose toxicology studies. In a 1 month oral toxicology study, two animals per sex per group were treated daily with either 0, 200, 600, or 2000 mg/kg droxidopa, and ECGs were recorded without anesthesia at baseline and during Weeks 2 and 4 (Report B-2-03). The ECGs were analyzed for P and R wave amplitude, PR, QRS, QT, and RR times as well as for HR. Treatment with droxidopa did not affect any of these parameters at the doses tested. In a 3-month oral toxicology study, dogs were treated with 0, 200, 600, or 2000 mg/kg/day (4-6/sex/group) and ECG measurements were taken at baseline and in Dosing Weeks 7 and 13 (Report B-2-04). The ECGs were examined for P and R wave amplitude, PR, QRS, QT and RR times as well as for HR. A summary of the data collected following 3 months of oral dosing is provided in Table 2.6.2-7.”

**Table 2: Electrocardiogram in Conscious Dogs Following Oral Administration of Droxidopa for 3 Months**

Dose (mg/kg)	Gender	PR Time (s)	QRS Time (s)	QT Time (s)	RR Time (s)	P Wave Amplitude (mV)	R Wave Amplitude (mV)	Heart Rate (bpm)
0 <sup>a</sup>	M	0.11 ± 0.006	0.04 ± 0.000	0.17 ± 0.010	0.60 ± 0.030	0.15 ± 0.056	2.50 ± 0.405	123 ± 7.6
	F	0.11 ± 0.009	0.04 ± 0.000	0.17 ± 0.008	0.45 ± 0.080	0.20 ± 0.045	1.99 ± 0.712	130 ± 21.8
200 <sup>b</sup>	M	0.11 ± 0.012	0.04 ± 0.000	0.17 ± 0.008	0.50 ± 0.096	0.19 ± 0.072	2.21 ± 0.219	125 ± 22.5
	F	0.11 ± 0.015	0.04 ± 0.005	0.16 ± 0.005	0.40 ± 0.058	0.16 ± 0.029	1.75 ± 0.770	154 ± 22.4
600 <sup>b</sup>	M	0.11 ± 0.008	0.04 ± 0.000	0.17 ± 0.013	0.54 ± 0.058	0.15 ± 0.054	1.81 ± 0.177	116 ± 11.3
	F	0.10 ± 0.010	0.04 ± 0.000	0.17 ± 0.010	0.47 ± 0.064	0.18 ± 0.044	1.80 ± 0.345	133 ± 17.6
2000 <sup>a</sup>	M	0.11 ± 0.005	0.04 ± 0.000	0.17 ± 0.015	0.47 ± 0.085	0.16 ± 0.050	2.17 ± 0.535	135 ± 22.6
	F	0.11 ± 0.010	0.04 ± 0.000	0.16 ± 0.008	0.38 ± 0.058	0.26 ± 0.099	1.80 ± 1.221	164 ± 31.6

<sup>a</sup> = n = 6/group.

<sup>b</sup> = n = 4/group.

Values represent the mean ± SD.

Source: Report B-2-04, Table 9, Table 10, Table 11, Table 12.

Source: eCTD 2.6.2, Table 2.6.2-7

### 3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.5.5 and 2.7.4

“A total of 444 patients were treated with droxidopa in the placebo-controlled Studies 301 and 302: 181 patients received droxidopa in the open-label titration phase only (i.e., non-randomized patients), 131 patients received droxidopa in the RCT phase, and 132 patients received placebo in the RCT phase. The highest proportion of patients received 600 mg TID (36.6%) and the lowest proportion of patients received 100 mg TID (6.1%).

“The incidence of AEs by System Organ Class (SOC) was generally similar between the droxidopa and placebo groups with the exception of Nervous system disorders (13.7% vs. 7.6%, respectively) and Injury, poisoning and procedural complications (1.5% vs. 7.6%, respectively; Table 5-3). Individual AEs (i.e., preferred terms) with a higher incidence in the droxidopa group compared with the placebo group included headache (6.1% vs. 3.0%, respectively) and dizziness (3.8% vs. 1.5%, respectively). Events with a higher incidence in the placebo group compared with the droxidopa group included fall (6.8% vs. 0.8%, respectively) and loss of consciousness (2.3% vs. 0, respectively).”

**Table 3: Summary of Most Common AEs ( $\geq 2\%$  of Patients in either Group) by System Organ Class and Preferred Term during the Randomized Controlled Treatment Phase in the Placebo-Controlled Study Grouping (Safety Set)**

System Organ Class Preferred Term	Placebo (N=132)		Droxidopa (N=131)	
	n (%)	E	n (%)	E
Number of AEs	31 (23.5)	58	30 (22.9)	63
Nervous system disorders	10 (7.6)	13	18 (13.7)	22
Headache	4 (3.0)	4	8 (6.1)	9
Dizziness	2 (1.5)	2	5 (3.8)	5
Loss of consciousness	3 (2.3)	4	0	0
General disorders and administration site conditions	4 (3.0)	6	4 (3.1)	8
Fatigue	3 (2.3)	3	2 (1.5)	2
Injury, poisoning, and procedural complications	10 (7.6)	12	2 (1.5)	3
Fall	9 (6.8)	10	1 (0.8)	2
Infections and infestations	4 (3.0)	4	4 (3.1)	4
Urinary tract infection	2 (1.5)	2	4 (3.1)	4

AE=adverse event; E=event.

Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of an AE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 10.1.

Source: ISS Table 2.1.2.1; Module 5.

Source: 2.5.5., Table 5-3

“AEs observed during the long-term extension studies were similar in type to those observed in the RCT and the open-label titration phases of the placebo-controlled studies.

“Events were most commonly reported in the SOC categories of Nervous system disorders (39.2%), Infections and infestations (24.6%), Injury, poisoning, and procedural complication (16.6%), and Investigations (15.9%; Table 5-4). The most commonly reported individual AEs were headache (13.3%), fall (12.6%), urinary tract infection (11.0%), syncope (8.3%), and dizziness (7.6%).

“There were a total of 6 deaths in the Chelsea-sponsored studies of droxidopa for the treatment of NOH. In addition, there were 10 other deaths in the Chelsea-sponsored studies that occurred outside the pre-specified reporting period (within 7 days of discontinuation of droxidopa therapy). All events were considered to be unrelated to study drug with the exception of hypoxic encephalopathy in Patient 130002 (which occurred 85 days after initiating therapy in Study 303) and bilateral multisegmental pneumonia in Patient 503004 (which occurred 184 days after initiating therapy in Study 304), both of which were considered to be possibly related to study drug. Narratives of deaths in the Chelsea-sponsored studies are provided in ISS Section 2.1.4 and in the individual study reports (CSR 303 [Section 14.3.3] and CSR 304 [Section 14.3.3]).

### Cardiovascular-related AEs

“The patient population in Chelsea’s clinical development program included a large number of patients with multiple comorbidities. Of the 444 patients who participated in

the open-label titration phase of Studies 301 and 302, 152 (34.2%) were classified as having a pre-existing cardiac disorder recorded in their medical history. The overall incidence of Cardiac disorder AEs was similar between those patients with and without a pre-existing cardiac condition, demonstrating that droxidopa did not notably exacerbate any pre-existing cardiac conditions among the patients in the open-label titration or RCT phases of the placebo-controlled studies (ISS Section 2.1.7.2.6).

“The SOC of Cardiac disorders do not capture all important cardiac-related events. Therefore, Chelsea evaluated all “cardiovascular-related” AEs across multiple SOC categories to capture all cardiovascular events relevant to the safety of droxidopa. These events include the following:

“(a) any AE within the SOC of Cardiac disorders; (b) any AE of circulatory collapse or hypertensive crisis from the SOC of Vascular disorders; and (c) any AE of chest pain, chest discomfort or sudden cardiac death from the SOC of General disorders and administration site conditions.

“There were 3 patients (0.6%) who died of cardiovascular-related SAEs: 1 patient died of cardiopulmonary arrest (for narrative see ISS Section 2.1.4.2, Study 302, Patient 114003); 1 patient died of sudden cardiac death (for narrative see ISS Section 2.1.4.3, Study 303, Patient 129002); and 1 patient died of circulatory collapse (for narrative see ISS Section 2.1.4.4, Study 304, Patient 105007). All were considered by the Investigator to be unrelated to droxidopa therapy.

“The incidence of cardiovascular-related AEs across all Phase 3 studies was low. No patients experienced cardiovascular-related AEs (ISS Section 2.1.7.2.1) and 2 droxidopa-treated patients (1.5%) experienced an AE of hypertension (ISS Section 2.1.7.1.4) during the RCT phase of the placebo-controlled studies. During the open-label titration phase (ISS Table 2-45; Table 2-65), 11 (2.5%) patients experienced AEs of hypertension or BP increased; a small number of patients experienced other cardiovascular-related AEs, including palpitations (2.3%) and angina pectoris or chest pain/chest discomfort (1.1%). All events were mild to moderate in severity.

“During the long-term extension studies, 9.3% of patients experienced cardiovascular-related AEs, and 3.7% of patients experienced AEs of hypertension or BP increased. A total of 2.3% of patients discontinued due to BP-related or cardiovascular-related AEs (ISS Section 2.1.7.2.3).”

*Reviewer’s comments: No ventricular arrhythmias or other clinically relevant ECG were reported in these studies. One patient died of sudden cardiac death 9 months after entering the open-label treatment period; the event seems unlikely related to droxidopa.*

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of droxidopa’s clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND (b) (4). The sponsor submitted the study report droxidopa QTc102 for droxidopa, including electronic datasets and waveforms to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A Double-Blind, Randomized, Crossover Trial to Define the ECG Effects of Droxidopa using a Clinical and a Supratherapeutic Dose Compared With Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: a Thorough ECG Trial

#### **4.2.2 Protocol Number**

Droxidopa QTc102

#### **4.2.3 Study Dates**

21 March 2011 to 27 April 2011

#### **4.2.4 Objectives**

Primary: To define the electrocardiogram (ECG) effects of droxidopa administered orally as a 600-mg therapeutic and a 2000-mg supratherapeutic dose compared with placebo and moxifloxacin in healthy adult male and female subjects.

Secondary: To evaluate the safety and pharmacokinetics of droxidopa when administered as a single 600-mg therapeutic and single 2000-mg supratherapeutic dose.

#### **4.2.5 Study Description**

##### **4.2.5.1 Design**

This is a randomized, double-blind, single-site, 4-period crossover study design. Each dosing occasion will be separated by a minimum 3-day washout period (from Day 1 of each period).

##### **4.2.5.2 Controls**

The Sponsor used both placebo and positive (moxifloxacin) controls.

##### **4.2.5.3 Blinding**

This study employed a double-blind, double-dummy study design. The droxidopa and matching placebo capsules were identical in appearance. Additionally, the moxifloxacin (overencapsulated 400-mg moxifloxacin tablets) and matching placebo capsules were identical in appearance.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

“Eligible subjects were enrolled and randomly assigned to 1 of 8 treatment sequences. Subjects crossed over into 4 treatment periods where they received a single dose of each of the following treatments under fasting conditions separated by a minimum 3-day washout period (from Day 1 of each period):

- Droxidopa 600 mg (therapeutic dose), oral capsules
- Droxidopa 2000 mg (supratherapeutic dose), oral capsules
- Placebo (matched to droxidopa), oral capsules
- Moxifloxacin 400 mg (positive control; over-encapsulated), oral capsules”

### 4.2.6.2 Sponsor’s Justification for Doses

“Droxidopa 600 mg was chosen because it is the therapeutic dose. The 2000-mg supratherapeutic dose of droxidopa (a greater than 6-fold increase in the minimal clinically effective dose) was selected to mimic the exposure in healthy volunteers that may occur in the target population and allow for the pharmacokinetics of QTc modeling to assess the effect of drug concentrations on cardiac repolarization.”

*(Source: Section 9.4.4 on page 42 of the study report)*

*Reviewer’s Comment: The 600-mg dose as the therapeutic dose in the thorough QT study is acceptable because it represents the highest clinical dose as dose is titrated from 100-600 mg t.i.d. for individual patient. The supratherapeutic dose of 2000 mg seems reasonable because it represents the maximum single dose tested in humans.  $C_{max}$  value in the thorough QT study is 2-fold following administration of 2000 mg of droxidopa compared with 600-mg dose. There is minimal accumulation of the drug upon t.i.d dosing and the steady state  $C_{max}$  is similar to single dose  $C_{max}$  (Appendix 6.1). Studies to assess the effect of intrinsic (hepatic and renal impairment) and extrinsic (drug-drug interaction studies) factors have not yet been conducted. It is likely that renal impairment may increase drug exposures because based on animal studies, the drug is primarily eliminated renally. The sponsor has submitted a clinical trial protocol (Study NOH 103) for studying the PK of droxidopa in renal impairment. This study will include patients with mild, moderate, severe renal impairment and ESRD. Based on studies in rats, the sponsor believes that the  $C_{max}$  and AUC could be as much as 5-fold value seen without renal impairment. Thus based on the limited information submitted so far, it is unclear if the supratherapeutic dose would cover the exposures expected in patients with renal impairment. It is important to note that no dose adjustments are recommended for mild and moderate renal impaired patients since droxidopa is to be titrated to individualized doses as studied in pivotal trials, which included mild/moderate renally impaired patients*

### 4.2.6.3 Instructions with Regard to Meals

“On the morning of Day 1 of each period, after at least an 8-hour fast, each subject received a single dose of study drug according to the randomly assigned treatment

sequence. After dosing, subjects were allowed to drink water ad libitum, but remained fasting until approximately 4 hours after dosing. Thereafter, meals (lunch, dinner, and evening snack) were served as regularly scheduled. Meal timing and components, activity levels, and general conditions in the Phase I unit were as similar as possible on Day –1 and Day 1 of each treatment period.”

*(Source: Section 9.4.5 on page 42 of the study report)*

*Reviewer’s Comment: High-fat meal decreases  $C_{max}$  by 35% and AUC by 20% as compared to fasted state (Appendix 6.1). Since food decreases exposures, the QT study which was conducted under fasted conditions is reasonable.*

#### **4.2.6.4 ECG and PK Assessments**

##### **ECG Assessments**

“On Day –1 of each period, ECGs were extracted from the H-12+ flash card in quadruplicate approximately 1 minute apart at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 23 h. On Day 1, ECGs were extracted in quadruplicate approximately 1 minute apart at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 23 h (Day 2) after dosing.”

*(Source: Section 9.5.1.1 on page 44 of the study report)*

##### **PK Assessments**

“Pharmacokinetic blood samples were collected on Day 1 of each period before dosing and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, and 23 h (Day 2) after dosing. Only samples collected after droxidopa administration were analyzed for droxidopa plasma concentrations. All ECG extractions were time-matched to PK samples, but were obtained before the actual PK sampling time.”

*(Source: Section 9.5.1.2 on page 47 of the study report)*

*Reviewer’s Comment: ECG/PK samples were collected frequently enough to monitor the effects of the drug over a 24-hour interval. Frequent samples were collected around  $T_{max}$  (2 h) of the drug in order to detect changes in the QT interval at maximum drug concentrations. PK samples were analyzed only for droxidopa plasma concentrations and the plasma concentrations of metabolites including 3-OM-DOPS and norepinephrine were not determined.*

##### **4.2.6.5 Baseline**

Time-matched ECG measures on Day-1 were used as baseline

##### **4.2.7 ECG Collection**

“Electrocardiograms were obtained digitally using a Mortara Instrument (Milwaukee, Wisconsin, USA) H-12+ ECG continuous 12-lead digital recorder. The stored ECGs were reviewed by the central ECG core laboratory. The ECGs used in the analysis were extracted at predetermined time points and were read centrally using a high-resolution manual on-screen caliper semiautomatic method with annotations.

“A total of 48 serial ECGs were to be analyzed on Day –1 and again on Day 1 for each subject in each of the 4 treatment periods. This resulted in approximately 384 serial ECG measurements per subject. Dropouts were not replaced and it was expected that no fewer than 44 subjects would be evaluable.

“ECGs were sent to (b) (4) a central ECG laboratory, for a treatment-blinded high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

“The 12-lead digital continuous ECG signal for each session in each subject was recorded on compact flash memory cards provided to the site. The subject’s unique identification number and demographic information were recorded for each card. Without knowledge of subject treatment assignment, (b) (4) generated a 10-second, 12-lead digital ECG at each time point specified in the protocol. If targeted ECG time points were artifactual and of poor quality, (b) (4) captured analyzable 10-second ECGs as close as possible to the targeted time points.

“Digital ECGs were transmitted to the central ECG laboratory’s validated data management system, (b) (4) Interval duration measurements were collected using computer assisted caliper placements on three consecutive beats. Trained analysts then reviewed all ECGs for correct lead and beat placement and adjudicated the pre-placed algorithm calipers as necessary using the proprietary validated electronic caliper system applied on a computer screen. A cardiologist then verified the interval durations and performed the morphology analysis, noting any T-U wave complex that is compatible with an effect on cardiac repolarization.

“The ECG analysis was conducted in Lead II, or in Lead V5 if Lead II was not analyzable. If V5 was not analyzable then Lead V2 was used, followed by the most appropriate lead if necessary. ECG readers were blinded to subject identifiers, treatment and visit. All ECGs for a given subject were analyzed by the same reader. Quality Assurance reports for inter- and intra-observer variability were produced by the central ECG laboratory and provided to the Sponsor.”

## **4.2.8 Sponsor’s Results**

### **4.2.8.1 Study Subjects**

Of the 52 subjects who were randomly assigned to study drug, all (100.0%) completed the study and were included in both the safety and PK populations.

Subject demographics and baseline characteristics are summarized in Table 4.

**Table 4: Summary of Demographics and Baseline Characteristics (Safety Population)**

No. of subjects (%)	Treatment Sequence <sup>a</sup>								Overall (N = 52)
	1 (n = 7)	2 (n = 6)	3 (n = 7)	4 (n = 6)	5 (n = 7)	6 (n = 6)	7 (n = 7)	8 (n = 6)	
<b>Age (years)</b>									
Mean (SD)	32.1 (5.11)	30.8 (10.59)	29.0 (10.05)	24.7 (5.47)	28.7 (6.50)	27.5 (5.58)	30.0 (8.64)	27.7 (4.97)	28.9 (7.26)
Median	29.0	29.0	25.0	23.0	27.0	28.5	31.0	26.0	27.5
Minimum, Maximum	28, 40	19, 45	19, 44	20, 35	21, 38	20, 34	20, 42	23, 36	19, 45
<b>Gender, No. (%)</b>									
Male	4 (57.1)	2 (33.3)	4 (57.1)	3 (50.0)	3 (42.9)	3 (50.0)	4 (57.1)	4 (66.7)	27 (51.9)
Female	3 (42.9)	4 (66.7)	3 (42.9)	3 (50.0)	4 (57.1)	3 (50.0)	3 (42.9)	2 (33.3)	25 (48.1)
<b>Race, No. (%)</b>									
White	5 (71.4)	5 (83.3)	6 (85.7)	6 (100.0)	3 (42.9)	2 (33.3)	5 (71.4)	4 (66.7)	36 (69.2)
Black or African American	2 (28.6)	1 (16.7)	1 (14.3)	0	4 (57.1)	3 (50.0)	2 (28.6)	2 (33.3)	15 (28.8)
Asian	0	0	0	0	0	1 (16.7)	0	0	1 (1.9)
<b>Ethnicity, No. (%)</b>									
Hispanic or Latino	1 (14.3)	2 (33.3)	4 (57.1)	5 (83.3)	2 (28.6)	1 (16.7)	4 (57.1)	4 (66.7)	23 (44.2)
Not Hispanic or Latino	6 (85.7)	4 (66.7)	3 (42.9)	1 (16.7)	5 (71.4)	5 (83.3)	3 (42.9)	2 (33.3)	29 (55.8)
<b>Height (cm)</b>									
Mean (SD)	170.86 (13.966)	171.77 (6.565)	164.67 (7.529)	162.08 (13.530)	170.71 (11.408)	166.83 (12.004)	166.19 (11.981)	168.87 (11.053)	167.78 (10.963)
Median	170.00	170.05	162.90	168.00	171.40	167.75	161.10	169.25	169.30
Minimum, Maximum	147.7, 188.3	165.4, 184.5	154.5, 176.7	142.0, 174.1	155.3, 186.1	150.1, 179.4	152.2, 189.3	154.0, 182.1	142.0, 189.3

Table 11-1 is continued on the next page.

No. of subjects (%)	Treatment Sequence <sup>a</sup>								Overall (N = 52)
	1 (n = 7)	2 (n = 6)	3 (n = 7)	4 (n = 6)	5 (n = 7)	6 (n = 6)	7 (n = 7)	8 (n = 6)	
<b>Weight (kg)</b>									
Mean (SD)	76.00 (16.072)	69.90 (11.713)	62.56 (8.487)	63.78 (10.856)	73.83 (14.203)	68.28 (7.696)	69.04 (6.993)	73.10 (14.182)	69.62 (11.809)
Median	76.80	72.45	57.90	63.50	69.80	68.05	69.80	73.80	69.65
Minimum, Maximum	52.7, 99.4	56.1, 81.9	55.0, 75.9	52.2, 80.4	52.5, 92.7	56.7, 80.5	59.6, 80.4	55.9, 94.4	52.2, 99.4
<b>BMI (kg/m<sup>2</sup>)</b>									
Mean (SD)	25.84 (3.176)	23.68 (3.754)	23.00 (1.989)	24.27 (2.610)	25.26 (3.720)	24.65 (2.832)	25.11 (2.790)	25.47 (2.775)	24.67 (2.940)
Median	26.80	23.20	23.00	24.90	25.70	24.05	25.30	24.20	24.20
Minimum, Maximum	20.7, 29.1	19.1, 28.1	19.8, 25.6	20.6, 27.3	19.7, 28.9	22.0, 29.2	21.6, 28.1	22.9, 29.3	19.1, 29.3

Abbreviations: BMI = body mass index; DS = dose suprathreshold, 2000-mg oral droxidopa; DT = dose therapeutic, 600-mg oral droxidopa; PC = positive control, 400-mg oral moxifloxacin (overencapsulated); and P = oral placebo to match droxidopa.

Note: Percentages were based on the number of subjects randomly assigned to each treatment sequence and overall.

<sup>a</sup> Treatment sequences were as follows:

- 1 = DT/DS/P/PC
- 2 = DS/PC/DT/P
- 3 = P/DT/PC/DS
- 4 = PC/P/DS/DT
- 5 = DS/P/DT/PC
- 6 = P/PC/DS/DT
- 7 = DT/DS/PC/P
- 8 = PC/DT/P/DS

Source: End-of-Text Table 14.1.2.

Source: CSR, Table 11-1

## 4.2.8.2 Statistical Analyses

### 4.2.8.2.1 Primary Analysis

“The time-matched analysis was conducted as the primary endpoint as recommended by ICH E14. Table details the 2-sided 90% or the equivalent 1-sided 95% upper confidence

boundary for each treatment at each time point showing the placebo- and baseline-corrected ( $\Delta\Delta$ ) analysis for each of the droxidopa doses and moxifloxacin for QTcI. “The time-matched analysis for the QTcI endpoint revealed that the moxifloxacin treatment met the assay sensitivity criteria outlined in the statistical plan and had the typical profile as shown in Figure 11-1. In addition, the criteria that the lower CI of at least 1 of the preselected time points for moxifloxacin is greater than or equal to 5 ms was met at all of the 5 time points, satisfying assay sensitivity for the study. Neither of the 2 droxidopa treatments demonstrated an upper bound that approached or exceeded 10 ms, again demonstrating no signal of any effect of this agent on cardiac repolarization.”

**Table 5: Placebo-Corrected Change From Baseline - Estimates from Mixed Effects General Linear Model QTcI (Sponsor’s Results)**

Time (h)	Droxidopa 600 mg (N = 52)			Droxidopa 2000 mg (N = 52)			Moxifloxacin 400 mg (N = 52)		
	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound	Estimate	Lower Bound	Upper Bound
0.5	-0.1	-2.3	2.0	-2.1	-4.3	0.1	2.4	-0.7	5.6
1	-0.0	-2.2	2.2	-3.3	-5.5	-1.1	12.4	9.3	15.6
2	-1.3	-3.5	0.9	-4.3	-6.5	-2.1	10.3	7.1	13.5
3	0.4	-1.7	2.6	-0.4	-2.6	1.8	13.7	10.5	16.9
4	-0.6	-2.8	1.6	2.4	0.2	4.6	12.9	9.7	16.0
5	-1.0	-3.1	1.2	1.0	-1.2	3.2	10.4	7.2	13.5
6	-2.5	-4.6	-0.3	-0.2	-2.4	2.0	8.5	5.3	11.6
8	0.7	-1.4	2.9	1.8	-0.4	4.0	10.1	6.9	13.3
10	0.3	-1.8	2.5	1.6	-0.7	3.8	5.9	2.8	9.1
12	3.7	1.5	5.9	2.5	0.3	4.7	9.6	6.4	12.8
18	-0.1	-2.2	2.1	1.5	-0.7	3.7	7.7	4.6	10.9
23	1.3	-0.9	3.5	3.8	1.5	6.1	8.1	4.8	11.3
Time averaged	0.1	-0.9	1.0	0.3	-0.6	1.3	9.3	8.4	10.3

Source: Sponsor’s report Table 11-2

#### 4.2.8.2.2 Additional Analyses

HR analysis:

“The mean placebo-corrected change from Baseline for HR interval duration for the 600-mg and 2000-mg droxidopa treatments showed a decrease of 1 bpm and 2 bpm, respectively. There were 1 and 2 subjects, respectively, who met bradycardic outlier criterion in the 600-mg and 2000-mg droxidopa treatments and no subjects who met tachycardic outlier criterion on the 2 droxidopa treatments versus 0 on placebo. The results of the time-matched analysis also showed changes of no clear clinical relevance”

PR analysis:

“The mean placebo-corrected change from Baseline for PR interval duration for the 600-mg and 2000-mg droxidopa treatments showed an increase of 1 ms and 1 ms, respectively, which was of no clinical relevance. One subject following each droxidopa treatment (Subject 001022) met the PR outlier criteria. One subject following each droxidopa treatment (Subject 001023) was noted to have atypical Mobitz I heart block (previously read as Mobitz II but was later determined to be more like an atypical Mobitz I) of no clear clinical relevance in these healthy subjects. The time-matched analysis also showed no clear signal of any effect on atrioventricular (AV) conduction.”

QRS Interval:

“The mean placebo-corrected change from Baseline for QRS duration for the 600-mg and 2000-mg droxidopa treatments showed a change of 0 ms and –1 ms, respectively, which was of no clinical relevance. No subjects in either droxidopa treatment met the QRS outlier criteria and the time-matched analysis did not show signal of any change.”

#### **4.2.8.3 Safety Analysis**

No deaths, SAEs, or TEAEs leading to study drug discontinuation were reported.

A summary of TEAEs reported by 2 or more subjects overall is presented in Table 6

The highest percentage of subjects overall (46.2%) reported TEAEs classified as gastrointestinal disorders (primarily abdominal pain, nausea, and vomiting TEAEs), which were reported more often after droxidopa 2000 mg (38.5%) than after droxidopa 600 mg (11.5%), placebo (11.5%), and moxifloxacin (7.7%).

**Table 6: Treatment-Emergent Adverse Events Reported by 2 or More Subjects Overall (Safety Population)**

	Droxidopa 600 mg Therapeutic (N = 52)	Droxidopa 2000 mg Suprathereapeutic (N = 52)	Placebo (N = 52)	Moxifloxacin Positive Control (N = 52)	Overall (N = 52)
<b>System Organ Class</b>					
<b>Preferred Term, No. (%)</b>					
Number of subjects with at least 1 TEAE	16 (30.8)	28 (53.8)	14 (26.9)	14 (26.9)	34 (65.4)
Gastrointestinal disorders	6 (11.5)	20 (38.5)	6 (11.5)	4 (7.7)	24 (46.2)
Abdominal pain	5 (9.6)	16 (30.8)	2 (3.8)	1 (1.9)	19 (36.5)
Nausea	4 (7.7)	11 (21.2)	1 (1.9)	3 (5.8)	15 (28.8)
Vomiting	1 (1.9)	7 (13.5)	0	1 (1.9)	9 (17.3)
Diarrhea	0	5 (9.6)	1 (1.9)	0	6 (11.5)
Dyspepsia	0	2 (3.8)	0	0	2 (3.8)
Skin and subcutaneous tissue disorders	7 (13.5)	3 (5.8)	4 (7.7)	7 (13.5)	20 (38.5)
Dermatitis contact	7 (13.5)	3 (5.8)	4 (7.7)	6 (11.5)	19 (36.5)
Nervous system disorders	7 (13.5)	11 (21.2)	4 (7.7)	6 (11.5)	17 (32.7)
Headache	5 (9.6)	8 (15.4)	3 (5.8)	4 (7.7)	13 (25.0)
Dizziness	1 (1.9)	2 (3.8)	1 (1.9)	5 (9.6)	7 (13.5)
General disorders and administrative site conditions	1 (1.9)	3 (5.8)	3 (5.8)	0	7 (13.5)
Feeling drunk	0	2 (3.8)	1 (1.9)	0	3 (5.8)
Investigations	0	4 (7.7)	0	1 (1.9)	5 (9.6)
Heart rate increased	0	4 (7.7)	0	1 (1.9)	5 (9.6)
Musculoskeletal and connective tissue disorders	0	4 (7.7)	0	0	4 (7.7)
Back pain	0	2 (3.8)	0	0	2 (3.8)
Reproductive system and breast disorders	0	0	0	2 (3.8)	2 (3.8)
Dysmenorrhea	0	0	0	2 (3.8)	2 (3.8)

Abbreviations: TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an AE that was not present before treatment with study drug but appeared after treatment, or as an AE that was presented before treatment with study drug but worsened in nature, severity, or frequency of conditions after treatment. At each level of subject summarization, a subject was counted once if the subject reported 1 or more events. Percentages were based on the number of subjects in the safety population who received the corresponding treatment and overall. Adverse events were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities, Version 13.1.

Source: End-of-Text Table 14.3.1.1.

Source: CSR, Table 12-1

Increased heart rate (verbatim term: sensation of increased HR) was reported by a higher percentage of subjects after droxidopa 2000 mg (4 subjects, 7.7%) than after droxidopa 600 mg (0%), placebo (0%), and moxifloxacin (1 subject, 1.9%). The investigator considered the sensation of increased HR in all 5 subjects to be possibly related to study drug

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The PK results of droxidopa are presented in Table 7.  $C_{max}$  and  $AUC_{0-24h}$  values in the thorough QT study were 2-fold and 2.3-fold higher following administration of 2000 mg of the supra-therapeutic dose compared with 600 mg of the therapeutic dose of droxidopa. The mean droxidopa concentration profiles for the therapeutic and the supra-therapeutic dose are shown in Figure 1.

**Table 7: Sponsor's Mean PK parameters**

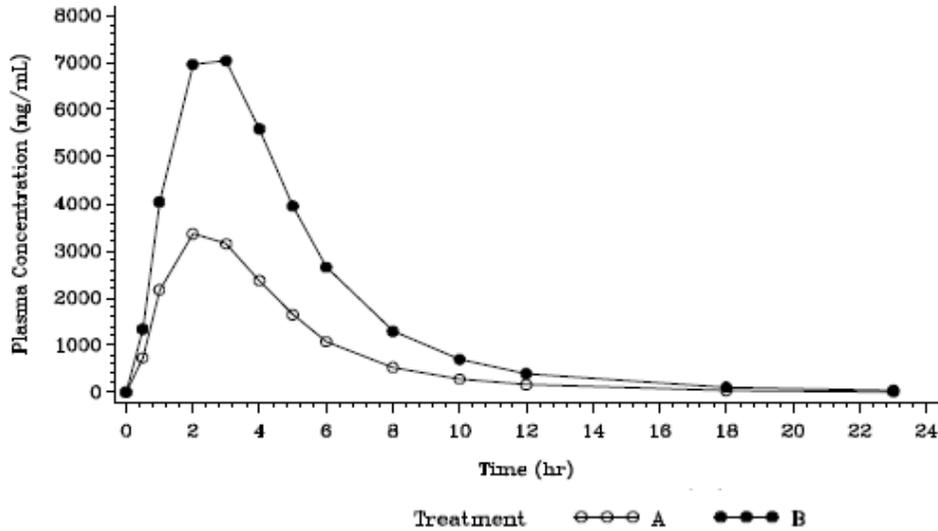
Parameter (unit)	Droxidopa 600 mg (N = 52)	Droxidopa 2000 mg (N = 52)
$AUC_{0-23h}$ (ng·h/mL)	16589 (37.6)	37510 (46.7)
$AUC_{0-inf}$	16637 (37.6)	37711 (46.5)
$C_{max}$ (ng/mL)	3966 (32.3)	7923 (41.6)
$T_{max}$ (h) <sup>a</sup>	2.05 (1.00, 5.00)	2.06 (2.00, 4.03)
$t_{1/2}$	2.85 (11.0)	3.35 (15.8)

Abbreviations: CV = coefficient of variation.

<sup>a</sup> For  $T_{max}$ , the median (minimum, maximum) values are presented.

Source: Table 11-5 on page 90 of study report

**Figure 1 : Sponsor’s Mean Droxidopa Concentration-Time profiles**



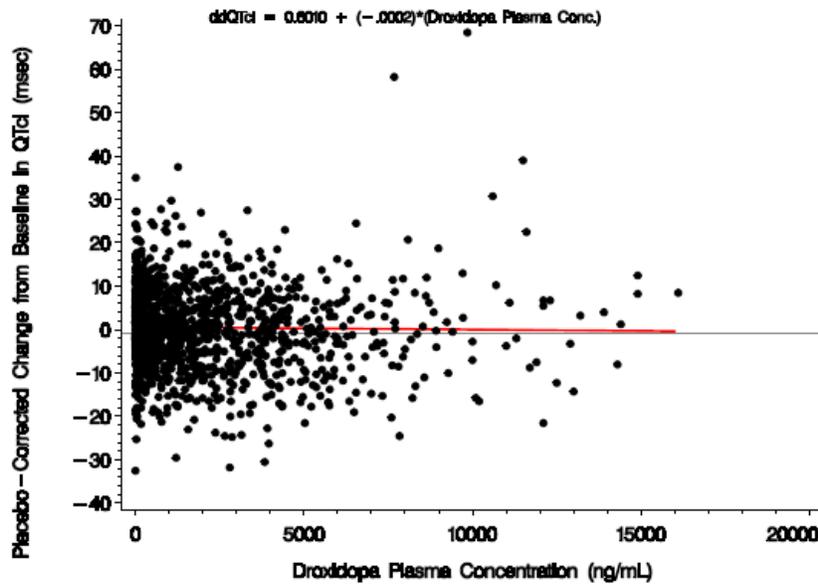
Abbreviations: A = Droxidopa 600 mg; B = Droxidopa 2000 mg

Source: Figure 11-7 on page 89 of study report

**4.2.8.4.2 Exposure-Response Analysis**

Sponsor’s  $\Delta\Delta QTcI$  vs. Droxidopa plasma concentration plot is shown in Figure 2. Across the studied concentration range, there appeared to be no increase in  $\Delta\Delta QTcI$ .

**Figure 2 : Sponsor’s  $\Delta\Delta QTcI$  vs. Droxidopa Plasma Concentration**



Source: Figure 11-6 on page 88 of study report

Reviewer's Comments: Our independent analysis is presented in Figure 5. There appeared to be no increase in  $\Delta\Delta QTcI$  with increasing drug concentrations.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 8, it appears that QTcI and QTcF have similar slopes that are not statistically significant from each other.

**Table 8: Comparison of QTcF and QTcI Using the Mixed Model**

Treatment Groups	Slope of QTcF	Slope of QTcI	diff_p_value
All	0.00705	0.00936	0.15749
Droxidopa 2000 mg	-.00089	0.00173	0.49422
Droxidopa 600 mg	0.00597	0.01074	0.20931
Moxifloxacin	0.01354	0.01659	0.44128
Placebo	0.00820	0.01513	0.14512

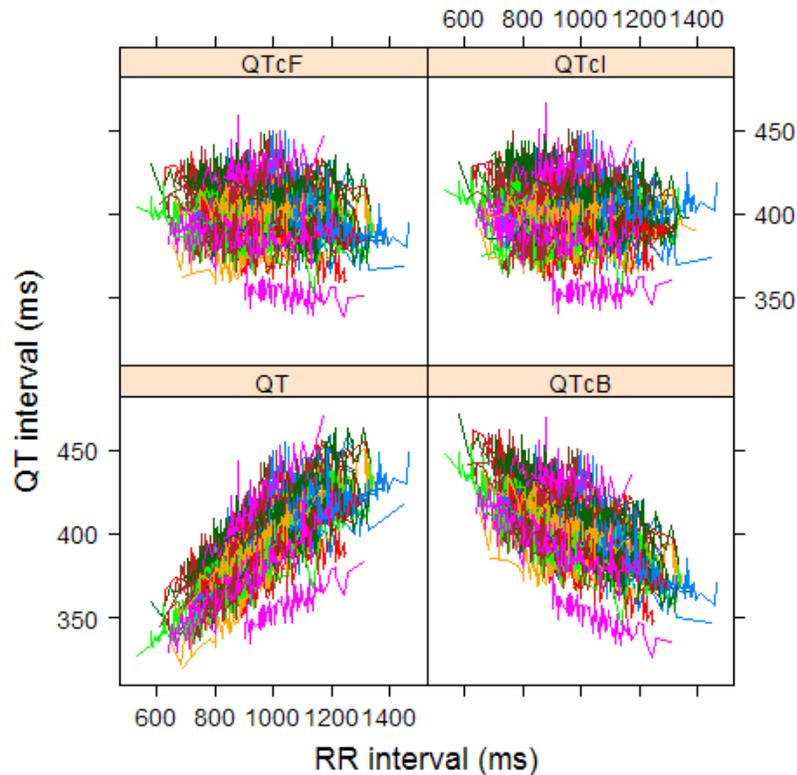
We also used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 9, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

**Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

method	Treatment									
	Droxidopa 2000 mg (DS)		Droxidopa 600 mg (DT)		Moxifloxacin		Placebo		All	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	52	0.0056	52	0.0052	52	0.0055	52	0.0037	52	0.0053
QTcF	52	0.0011	52	0.0019	52	0.0017	52	0.0020	52	0.0008
QTcI	52	0.0006	52	0.0014	52	0.0017	52	0.0014	52	0.0005

The relationship between different correction methods and RR is presented in Figure 3.

**Figure 3: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Droxidopa

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcI effect. The model includes treatment, sequence and period as fixed effects and subject as a random effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

**Table 10: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group = Droxidopa 600 mg**

	<b>Droxidopa 600 mg <math>\Delta</math>QTcI</b>	<b>Placebo <math>\Delta</math>QTcI</b>	<b><math>\Delta\Delta</math>QTcI</b>	
<b>Time (h)</b>	<b>LS Mean (ms)</b>	<b>LS Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
0.5	-3.4	-3.7	0.2	(-1.7, 2.2)
1	-3.8	-3.8	0.0	(-2.2, 2.3)
2	-3.3	-2.2	-1.0	(-3.1, 1.0)
3	-2.9	-3.3	0.4	(-2.2, 3.1)
4	-2.5	-1.8	-0.7	(-3.1, 1.6)
5	-4.4	-3.7	-0.7	(-3.0, 1.6)
6	-4.3	-2.9	-1.4	(-3.2, 0.3)
8	-2.5	-3.4	0.9	(-1.2, 3.0)
10	-2.4	-2.9	0.6	(-1.4, 2.6)
12	-0.9	-4.5	3.6	(1.8, 5.3)
18	-1.2	-1.4	0.2	(-2.1, 2.5)
23	-1.1	-2.7	1.6	(-0.4, 3.6)

**Table 11: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Treatment Group = Droxidopa 2000 mg**

Time (h)	Droxidopa 2000 mg $\Delta$ QTcI	Placebo $\Delta$ QTcI	$\Delta\Delta$ QTcI	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-5.2	-3.7	-1.5	(-3.5, 0.4)
1	-6.9	-3.8	-3.1	(-5.4, -0.9)
2	-6.1	-2.2	-3.9	(-6.0, -1.8)
3	-3.7	-3.3	-0.4	(-3.1, 2.2)
4	0.2	-1.8	2.0	(-0.3, 4.4)
5	-2.4	-3.7	1.3	(-1.0, 3.6)
6	-2.7	-2.9	0.2	(-1.6, 2.0)
8	-1.4	-3.4	1.9	(-0.2, 4.1)
10	-1.1	-2.9	1.8	(-0.2, 3.8)
12	-1.8	-4.5	2.7	(1.0, 4.5)
18	0.7	-1.4	2.1	(-0.2, 4.3)
23	0.7	-2.7	3.4	(1.4, 5.5)

The largest upper bounds of the 2-sided 90% CI for the mean difference between droxidopa 600 mg and placebo, and between droxidopa 2000 mg and placebo were 5.3 ms and 5.5 ms, respectively.

#### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 12. The largest unadjusted 90% lower confidence by considering Bonferroni multiple endpoint adjustment of 3 time points was 9.9 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

**Table 12: Analysis Results of  $\Delta$ QTcI and  $\Delta\Delta$ QTcI for Moxifloxacin**

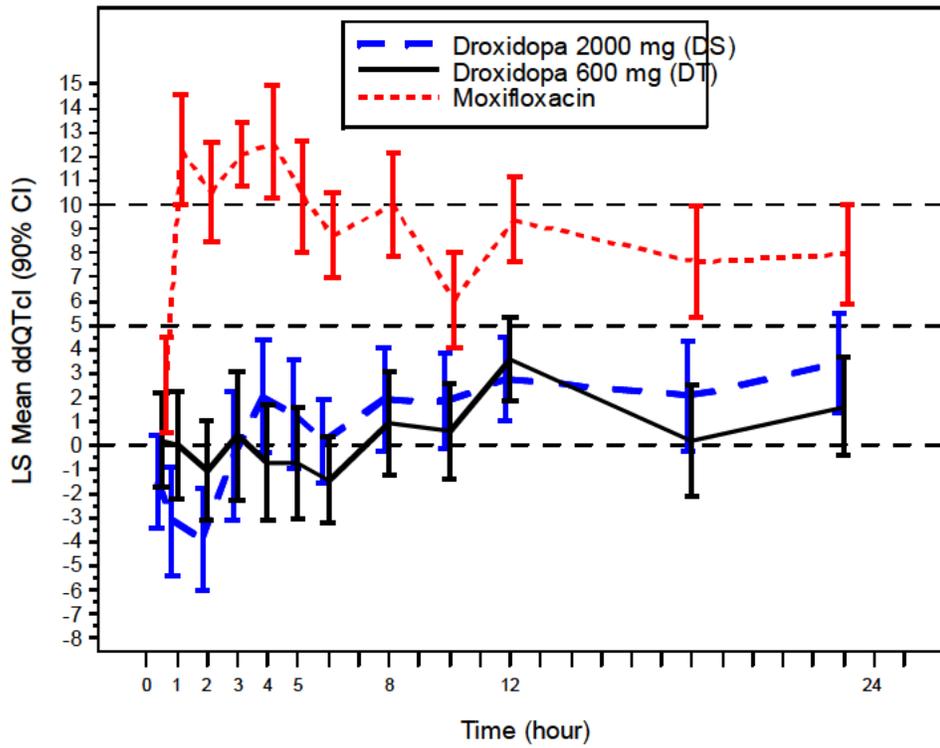
	Moxifloxacin in 400 mg $\Delta$ QTcI	Placebo $\Delta$ QTcI	$\Delta\Delta$ QTcI	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-1.2	-3.7	2.5	(-0.0, 5.0)
1	8.5	-3.8	12.3	(9.3, 15.2)
2	8.2	-2.2	10.5	(7.8, 13.2)
3	10.1	-3.3	13.4	(9.9, 16.9)
4	10.7	-1.8	12.6	(9.5, 15.6)
5	6.6	-3.7	10.3	(7.3, 13.3)
6	5.9	-2.9	8.7	(6.4, 11.0)
8	6.6	-3.4	10.0	(7.2, 12.8)
10	3.1	-2.9	6.0	(3.5, 8.6)
12	4.9	-4.5	9.4	(7.1, 11.7)
18	6.2	-1.4	7.6	(4.7, 10.6)
23	5.2	-2.7	7.9	(5.3, 10.6)

\* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcI Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcI for different treatment groups.

Figure 4: Mean and 90% CI  $\Delta\Delta QTcI$  Timecourse



(Note: CIs are all unadjusted including moxifloxacin)

#### 5.2.1.4 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcI values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

**Table 13: Categorical Analysis for QTcI**

Treatment Group	Total N		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	52	623	52 (100%)	623 (100%)	0 (0.0%)	0 (0.0%)
Droxidopa 2000 mg	52	623	51 (98.1%)	622 (99.8%)	1 (1.9%)	1 (0.2%)
Droxidopa 600 mg	52	623	52 (100%)	623 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	52	622	52 (100%)	622 (100%)	0 (0.0%)	0 (0.0%)
Placebo	52	621	52 (100%)	621 (100%)	0 (0.0%)	0 (0.0%)

Table 14 lists the categorical analysis results for  $\Delta$ QTcI. Only one subject had one observation of change from baseline above 60 ms.

**Table 14: Categorical Analysis of  $\Delta$ QTcI**

Treatment Group	Total N		Value $\leq$ 30 ms		30 ms<Value $\leq$ 60 ms		Value>60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Droxidopa 2000 mg	52	619	49 (94.2%)	615 (99.4%)	2 (3.8%)	3 (0.5%)	1 (1.9%)	1 (0.2%)
Droxidopa 600 mg	52	623	52 (100%)	623 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moxifloxacin	52	621	51 (98.1%)	619 (99.7%)	1 (1.9%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Placebo	52	621	52 (100%)	621 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

#### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest upper

limits of 90% CI for the HR mean differences between droxidopa 600 mg and placebo, and between droxidopa 2000 mg and placebo were 2.2 bpm and 2.9 bpm, respectively.

**Table 15: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Droxidopa 600 mg**

	Droxidopa 600 mg $\Delta$ HR	Placebo $\Delta$ HR	$\Delta\Delta$ HR	
Time (h)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	1.2	2.0	-0.8	(-2.1, 0.5)
1	0.2	3.0	-2.8	(-4.3, -1.3)
2	0.2	2.1	-1.9	(-3.8, -0.1)
3	-1.3	0.6	-1.9	(-3.5, -0.3)
4	-2.7	-0.6	-2.2	(-3.8, -0.5)
5	-5.2	-2.7	-2.4	(-4.1, -0.7)
6	-3.5	-2.2	-1.3	(-3.0, 0.4)
8	-4.1	-4.3	0.2	(-1.3, 1.7)
10	-1.8	0.2	-2.0	(-3.6, -0.5)
12	0.6	0.6	-0.0	(-1.6, 1.6)
18	1.1	1.7	-0.5	(-2.3, 1.2)
23	1.9	1.5	0.4	(-1.3, 2.2)

**Table 16: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = Droxidopa 2000 mg**

	Droxidopa 2000 mg $\Delta$ HR	Placebo $\Delta$ HR	$\Delta\Delta$ HR	
Time (h)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	1.1	2.0	-0.9	(-2.2, 0.4)
1	-0.2	3.0	-3.2	(-4.7, -1.7)
2	-0.2	2.1	-2.3	(-4.1, -0.4)
3	-2.3	0.6	-2.9	(-4.5, -1.3)
4	-2.3	-0.6	-1.7	(-3.4, -0.1)
5	-4.3	-2.7	-1.6	(-3.3, 0.1)
6	-4.7	-2.2	-2.5	(-4.2, -0.8)
8	-2.9	-4.3	1.4	(-0.1, 2.9)
10	-1.7	0.2	-1.9	(-3.5, -0.3)
12	-0.1	0.6	-0.7	(-2.3, 0.9)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 17 and Table 18. The largest upper limits of 90% CI for the PR mean differences between droxidopa 600 mg and placebo, and between droxidopa 2000 mg and placebo were 5.6 ms and 5.9 ms, respectively.

**Table 17: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Droxidopa 600 mg**

	<b>Droxidopa 600 mg <math>\Delta</math>PR</b>	<b>Placebo <math>\Delta</math>PR</b>	<b><math>\Delta\Delta</math>PR</b>	
<b>Time (h)</b>	<b>LS Mean (ms)</b>	<b>LS Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
0.5	0.5	-0.9	1.4	(-0.3, 3.2)
1	0.1	1.2	-1.0	(-3.2, 1.1)
2	0.1	0.1	-0.1	(-2.4, 2.2)
3	2.4	0.2	2.2	(-0.5, 4.9)
4	3.8	1.1	2.7	(-0.1, 5.6)
5	1.3	0.8	0.5	(-1.8, 2.8)
6	2.7	1.2	1.6	(-0.5, 3.7)
8	2.3	1.3	1.0	(-1.0, 3.0)
10	-2.7	-3.8	1.1	(-0.6, 2.9)
12	-1.4	-2.3	1.0	(-0.6, 2.5)
18	-2.2	-2.4	0.3	(-1.8, 2.3)
23	-2.1	-0.1	-2.0	(-3.8, -0.1)

**Table 18: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Droxidopa 2000 mg**

	Droxidopa 2000 mg $\Delta$ PR	Placebo $\Delta$ PR	$\Delta\Delta$ PR	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.2	-0.9	0.7	(-1.0, 2.5)
1	-0.4	1.2	-1.5	(-3.7, 0.6)
2	0.0	0.1	-0.1	(-2.5, 2.2)
3	3.4	0.2	3.2	(0.5, 5.9)
4	2.7	1.1	1.6	(-1.2, 4.5)
5	3.9	0.8	3.1	(0.8, 5.3)
6	4.9	1.2	3.7	(1.6, 5.8)
8	2.1	1.3	0.8	(-1.2, 2.8)
10	-3.5	-3.8	0.4	(-1.4, 2.1)
12	-1.4	-2.3	0.9	(-0.6, 2.5)
18	-4.6	-2.4	-2.1	(-4.2, -0.1)
23	-1.2	-0.1	-1.0	(-2.9, 0.8)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 19 and

Table 20. The largest upper limits of 90% CI for the QRS mean differences between droxidopa 600 mg and placebo, and between droxidopa 2000 mg and placebo were 1.2 ms and 0.8 ms, respectively.

**Table 19: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Droxidopa 600 mg**

	<b>Droxidopa 600 mg <math>\Delta</math>QRS</b>	<b>Placebo <math>\Delta</math>QRS</b>	<b><math>\Delta\Delta</math>QRS</b>	
<b>Time (h)</b>	<b>LS Mean (ms)</b>	<b>LS Mean (ms)</b>	<b>Diff LS Mean (ms)</b>	<b>90% CI (ms)</b>
0.5	0.6	0.4	0.1	(-0.7, 1.0)
1	0.8	0.4	0.4	(-0.5, 1.2)
2	0.2	-0.0	0.2	(-0.5, 0.9)
3	0.3	0.4	-0.1	(-1.0, 0.7)
4	-0.2	0.1	-0.3	(-1.0, 0.5)
5	-1.1	-0.8	-0.3	(-1.0, 0.3)
6	-0.8	-0.1	-0.6	(-1.4, 0.1)
8	0.2	0.7	-0.5	(-1.2, 0.2)
10	-0.7	-0.9	0.2	(-0.5, 0.9)
12	-0.2	-0.1	-0.1	(-0.8, 0.6)
18	-0.6	0.0	-0.7	(-1.4, 0.1)
23	-0.3	-0.0	-0.3	(-1.1, 0.5)

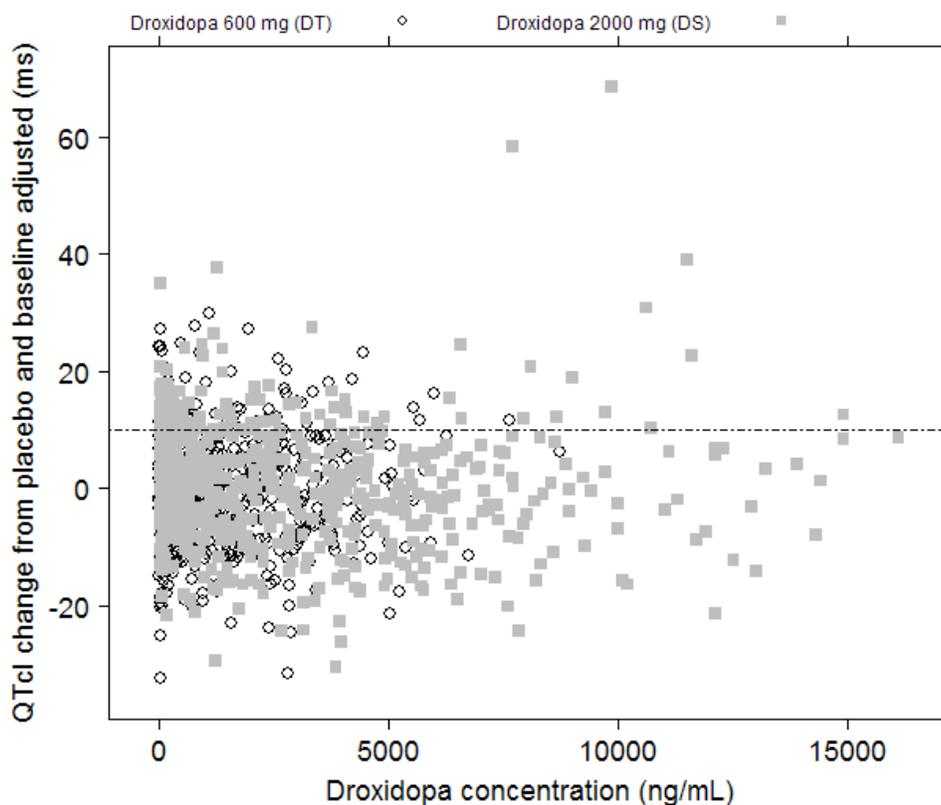
**Table 20: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Droxidopa 2000 mg**

	Droxidopa 2000 mg $\Delta$ QRS	Placebo $\Delta$ QRS	$\Delta\Delta$ QRS	
Time (h)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	0.4	0.4	-0.0	(-0.9, 0.8)
1	0.1	0.4	-0.3	(-1.2, 0.5)
2	-0.7	-0.0	-0.7	(-1.4, 0.1)
3	-0.9	0.4	-1.3	(-2.1, -0.4)
4	-0.4	0.1	-0.5	(-1.3, 0.3)
5	-1.4	-0.8	-0.6	(-1.2, 0.1)
6	-0.6	-0.1	-0.5	(-1.2, 0.3)
8	-0.6	0.7	-1.4	(-2.1, -0.6)
10	-1.1	-0.9	-0.1	(-0.8, 0.6)
12	-0.6	-0.1	-0.5	(-1.2, 0.1)
18	0.0	0.0	-0.0	(-0.8, 0.8)
23	-0.9	-0.0	-0.9	(-1.7, -0.0)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between  $\Delta\Delta$ QTcI and droxidopa concentrations is visualized in Figure 5 with no evident exposure-response relationship.

**Figure 5:  $\Delta\Delta$ QTcI vs. Droxidopa concentration**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

No seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

### 5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 99% of the ECGs were annotated in the primary lead II, with less than 0.02% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

Four subjects in each dose group had PR > 200 ms. Three of them had PR > 200 ms at baseline. None of them had a postbaseline PR > 220 ms.

No subject experienced a QRS > 110 ms in the droxidopa treatment groups.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose Include maximum proposed clinical dosing regimen	Titrated from 100-600 mg t.i.d. by individual patient	
Maximum tolerated dose Include if studied or NOAEL dose	NOAEL = 2000 mg/kg in chronic dog tox	
Principal adverse events Include most common adverse events; dose limiting adverse events	The most common adverse events were mild headache and nausea The dose limiting adverse event in patients with neurogenic orthostatic hypotension was supine hypertension, defined as sustained SBP >180 mmHg	
Maximum dose tested Single Dose Specify dose	2000 mg is the maximum single dose tested in humans.	
Multiple Dose Specify dosing interval and duration	600 mg t.i.d. for >1 year	
Exposures Achieved at Maximum Tested Dose Single Dose* Mean (%CV) Cmax and AUC	300 mg Cmax: 3.2 ug/ml AUC: 13.9 ug•hr/ml	900 mg Cmax: 2.5 ug/ml AUC: 12.0 ug•hr/ml
Multiple Dose Mean (%CV) Cmax and AUC	300 mg t.i.d., 24 hours Cmax: 3.7 ug/ml (32% CV) AUC: 31.6 ug•hr/ml (27% CV)	
Range of linear PK Specify dosing regimen	With single doses in healthy human male volunteers, PK was linear from 100 to 600 mg, and less than linear at 900 mg.	
Accumulation at steady state Mean (%CV); specify dosing regimen	The drug has a half life of approximately 2.5 to 3 hours; steady state Cmax equals single dose Cmax. In t.i.d. dosing 3 peaks are seen each ~2 hr following dosing (doses at 0, 4 and 8 hr)	
Metabolites Include listing of all metabolites and preclinical findings related to QTc	3-OM-DOPS, protocatechuic acid, vanilic acid, norepinephrine.	
Absorption Absolute/Relative Bioavailability Mean (%CV)	Not determined in humans (65-90% in rats)	
Tmax*· Median (range) for parent · Median (range) for metabolites	Droxidopa: 2.0 hr (3)	
Distribution Vd/F or Vd Mean (%CV) % bound Mean (%CV)	Vd/F unknown % bound: 50% at 1 ug/ml	
Elimination Route · Primary route; percent dose eliminated · Other routes	Primary elimination route is urine (~70% in animal studies) Secondary elimination in feces (~10-20% in animal studies) and expired air (~10-20% in animal studies).	
Terminal t½*· Mean (%CV) for parent · Mean (%CV) for metabolites	300 mg Droxidopa: 2.8 hr (11.5%)	900 mg Droxidopa: 2.9 hr 3-OM-DOPS: 5.1 hr
CL/F or CL Mean (%CV)	Not determined	
Intrinsic Factors Age Specify mean changes in Cmax and AUC		
Sex	Not determined	
Race	Not determined	
Hepatic & Renal Impairment	Not determined	
Extrinsic Factors Drug interactions Include listing of studied DDI studies with mean changes in Cmax and AUC		
Food Effects* Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)	High fat meal: Cmax decreased ~35%, AUC decreased ~20%	
Expected High Clinical Exposure Scenario Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	In renal failure Cmax and AUC could be increased as much as 5 fold based on studies in rats. In humans dosing would be adjusted to lower doses and less than t.i.d. in these patients.	

\* Note: Study values on left are from a recently conducted PK study healthy elderly subject. Study values on right are from studies conducted in healthy young males in the EU in the mid-1990s.

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/s/  
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QIANYU DANG  
02/15/2012

JOANNE ZHANG  
02/15/2012

DHANANJAY D MARATHE  
02/15/2012

MONICA L FISZMAN  
02/15/2012

NITIN MEHROTRA  
02/16/2012

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

---

DATE: January 24, 2012

TO: Norman Stockbridge, M.D.  
Director  
Division of Cardiovascular and Renal Products  
Office of New Drugs

FROM: Jangik Lee, Pharm.D., Ph.D.  
Bioequivalence Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance  
Office of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 203-202, Droxidopa Capsules  
100 mg, 200 mg and 300 mg, sponsored by Chelsea  
Therapeutics, Inc.

At the request of the Division of Cardiovascular and Renal Products (DCRP), Division of Bioequivalence and GLP Compliance (DBGC) conducted the audits of the clinical and analytical portions of the following pharmacokinetic study:

**Study number:** 101

**Study title:** "A randomized, open-label, three-period, three-sequence, single-dose crossover and separate three-daily-dose treatment period study comparing the pharmacokinetic profiles following oral dosing of 300 mg of Droxidopa in the fed versus fasted state, the bioequivalence of three 100 mg capsules of Droxidopa versus a single 300 mg capsule of Droxidopa, and 300 mg of Droxidopa given three times at four hour intervals in healthy, elderly subjects"

The inspection of the clinical portions was conducted at Cetero Research, Fargo, ND. The inspection of the bioanalytical

portions was conducted at [REDACTED] (b)(4). Following the inspection at Cetero Research (12/12-12/15/2011), there were no objectionable findings and [REDACTED] as issued. Following the inspection at [REDACTED] (b)(4), Form FDA 483 was issued (at [REDACTED]). On 1/9/2012, DBGCC received a written response from [REDACTED] (b)(4) (attached). Our evaluations of the Form FDA 483 observations and the [REDACTED] (b)(4) response follow:

**BIOANALYTICAL INSPECTION:**

The inspection of the analytical site focused on droxidopa assay for the bioequivalence part (Part I) of Study 101, as requested by DCRP.

1. Failure to document technical source data in the laboratory operations during validation and study runs, including preparation of droxidopa stock solutions, internal standard solutions, calibrators, quality control samples and subject samples, and pre-chromatographic sample extractions for droxidopa

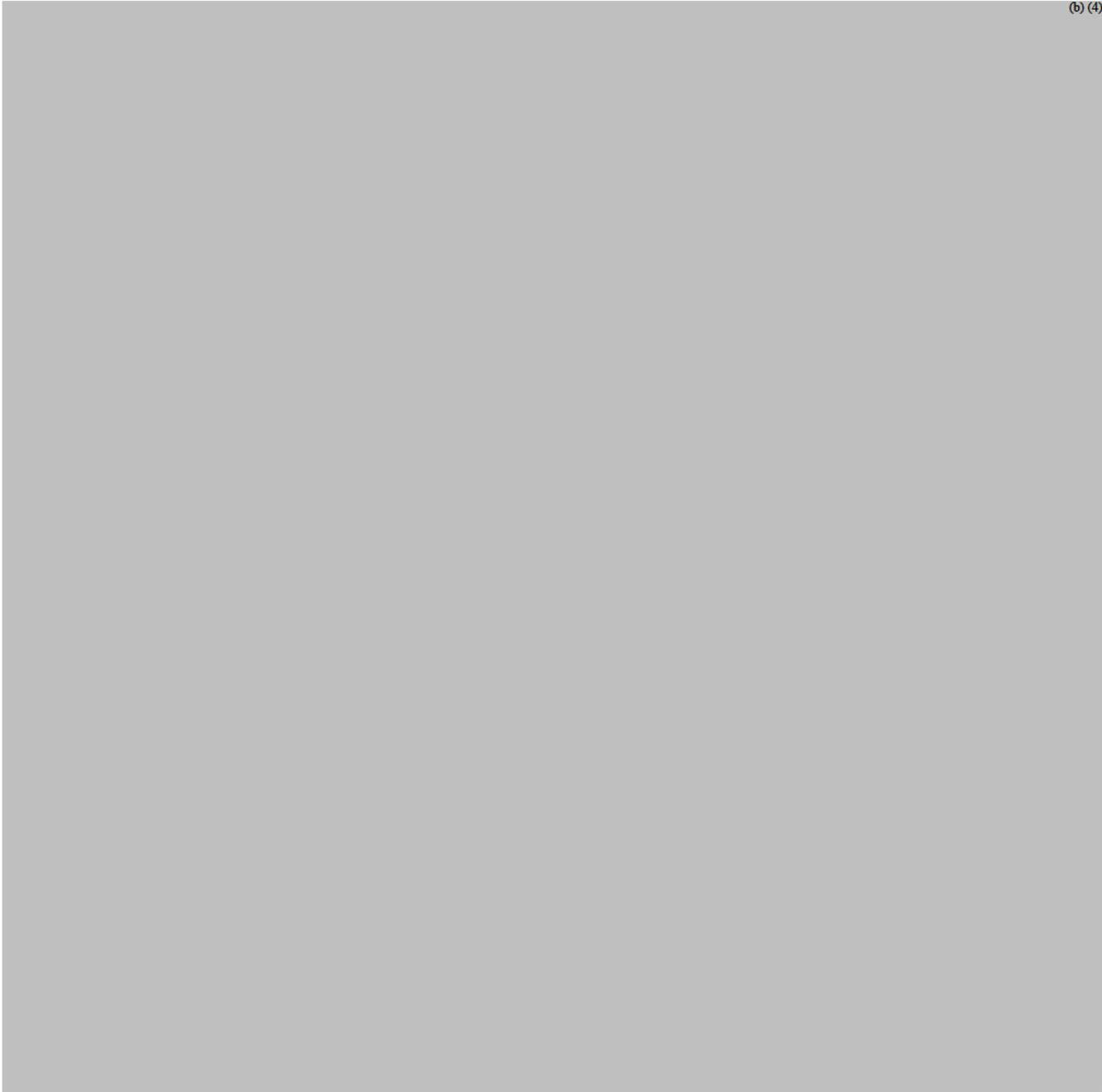
(b)(4)

(b) (4)

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**2. Failure to assure accurate droxidopa concentrations of calibration and quality control samples**

(b) (4)

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(b) (4)

**CONCLUSION**

Following the evaluation of Form FDA-483 Observations and the written response from (b) (4) DBGC recommends that the bioanalytical data in (b) (4) bioequivalence part of Study 101 are not reliable.

After you have reviewed this transmittal memorandum, please append it to the original NDA submission.

Jangik Lee, Pharm.D., Ph.D.

**Final Classifications:**

NAI - Cetero Research, Fargo, ND  
FEI #: 1720861

VAI - [REDACTED] (b) (4)

**Attachments:**

1. Form FDA-483 issued to [REDACTED] (b) (4)
2. Responses to Forms FDA-[REDACTED] from [REDACTED] (b) (4)

**CC:**

OSI: Ball/Moreno  
DBGC: Taylor/Haidar/Patel/Dejernett/CF  
DCRP: Stockbridge/Park  
DCPI: Madabushi/Sabarinath  
MIN-DO: Smith/Holaday  
DET-DO: Dlugosz/Waters  
Draft: JIL 1/20/2012  
Edit: MFS 1/23/2012  
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/s/  
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JANGIK I LEE  
01/24/2012

MICHAEL F SKELLY  
01/24/2012  
Skelly signing on behalf of Dr. Haidar

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2011-118
APPLICATION NUMBER	<b>NDA 203202</b>
LETTER DATE	<b>September 23, 2011</b>
PDUFA GOAL DATE	March 28, 2012
DATE OF CONSULT REQUEST	October 17, 2011
REVIEW DIVISION	DCARP
MEDICAL REVIEWER	<b>Melanie Blank</b>
REVIEW DIVISION PM	Anna Park
SEALD REVIEWER(S)	<b>Elektra J. Papadopoulos</b>
REVIEW COMPLETION DATE	<b>January 23, 2012</b>
ESTABLISHED NAME	Droxidopa
PROPOSED TRADE NAME	Nothera
APPLICANT	Chelsea Therapeutics, Inc.
ENDPOINT(S) CONCEPT(S)	Symptoms and symptom impacts associated with neurogenic orthostatic hypotension (NOH)
MEASURE(S)	Orthostatic Hypotension Questionnaire (OHQ)
CLINICAL OUTCOME ASSESSMENT TYPE	<b>PRO</b>
INDICATION	Symptomatic neurogenic orthostatic hypotension (NOH)
INTENDED POPULATION(S)	Symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta hydroxylase deficiency, or non-diabetic autonomic neuropathy

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### A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Cardiovascular and Renal Products (DCRP) regarding NDA 203202 for droxidopa for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta hydroxylase deficiency, or non-diabetic autonomic neuropathy. The Orthostatic Hypotension Questionnaire (OHQ) overall score was used as a primary endpoint in the phase 3 clinical trials. The OHQ overall score comprises two subscales measuring (a) OH symptom intensity (Orthostatic Hypotension Symptom Assessment, or OHSA) and (b) OH symptom impact on daily activities (Orthostatic Hypotension Daily Activities Scale, OHDAS).

The FDA's 2009 *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (the "PRO Guidance") defines content validity of a PRO instrument as evidence that the items and domains of that instrument are appropriate and complete relative to its intended concept, population and use. Therefore, documentation of content validity includes evidence from qualitative research in the targeted patient population (e.g., patient interviews and focus groups) demonstrating that the instrument measures the concept of interest.

This review concludes that the qualitative research does not support the content validity of the OHQ total score nor its subscales (OHSA and OHDAS) for the following reasons.

#### OHDAS:

- The OHDAS is not a comprehensive assessment of the impact of NOH on a patient's daily activities, as the name of the scale implies, because it does not assess the core disease-defining impacts, i.e., those activities that require positional changes (e.g., from lying to sitting to standing). The qualitative research suggests that patients may also experience symptoms of orthostatic hypotension brought on by other factors (e.g., heat, exercise) that may also affect their daily activities. Several of the patient quotes provided in the tables do not appear to fit with the concepts to which they were mapped. For example, the quote "stooping over and raise up real fast" does not fit with Item 1 (Activities that require standing for a short time).
- It is unclear whether the OHDAS is measuring (a) patients' perceived limitations caused by NOH symptoms in activities that require standing or walking or (b) what activities they actually do and with how much difficulty. The PRO Guidance states that items that ask patients to respond hypothetically may cause patients to respond on the basis of their desired

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condition rather than on their actual condition and therefore are not recommended. In the case of the OHDAS, patients may report on their beliefs regarding the level of interference resulting from NOH symptoms, but it is unclear what level of activity is actually performed and with how much difficulty. In this regard, it is preferable to ask the patients to rate their symptoms (e.g., dizziness or lightheadedness) in the context of typical daily activities e.g., eating, bathing and other self-care activities, and performing usual activities outside the home (e.g., errands) than to try to measure the concept of “interference with daily activities.”

- The OHDAS includes a response option that reads “cannot do for other reasons.” The clinical trial population includes patients who may have difficulty walking for reasons unrelated to their NOH (e.g., Parkinson’s disease). Therefore, it may be difficult for patients to assess the extent of interference from NOH relative to other potential limiting factors.
- Finally, the qualitative research with patients indicated that the individual items in the OHDAS are inadequately defined. For example, patients participating in the cognitive interviews interpreted Item #1 (activities that require standing a short time) variably. Patient interviews revealed differences in interpretation such that it is unclear whether the item is inquiring about standing still in one position, moving while standing (e.g., shifting weight) or rising to a standing position. Furthermore, patients did not understand what was meant by “short time” and some felt that the item should be reworded to include a better definition and examples. Similar concerns with regard to lack of definition of “short time” and “long time” apply to all four items in the OHDAS.

### **OHSA:**

- The OHSA is not a comprehensive measure of patient symptoms because it excludes symptoms of imbalance reported in the qualitative research. Additionally, another attribute of the disease that was described in the qualitative research, falling, is not captured anywhere in the OHQ.
- The OHSA includes some items that showed no discernable effect in the droxidopa phase 3 study, Study 301. No effect was shown on item #5 (concentration) or on item #6 (head and neck discomfort). Additionally, in Study 302, the effect on OHSA Item 2 (vision) numerically favored placebo, although the difference was modest (0.3 units). However, the fact that treatment effect on OHSA Item 2 in this study went in the opposite direction from the other OHSA items indicates that the use of an overall OHSA score is not empirically justified.
- The OHSA includes an item on fatigue (item #4) that should not be described as such in labeling, if this product is approved. The term “fatigue” was not used by patients in the qualitative research; instead, patients referred more commonly to “tiredness” or “weakness.” Additionally, several patients in the cognitive debriefing study indicated that they felt item #3

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(weakness) and item #4 (fatigue) were redundant, or nearly so. In general, experts and patients define fatigue differently. To adequately measure fatigue in this population it is necessary to include: (1) a clear definition of fatigue as it relates to patients with NOH; (2) a clear conceptual framework describing fatigue in NOH including physical and mental components as components, as appropriate; and (3) methods for measuring fatigue symptoms and effect in the presence of comorbid factors (e.g., depression and concomitant medication effects). These elements are not addressed in the PRO dossier.

### Overall:

- The OHQ combines symptoms and symptom impacts into a single overall score (OHQ composite). According to the FDA PRO Guidance, the development and use of a score comprised of more than one component involves consideration of the empirical evidence of the following: the components are of similar importance to patients, the components are equally likely to occur with similar frequency, and the components are likely to have roughly similar treatment effects. The fact that NOH symptoms and NOH symptom impacts, which are expected to be more distal to the effect of treatment than NOH symptoms, are combined into a single overall score may present challenges in interpretation of the measure. Additionally, it is unclear whether there is adequate empiric support for combining these two domains into an overall score
- The OHQ requires patients to distinguish which symptoms are due to their NOH. Some of the symptoms listed in the OHSAs are nonspecific (e.g., fatigue) and can be attributable to a number of causes unrelated to NOH. For example, patients with Parkinson's disease frequently report fatigue, a symptom that could be due to a variety of factors other than NOH (e.g., sleeplessness and medications). When multiple factors potentially underlie a patient's symptom, it is generally impossible for the patient to accurately rate that symptom based on their attribution to a specific cause; to request a patient to do so would threaten the validity of the assessment and is not recommended.
- The recall period for all items on the OHQ is for the one week prior to assessment and subjects are asked to think about their NOH-related symptoms (OHSAs) and symptom impacts (OHDAS) "on the average over the past week" to answer the OHQ questions. According to the PRO Guidance, PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time, are likely to undermine content validity. Response is likely to be influenced by the patient's state at the time of recall.
- The qualitative research report does not include a description of the underlying diagnoses (e.g., Parkinson's disease, multiple system atrophy and pure autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy) in the table describing the demographic and health information of the sample of participants in the qualitative studies (both concept elicitation and cognitive interviews). Patients interviewed were

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classified as having mild, moderate or severe NOH, but the criteria used for this classification were not described. Therefore, it is unclear how well the patients participating in qualitative research are reflective of those participating in phase 3 clinical studies with respect to these parameters.

Therefore, if droxidopa is approved, we do not advise including a reference to the assessment used to support treatment benefit in the *Indications* section of labeling. Statements that name the OHQ overall score or its subscales (OHSA and OHDAS) should be avoided in all sections of labeling. Additionally, Figure 2 of the proposed product labeling describing the results of Study 301 and the text describing the results of Studies 301 and 302 include general claims related to impact on “activities of daily living” that are not substantiated and should be removed. Generally, we discourage claims expressed in terms of domain or instrument titles because they often do not represent the concept measured and, in this particular case, we do not have demonstration of the content validity of the overall instrument or its subscales to measure the targeted concepts.

Instead, we recommend that the concept contained in item 1 of the OHSA (Dizziness, lightheadedness, feeling faint, or feeling like you might black out) should be described in the *Clinical Studies* section of product labeling, if droxidopa is approved. We suggest this approach because (a) the symptoms described in item #1 represent core symptoms of NOH; (b) the symptoms described in some of the other items are not documented to be core disease-defining symptoms of OH and present particular difficulties with undocumented validity and interpretation of result; and (c) not all of the symptoms measured were affected by treatment and some symptoms such as imbalance and falling were not measured so a general claim that NOH symptoms were improved is unsubstantiated. Please also see section 1.2 (Sponsor’s Proposed Labeling) for other comments with regard to the description of the OHQ results in labeling.

## B. SUGGESTED COMMENTS TO APPLICANT

No comments to the applicant are suggested at this time.

## **C. STUDY ENDPOINT REVIEW**

### **1 CONTEXT OF USE**

#### **1.1 Target Population**

The droxidopa development program has sought to evaluate the effect of treatment on symptomatic NOH in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta hydroxylase deficiency, or non-diabetic autonomic neuropathy. Orthostatic hypotension is a diagnostic criterion of the pure autonomic failure; it is noted that some patients with the manifestations of pure autonomic failure may later prove to have other disorders such as multiple system atrophy or Parkinson's disease.

Orthostatic hypotension is defined in the published literature as a reduction in systolic blood pressure of at least 20 mm Hg or a reduction in diastolic blood pressure of at least 10 mm Hg during the first 3 minutes of standing or a head-up tilt on a tilt table.<sup>1</sup>

According to the published literature,<sup>2</sup> characteristic symptoms of orthostatic hypotension include light-headedness, dizziness, presyncope, and syncope in response to sudden postural change. Additionally, non-specific symptoms may be associated, such as generalized weakness, fatigue, nausea, cognitive slowing, leg buckling or headache. Neck pain may occur in the suboccipital, posterior cervical and shoulder region (i.e., coat-hanger headache), which may be due to ischemia in the trapezius and neck muscles. Patients may also have orthostatic dyspnea or angina.

Midodrine hydrochloride (an alpha1-agonist) is the only medication approved by the FDA for the treatment of symptomatic orthostatic hypotension and was approved in 1996. The indication is based on midodrine hydrochloride tablet's effect on increases in 1-minute standing systolic blood pressure, a biomarker that has not been demonstrated to be a valid surrogate marker of treatment benefit. Therefore, at present, the treatment benefit of midodrine hydrochloride tablets has not been established and further clinical trials to evaluate direct evidence of treatment benefit are underway.

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<sup>1</sup>The definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Auton Nerv Syst* 1996; 58:123-4.

<sup>2</sup>Freeman, R. Neurogenic Orthostatic Hypotension. *N Engl J Med* 2008;358: 615-24.

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### 1.2 Sponsor's Proposed Labeling

The sponsor seeks the following indication statement and labeling claims (*italics*).

*Droxidopa (NORTHERA™) is indicated for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), dopamine beta hydroxylase (DβH) deficiency and non-diabetic autonomic neuropathy (NDAN). The clinical benefits of NORTHERA™ on NOH symptoms and the impact of these symptoms on a patient's ability to perform daily activities that require standing or walking have been demonstrated in placebo-controlled clinical trials.*

The clinical studies section of the sponsor's proposed labeling includes the following statements regarding Study 301 (*italics*).

*In Study 301, the change in the OHQ composite score from randomization to the end of the study showed a clinically meaningful and statistically significant benefit favoring NORTHERA (p=0.003, Table 5).*

*Evaluation of NOH symptom intensity (OHSA Composite) showed a clinically meaningful and statistically significant benefit of NORTHERA versus placebo (p=0.010). Evaluation of daily activities (OHDAS composite) showed a clinically meaningful and statistically significant benefit of NORTHERA versus placebo (p=0.003). Patients receiving NORTHERA also experienced a significant change in SBP versus placebo (p<0.001), but not in DBP (p=0.219) as measured three minutes after standing from a supine position.*

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**Table 5**                      **Improvement in Efficacy measures***(Randomization to End of Study)*

	<b>Placebo (n=79)</b>	<b>NORTHERA (n=81)</b>	<b>Improvement Over Placebo</b>	<b>p-value</b>
Global Assessment (OHQ) Mean (SD)	0.93 (1.69)	1.83 (2.07)	0.90	0.003
Symptom Composite (OHSA) Mean (SD)	0.95 (1.901)	1.68 (2.125)	0.73	0.010
Symptom Impact on Daily Activities (OHDAS) Mean (SD)	0.92 (1.816)	1.98 (2.310)	1.06	0.003
Systolic Blood Pressure, Standing (+3 min) mmHg (SD)	3.9 (16.3)	11.2 (22.9) <sup>1</sup>	7.3 mmHg	<0.001
Diastolic Blood Pressure Standing (+3 min) mmHg (SD)	3.4 (10.4)	5.5 (13.4) <sup>1</sup>	2.1 mmHg	>0.2

<sup>1</sup>n=82

Abbreviations: OHDAS=orthostatic hypotension daily activity scale; OHQ=orthostatic hypotension questionnaire; OHSA=orthostatic hypotension symptom assessment

*Patients treated with NORTHERA were more likely to show improvements in symptoms versus placebo across the individual items of the OHQ. NORTHERA showed statistically significant improvements over placebo in 4 of 6 individual items of the OHSA: dizziness (p<0.001), vision (p=0.013), weakness (p=0.007), and fatigue (p=0.030), and in all 4 individual items of the OHDAS: standing a short time (p=0.003), standing a long time (p=0.001), walking a short time (p=0.009), and walking a long time (p=0.007). The improvement in item scores of NORTHERA versus placebo is shown in Figure 2.*

*Reviewer's comment: The highlighted statement should be removed, because it implies that all of the items in the OHSA demonstrated a treatment effect, when 2 of the 6 items in the OHSA failed to demonstrate a treatment effect.*

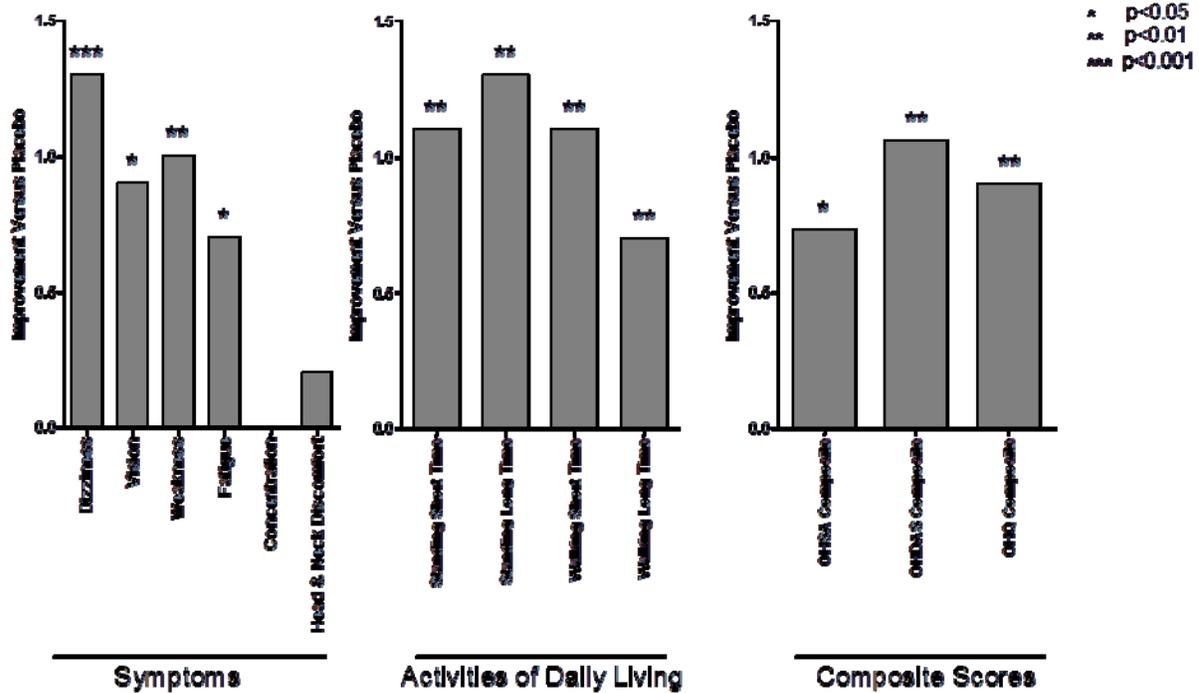
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Figure 2 *NORTHERA Improvement Versus Placebo Study 301  
Randomization to End of Study*



The clinical results of Study 302 are described as follows in proposed product labeling (*italics*).

### *Clinical Results*

*The change in the OHQ composite score from randomization to the end of the study showed benefits favoring NORTHERA. Patients treated with NORTHERA had a clinically meaningful 1.11 unit improvement versus placebo in a post-hoc analysis of the OHQ (p=0.026).*

*Evaluation of NOH symptom intensity (OHS composite) showed a trend for improvement in NORTHERA patients compared with placebo (p=0.16). Evaluation of symptom impact on daily activities (OHDAS composite) showed a clinically meaningful and statistically significant effect of NORTHERA treatment compared with placebo (p<0.04).*

*Patients treated with NORTHERA were more likely to show greater improvements in symptoms versus placebo across the individual items of the OHQ. NORTHERA demonstrated a trend for improvements over placebo in 5 of 6 individual items of the OHS, and in all 4 individual items of the OHDAS.*

### *Reviewer's comments:*

- Study 302 failed to meet its primary efficacy endpoint, which was a comparison between treatment groups using OHS Item 1 (dizziness). The proposed labeling describes a change on the OHQ composite score, which was noted as a result of a post-hoc, exploratory analysis.*

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- *The review of the OHQ fails to demonstrate that the tool is well-defined and reliable measure of the following concepts: “ability to perform daily activities that require standing or walking.” This reviewer recommends removal of these statements from labeling if this drug is approved. Consequently, the OHQ composite score should not be described in product labeling, because it comprises both “symptoms” and “activities of daily living” in an overall score.*
- *Figure 2 of product labeling describing the results of Study 301 and the text describing the results of Studies 301 and 302 include general claims related to impact on “activities of daily living” that are not substantiated and should be removed. Furthermore, the scale used in Figure 2 (0-1.5) is suggestive of a larger treatment effect than was actually demonstrated, because each of the items of the OHQ are scored on a scale from 0-10.*

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### 1.3 Endpoint Model

An endpoint model is used to describe the hierarchy of relationships among all endpoints, both PRO and non-PRO, that corresponds to the clinical trial's objectives, design, and data analysis plan. The following figure shows the endpoint model used for the droxidopa phase 3 studies.

**Figure 1 Endpoint Model: Droxidopa Phase 3 Clinical Studies**

Concept	Endpoint <sup>1</sup>	Measurement Basis
<b>Primary</b>		
NOH symptoms and symptom impacts	→ Mean change in the OHQ composite score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
<b>Secondary</b>		
NOH symptom impacts	→ Mean change in OHDAS composite score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
NOH symptoms	→ Mean change in OHSA composite score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
Impact of NOH symptoms on daily activities that require standing for short time	→ Mean change in OHDAS Item 1 score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
Impact of NOH symptoms on daily activities that require walking for short time	→ Mean change in OHDAS Item 3 score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
Dizziness/lightheadedness due to NOH	→ Mean change in OHSA Item 1 score from Randomization (Visit 4) to the End of Study (Visit 5)	Patient-reported outcome
Global improvement in NOH	→ Difference between treatment arms in Clinical Global Impression of Change (CGI-S) score at End of Study (Visit 5)	Patient-reported outcome
Global improvement in NOH	→ Difference in clinician-recorded CGI-S score at End of the Study (Visit 5)	Clinician-reported outcome
Blood pressure upon standing	→ Mean change in SBP and DBP upon standing from Randomization (Visit 4) to the End of Study (Visit 5).	Clinical measurement

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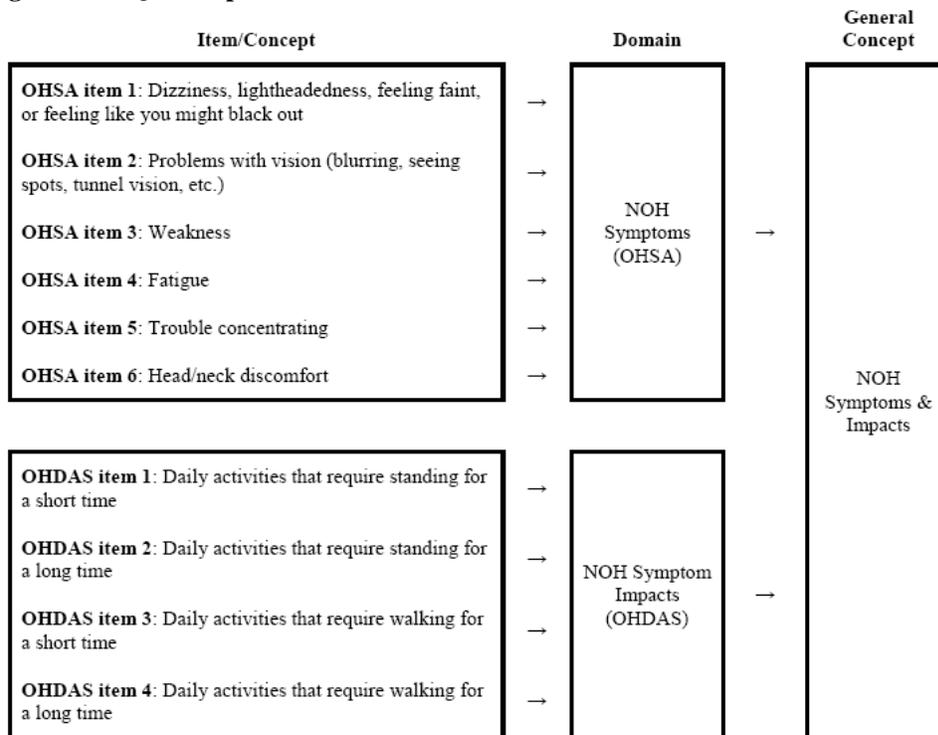
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*Reviewer's comment: This conceptual framework is inconsistent with the concepts claimed in the sponsor's proposed draft product labeling. The sponsor's submission uses the terms and phrases "activities of daily living that require standing or walking", "activities of daily living" and "NOH symptom impacts" interchangeably. However, these are not equivalent terms. The OHDAS is not a complete measure of symptom impact on daily activities because it omits impacts on activities that require positional changes (e.g., from lying to sitting to standing). Furthermore, the qualitative research does not support a common understanding of the items in this OHDAS subscale (see Section 4 of this review for more detail); this is a critical element needed to support an instrument's content validity.*

## 2 CONCEPT OF MEASUREMENT AND CONCEPTUAL FRAMEWORK

The following is a conceptual framework of the OHQ as shown in the PRO dossier.

Figure 2 OHQ Conceptual Framework



The OHQ has two subscales: the NOH symptoms and NOH symptom impacts. The mean scores from each of the two subscales are averaged to generate an OHQ composite score that represents both symptoms and symptom impacts.

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### *Reviewer's comments:*

*According to the FDA PRO Guidance, the development and use of a score comprised of more than one component involves consideration of the empirical evidence of the following: the components are of similar importance to patients, the components are equally likely to occur with similar frequency, and the components are likely to have roughly similar treatment effects.*

*The fact that NOH symptoms and NOH symptom impacts, which are expected to be more distal to the effect of treatment than NOH symptoms, are combined into a single overall score may present challenges in interpretation of the measure. Additionally, it is unclear whether there is adequate empiric support for combining these two domains into an overall score.*

## **3 CLINICAL OUTCOME ASSESSMENT MEASURE**

The OHQ (Malamut, 2005) is a patient-reported outcome instrument made up of two subscales as follows:

- (1) The Orthostatic Hypotension Symptom Assessment (OHSA) scale includes six items that rate the presence and severity of NOH symptoms (dizziness/lightheadedness, problems with vision, weakness, fatigue, trouble concentrating, and head/neck discomfort).
- (2) The Orthostatic Hypotension Daily Activity Scale (OHDAS) includes four items that rate the impact that NOH symptoms have on daily activities that require standing (two items) or walking (two items).

The OHQ is administered on paper and all ten items require patients to record their responses using an 11-point horizontal numeric rating scale. For the OHSA subscale, patients are to report on the average symptom severity during the week prior to assessment. For the OHDAS subscale, subjects are asked to rate the impact of NOH symptoms “on the average over the past week,” where 0=No interference and 10=Complete interference and, additionally, patients have the option of indicating that they cannot perform the evaluated activities for reasons other than NOH. As described above, the two subscales are averaged together to produce an overall score representing symptoms and symptom impacts.

*Reviewer's comments: The recall period for all items on the OHQ is for the one week prior to assessment and subjects are asked to think about their NOH-related symptoms (OHSA) and symptom impacts (OHDAS) “on the average over the past week” to answer the OHQ questions. According to the 2009 FDA PRO Guidance, PRO instruments that call for patients to rely on memory, especially if they must recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time, are likely to undermine content validity. Response is likely to be influenced by the patient's state at the time of recall.*

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The OHQ is self-administered (i.e., completed by the patient) on a paper format at three times during the pivotal trial (Study 301); at Baseline (Visit 2), Randomization (Visit 4), and End of Study (Visit 5). Where possible, all assessments were to be conducted at approximately the same time of day at each clinic visit (in the morning after breakfast, but before lunch), 3 hours after their first dose of droxidopa for the day (corresponding time of day for Visit 4). The time of assessments was documented on the case report form.

Study sites were instructed to read the instructions to patients then give the instructions and scoring sheet to the patient to complete. The questionnaire includes specific instructions that are read aloud to the patients before the questions are answered.

## 4 CONTENT VALIDITY

Patient input into the concepts of importance and relevance in NOH was obtained via a qualitative concept elicitation study to create an opportunity for NOH patients to spontaneously report on their NOH-related symptoms and impacts.

A total of 20 patients (maximum of 6 diabetic patients) were to be recruited to participate in individual face-to-face concept elicitation interviews.

In order to obtain high quality information, patients will need to meet **all** of the study **inclusion and none of the exclusion** criteria. Inclusion and exclusion criteria for patients are listed below.

### **Inclusion Criteria:**

- At least 18 years of age;
- Clinical diagnosis of systematic orthostatic hypotension associated with Autonomic Failure (PD, MSA, and PAF), Dopamine beta Hydroxylase Deficiency, or Diabetic or non-Diabetic Autonomic Neuropathies;
- Within two weeks, patient has a documented fall in systolic blood pressure of at least 20mmHg, or in diastolic blood pressure of at least 10mmHg, within three minutes after standing;
- Fluent in US English (i.e., able to speak, read, and write).

### **Exclusion Criteria:**

- Previously participated in a clinical trial which utilized the Orthostatic Hypotension Questionnaire (OHQ);
- Patient has, within two weeks, increased dose, frequency, and/or type of medication prescribed for Orthostatic Hypotension;
- Patient has a history (within the past year) of alcohol abuse, or of known or suspected drug or substance abuse;

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- Patient is pregnant or breast feeding;
- Patient has a clinical diagnosis of significant Cardiogenic Orthostatic Hypotension, severe hepatic failure, or end stage renal disease;
- Patient has a known malignancy, with the exception of basal cell carcinoma (Patients previously treated for a malignancy who have not shown any signs of reoccurrence within the past year and for whom the Investigator is willing to document that in their opinion the malignancy was successfully treated will be eligible for inclusion);
- In the Investigator's opinion, patient is suffering from a mental disorder that interferes with the diagnosis and/or with the conduct of the study (e.g., schizophrenia, major depression, dementia);
- Patient has participated in a clinical trial with an investigational agent, related to the treatment of Orthostatic Hypotension or cardiovascular illness, within four weeks; and
- Patient has a condition or is in a situation that would put the patient at significant risk, confound the study results, or may interfere significantly with the patient's involvement with the study

Interviewers were to follow a semi-structured concept elicitation interview guide and the qualitative data were to be analyzed using ATLAS.ti version 6.0.

Researchers were to develop a coding scheme to be applied to all transcripts. The preliminary coding scheme was to be based on the interview guide. Four coders were to code the first transcript separately, and then meet to review the coded transcript together and discuss any issues or questions. The coding scheme was to be modified as the coders analyze the transcripts and add or modify codes. Using the coding scheme, patients' experiences related to NOH will be classified and organized.

Saturation of concept refers to the stage in the qualitative data collection and analysis process when further data and analysis cease to generate any new or distinctive categories, high level concepts, or substantive codes. Researchers were to evaluate saturation using a saturation grid to compare the amount of new information that is observed.

Following concept elicitation, the researchers were to assess for patient understanding of the items through cognitive interviews. A total of 20 patients were to be recruited to participate in individual face-to-face cognitive interviews, where they were to be asked to complete the OHQ and provide feedback using a "think aloud" technique. In this way patients could comment about the process they used to arrive at each answer and to identify words, terms, or concepts that they may not understand or might interpret differently than intended.

### **Results:**

#### **Patient Characteristics:**

A total of 20 patients across five clinical sites in the United States were interviewed (n=6 in Punta Gorda, FL; n=2 in Winston-Salem, NC; n=6 in St. Louis, MO; n=5 in Los Angeles, CA; and n=1 in Chicago, IL).

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**Table 1 Demographic and Health Information for Participants in Concept Elicitation Interviews**

<b>Characteristics</b>	<b>Total (N=20) n (%)</b>
<b>Gender</b>	
• Male	12 (60%)
• Female	8 (40%)
<b>Age</b>	
• Range	[32 – 84]
• Mean (SD)	67.35 (12.69)
<b>Spanish/Hispanic/Latino</b>	
• No	20 (100%)
<b>Race</b>	
• White	16 (80%)
• African American	2 (10%)
• Multiracial	2 (10%)
<b>Education</b>	
• High school diploma or GED	6 (30%)
• Some college or certificate program	7 (35%)
• College or university degree	5 (25%)
• Graduate degree	2 (10%)
<b>Work Status*</b>	
• Working full-time	3 (15%)
• Homemaker	1 (5%)
• Retired	14 (70%)
• Unemployed	1 (5%)
• Other- Disabled	1 (5%)
<b>Annual Household Income</b>	
• Under \$25,000	5 (25%)
• \$25,000 to \$49,999	4 (20%)
• \$50,000 to \$74,999	6 (30%)
• \$75,000 to \$99,999	2 (10%)
• \$100,000 and over	1 (10%)
<b>Marital or Relationship Status</b>	
• Married	16 (80%)
• Separated	1 (5%)
• Divorced	2 (10%)
• Widowed	1 (5%)
<b>General Health</b>	
• Very good	2 (10%)

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**Table 1 Continued**

Characteristics	Total (N=20) n (%)
• Good	9 (45%)
• Fair	8 (40%)
• Not answered	1 (5%)
<b>Treatments previously or currently used*</b>	
• None	9 (45%)
• Fludrocortisone (Florinef)	4 (20%)
• Midodrine (Amatine, ProAmatine, Gutron)	2 (10%)
• Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen)	3 (15%)
• Caffeine pills	1 (5%)
• Compression stockings	4 (20%)
• Other – Toprol xl- 25 mg	1 (5%)
• Other – Amlodipine besylate	1 (5%)
<b>Severity of orthostatic hypotension/low blood pressure</b>	
• Mild	7 (35%)
• Moderate	12 (60%)
• Severe	1 (5%)

The participants' ages ranged from 32 to 84 years (mean=67 years), 40% (8/20) were female, 80% (16/20) were Caucasian. A total of 30% (6/20) had a high school degree only and the remainder had at least some college.

Four patients reported receiving a diagnosis of NOH more than 10 years prior to the interview; most patients reported receiving the diagnosis within five years.

Nearly half of the patients (9 out of 20) did not report previous or current use of any specific therapy for their NOH.

In the droxidopa phase 3 trial, Study 301, the mean age was ~56 years, 97% of the patients were Caucasian, and 52% were male. In Study 301, the proportion of patients with PD, MSA and PAF were 41%, 16% and 33%, respectively, and the mean baseline OHQ composite scores were 5.6 to 6.0 across treatment groups; approximately 60% of the patients were enrolled in non-US sites.

*Reviewer's comments: The PRO dossier did not include a description of the underlying diagnoses (e.g., Parkinson's disease, multiple system atrophy and pure autonomic failure, dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy) in the table describing the demographic and health information of the sample of participants in the qualitative studies (both concept elicitation and cognitive interviews). Although 13 of the 20 patients were classified as at least moderate, is also unclear how patients were categorized into "mild, moderate and severe" orthostatic hypotension in the qualitative studies (see table above).*

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*Additionally, it is unclear how this compares with the demographic and disease characteristics in the phase 3 clinical trials for droxidopa. If the populations are not similar, we cannot be certain of the content validity of this instrument in the context of use under review.*

**Saturation:**

Saturation is defined as the point at which it appears that additional interviews would provide no unique concepts or information from the patient perspective. The following table demonstrates the concepts elicited by serial cohort of patients interviews.

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**Table 2 Summary saturation matrix for spontaneously elicited NOH symptoms and symptom impacts (N=20)**

Concept	Cohort 1 (1-5)	Cohort 2 (6-10)	Cohort 3 (11-15)	Cohort 4 (16-20)
<b>NOH Symptom Concepts<sup>1</sup></b>				
Dizziness/lightheadedness	X	X	X	X
Vision problems		X	X	X
Weakness	X	X	X	X
Fatigue	X	X	X	X
Trouble concentrating		X	X	
Head/neck discomfort		X	X	X
Imbalance	X	X	X	X
Falling	X	X	X	X
Disoriented	X			
Memory problem			X	
Nausea		X		
Pain		X		
Leg pain			X	
<b>NOH Symptom Impact Concepts<sup>2</sup></b>				
Daily activities that require standing for a short time	X	X	X	X
Daily activities that require standing for a long time	X	X	X	X
Daily activities that require walking for a short time	X	X	X	X
Daily activities that require walking for a long time		X	X	X

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*Reviewer's comments: Table 2 shows that two patient-reported attributes of NOH falling and imbalance were noted in all four cohorts; however, neither is addressed in the OHQ. This appears to be an important missing item.*

*The term "fatigue" was not typically used by the patients participating in the qualitative research; instead patients used terms such as "tiredness." Therefore, results summaries should avoid use of the term "fatigue."*

The concept tracking matrix found the PRO dossier included the following section related to activities.

**Table 3 Excerpt from Concept Tracking Matrix (Activities)**

Concept Code	Patient language for concept code	Patients (Total n=20)	Experts (Total n=3)	OHQ item	Comprehension (% of patients in CIs)
<b>Impacts</b>					
ADLs, slow movement, bending down	... just taking a shower.... Is very time-consuming, it seems.... Getting dressed ... everything is just slower I have cats. When I stoop down to feed the cats or when stoop down to give them medicine and get back up, sometimes I have that dizzy, little dizzy spell if I stoop over and raise up real fast, I get light-headed I would say it really doesn't affect anything I want to do. Uh, other than it may delay something I want to do.... I'll have to wait until my blood pressure gets back to where it's supposed to be before I can do what I want to do	8	3	OHDAS Item 1: Activities that require standing for a short time	87%
Standing for long time	As long as I can – you know, and again, I can't just stand. I have to have my back against something.... You know, it's some – I don't want to stand just in the middle of the room If – again ... just doing it longer than say 15, 20 minutes and then I start feeling lightheaded	10	3	OHDAS Item 2: Activities that require standing for a long time	82%
Walking, leisure activities that require walking	That's why I've got to rent DVDs. Can't go to the show or I can't sit through a movie - I have to be careful whatever I do. Like for instance, I live on the water.... And ... I don't go down to the dock anymore. I'm afraid of falling	7	3	OHDAS Item 3: Activities that require walking for a short time	64%
Walking for a long time, exercising	The only problem's like when I'm standing up, or when I'm walking too much Well, I don't do – go the grocery store anymore, I just have trouble moving around and I get tired Well, if I just jumped in like I used to do during a 20-minute cardio thing ... it's not right. I don't feel good I don't play golf any more.... I used to be a very good dancer. I think the blood pressure does it	9	2	OHDAS Item 4: Activities that require walking for a long time	58%

*Reviewer's comments: Several of the quotes provided in the tables do not appear to fit with the concepts to which they were mapped. For example, the quote "stooping over and raise up real fast" does not fit with Item 1 (Activities that require standing for a short time). It is also unclear how the quote "can't go to the show or I can't sit through a movie" fits with Item 3 (Activities that require walking for a short time).*

Patient quotes regarding general activities of daily living are shown in the following table.

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**Table 4 Patient Quotes: General Activities of Daily Living**

Impacts	
Patient Quotes	
(N=20)	
<b>Activities of daily living</b>	
<p><b>Activities of daily living - General</b></p> <p><b>Total (n=11) – 101, 102, 113, 114, 203, 301, 302, 303, 310, 403, 604</b></p> <p>Spontaneous (n=10) – 101, 102, 113, 114, 203, 301, 302, 303, 310, 403, 604</p>	<p>(101) ... just taking a shower.... Is very time-consuming, it seems..... Getting dressed ... everything is just slower.... And I don't know whether that's the blood pressure or that's Parkinson's.; A: And I try ... and do those projects ... I don't like it when my dishwasher is full of clean clothes - clean dishes - and my washer and dryer have to be on for the dirty clothes.... So I'll do one one day and one the next day. Q: ... <i>So like you said, you don't plan on too many projects a day?</i> A: Yeah.... It's a coping mechanism, very definitely.; And the low, I really have to - you know, I - I try very hard. You know, just getting something out of the refrigerator.... On the bottom shelf. Anytime I have to lean over..... And I'm one of these people that likes to wipe up spots on the floor. You know, I can still touch the floor, but you know, then getting back up is hard, you know?... And in the shower, I want to ... scrub a little bit of the floor or something, and then I realize that ... get up very slowly, but you still - you still have to ... get centered..... And stand up.; ... I can't scrub the kitchen floor or scrub the shower floor like I used to.; We do an exercise - we have an exercise class that meets twice a week over at the wellness center.... And we do some that ... go all the way down to the floor..... Well, if I can keep my head up as much as possible, I'm OK.</p> <p>(102) ... I have to be careful whatever I do. Like for instance, I live on the water..... And ... I don't go down to the dock anymore. I'm afraid of falling.</p> <p>(113) And don't do nothing in our only garden.</p> <p>(114) A: And I suppose that does keep me from doing the blood pressure, because I hate to be out and about and.... I think it's a - a combination of blood pressure and Parkinson's, and the whole thing.; A: Well, I don't ... go the grocery store anymore.... Well, I just have trouble moving around and I get tired. Q: ... <i>You get tired. Can you tell me a little bit more about that?</i> A: Well, ... I just generally get tired and I have to sit down for a few minutes.; A: Well, you're just getting dressed and that ... general things that I do every day. And s - some days are more difficult than - Q: OK. <i>And ... what about them is a little bit more difficult than it used to be?</i> A: I just can't move around as fast.; Q: <i>And what kind of things are you referring to that it takes you more time to do?</i> A: Well, it takes me longer to get dressed.... And ... any activities I'm doing around the house, it just takes longer ... for me to do.... Well - why does it take me longer? I don't know. I just can't move that fast anymore. Q: ... <i>And do you think that's due to your low blood pressure?</i> A: I think a lot of it is. Q: <i>And ... what kind of activities around the house were you referring to?</i> A: Well, like washing dishes, cleaning up the kitchen.... Just normal things ... that I do.</p> <p>(203) I have cats. When I stoop down to feed the cats or when stoop down to give them medicine and get back up, sometimes I have that dizzy, little dizzy spell..... Because this is down on the floor... all the way to the floor and then back up again. And that's one of the things, um. If I stoop down to pick up something or sometimes and sometimes not.; Uh, some days I am more dizzy than other days and that</p>

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Impacts	
Patient Quotes (N=20)	
	<p>contributes to a bad day. That means I don't do as much as I would normally do. I'm not as active as I would normally be.; Getting something out of a high cabinet.; Picking up something off of the floor. That's it.; If I am trying to change a light bulb over my head with my arms up, I get dizzy.</p> <p><b>(301)</b> Q: <i>Or like, if - like let's say like your hands were up in the air for a certain period of time, do you ever feel anything come on when that happens?</i> A: Um - then I would feel sometimes, sometimes yell, like, my husband, he has me helping him with something, I have to put my hands up for a long while. I can't do that very long, ... they get real tired, ... I can't hold them up very long.; Q: <i>Is this the sluggishness or tiredness that you experience in the morning, does that ever impact anything that you do?</i> A: No, other than just ... maybe taking it easy for a couple of hours, and then whenever I get a little more energy or whatever, then I do my laundry, or go shopping, or whatever.; Q: <i>And what about on ... when you said sometimes you feel sluggish and you think that might be because of your low blood pressure. Um, what are those days like for you. Is there anything that you don't do that you normally would?</i> A: ... probably not as active, maybe.</p> <p><b>(302)</b> I'm just totally useless, weak. I have no ability to do anything. I just feel washed out.; Q: <i>And can you tell me what you mean, when you say weak?</i> A: Uh, unable to do anything, for a period of time.; A: Oh, if I stoop over and raise up real fast, I get light-headed ..... but it's not the same as the falling.... I can reach down and grab something, pick it up, put it on a table or something. When I go to get up, then I get a little light-headed. Just like that.; Just when it occurs ... that you got to stop, and go on, and you keep going.; If there's a little tree branch in the yard, I pick it up. So you're bending over there. Uh, sweeping the floor. Standing at the sink doing dishes, you're bent over there.; Have to stand at the sink and you're bent over doing the dishes in the sink and you get lightheaded.; Well, like I said, the yard work, or getting up off my knees after being down for five minutes or so.; If I'm down on my knees for awhile, doing something, like gardening, or something like that.</p> <p><b>(303)</b> Q: <i>Is it in a certain part of your body or -</i> A: Drained? Q: <i>Yeah.</i> A: The whole body...Yeah, it just - like blah... Q: <i>Just blah.</i> A: God, I hope I don't have to go to the bathroom, you know? Q: <i>Um, so are you able to move at all, or is it -</i> A: I can force myself to move, yeah...that's not a problem, it's just that I don't want to. You know, that's the best way to say it. I just don't feel I have the energy and I don't really want to get up and do anything.</p> <p><b>(310)</b> It used to be when I was doing a lot of ... hard work out in the yard or something, but that's the last two or three times it's happened.; Q: <i>What about ... you mentioned a couple times like during work out in the yard. Is there anything that you don't do anymore in the yard, or that you can't do as long?</i> A: Um, no. I just slow down and don't do it ... quite as fast. Q: <i>OK. And what do you slow down doing?</i> A: All of it. Q: <i>All of it?</i> A: Yep. Q: <i>That's like you said it was like using a chainsaw and like what else do you do?</i> A: Oh, get out there and push-mow the yard, run a weed eater.</p>
Impacts	
Patient Quotes (N=20)	
	<p><b>(403)</b> I know I've got to do it in moderation. I can't do what I did 10 years ago. It's just that if I want to, I can't.</p> <p><b>(604)</b> It - it really does affect my life because I'm afraid to p - drive very far, be by myself -; Watching my grandchild. I mean not that I do it that often, but when I do watch ... she's a four-year-old and ... I mean what - is she going to know what to do?; A: Um, actually, I was in Walmart ..... but there was a bench and I sat down ... quickly. Q: <i>So were you walking or you were standing?</i> A: I was walking. I was shopping. I felt perfectly fine..... I mean everything was fine and all of the sudden, it just came across me. I sat down. It went away quickly ..... and I left the store because I thought if this is it, I'm not interested in shopping anymore.;</p>

*Reviewer's comments: These patient quotes show the variety of impacts that patients report on their general daily activities. Limitations reported include activities that require moving around (e.g., shopping), activities that include sitting (e.g., driving), activities that require reaching down and getting up (e.g., picking up something off the floor), activities requiring kneeling (e.g., gardening), activities that require raising one's hands over one's head (e.g., changing a light bulb) and others. The quotes demonstrate that a general lack of energy (e.g., sluggishness or tiredness) as well as light-headedness can impact patient's performance of activities of daily living in this patient population, which included patients who reported having Parkinson's disease.*

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*Reviewer's comments: Cognitive debriefing or other forms of patient interview in the targeted clinical trial population should demonstrate that the items are comprehensive with respect to the measurement concept and that patients understand the questions asked and respond in a way that was intended. However, qualitative research did not confirm that patients understood the items found in the OHDAS scale. Furthermore, there is ambiguity regarding what this scale is intended to measure for several reasons. First, it is not a comprehensive assessment of the impact of NOH on patient's daily activities as the name of the scale implies, because it does not assess the core disease-defining impacts, i.e., those activities that require positional changes (e.g., from lying to sitting to standing).*

*The second major reason that the scale is ambiguous is that it is unclear whether the scale is measuring (a) patients' perceived abilities to perform activities that require standing or walking or (b) what they actually do. The final PRO guidance document states that items that ask patients to respond hypothetically may cause patients to respond on the basis of their desired condition rather than on their actual condition and therefore are not recommended. For example, in assessing the concept "ability to perform daily activities," it is more appropriate to ask whether or not the patient performed specific activities (and if so, with how much difficulty) than whether or not the patient perceived that he or she can perform daily activities, because patients may report they are able to perform a task even when they never do the task. In this regard, it is clearer to ask the patients to rate their symptoms in the context of daily activities.*

*Finally, the individual items in the OHDAS are inadequately defined. For example, patients participating in the cognitive interviews interpreted Item #1 (activities that require standing a short time) variably. Patients' responses showed there were differences in interpretation such that it is unclear whether the item is inquiring about standing still in one position, moving while standing (e.g., shifting weight) or rising to a standing position from lying or sitting. Furthermore, patients did not understand what was meant by short time and felt that the item should be reworded to include a better definition and examples. For example, one patient asked, "What do you mean short time? 10 minutes? 20 minutes? 30 minutes?" Another patient commented that a standing a short time could vary from seconds ("standing momentarily to greet a person") to longer periods of time (e.g., "time to make a martini").*

## **5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)**

This section describes reliability, construct validity and ability to detect change; however, it is important to note that these psychometric properties of an instrument cannot be adequately interpreted without demonstrating adequate content validity. Furthermore, these analyses are drawn from data obtained from another drug development program (that of midodrine

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hydrochloride) and not from the droxidopa phase 3 studies. An evaluation of the OHQ's psychometric properties using data from the droxidopa phase 3 studies was not provided in the PRO dossier.

### **Internal Consistency Reliability:**

Internal consistency of scores generated by the OHQ was evaluated by Cronbach's coefficient alpha. Alpha scores range from 0.00 and 1.00, with the desired scores greater than 0.70. At the baseline assessment (n=136), the alpha coefficient was 0.89 for the OHQ composite score and 0.84 for each of the OHSA and OHDAS composite scores.

### **Test-retest Reliability:**

Evidence that scores are stable over time when no change has occurred in the concept of interest (test-retest reliability) of the OHQ was assessed with the intraclass correlation coefficient (ICC) and based on a clinically stable group of patients between the Baseline (Visit 3) and the Cross-over Visits (Visits 5 and 6).

Patients were identified as stable if they scored "4" (no change) on the clinician-scored Clinical Global Impression of Severity (CGI-S) and patient-scored CGI-S from Baseline to Visit 5. The ICC was 0.86 (n=18) for the OHQ composite score and 0.92 (n=18) and 0.87 (n=18) for the OHSA and OHDAS composite scores, respectively.

*Reviewer's comments: The sponsor's PRO dossier stated that patients participating in the psychometric evaluation study were given an opportunity to see their baseline visit or "test" scores prior to completing the OHQ at the time of "retest." This may have artificially increased the reported reliability estimates. (In response to an information request from the Agency, the sponsor clarified that in the phase 3 droxidopa studies, patients were **not** given access to their previous scores.)*

### **Construct Validity:**

Construct validity is determined by evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.

The sponsor provided Table 4 below as evidence of construct validity of the OHQ. Pearson correlation coefficients (r) were computed between the OHQ scores and scores generated by (a) the two CGI-S scales (one was a clinician-reported outcome and the other a PRO) and (b) the SF-36 generic health questionnaire scales. The sponsor used the following guidelines to interpret these correlations: "small relationship", r=0.1–0.23; "medium relationship", r=0.24–0.36; and "large relationship", r=0.37 or larger.

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1. It was expected that the OHQ composite score would have large observed relationships with the CGI-S scales and that the relationship would be strongest with the patient-reported version of the CGI-S. These expectations were met at each of the three assessment time points.
2. The associations between the OHQ composite score and the SF-36 scale and summary measure scores, as more distal health-related quality of life (HRQoL) domains, were expected to be moderate to large but less strong than associations between it and the OH severity measures described above. This expectation was confirmed,

**Table 5 Pearson correlations of the OHSA composite and OHDAS composite scores with Clinical Global Impression of Severity scores and SF-36 scores at Baseline (n=137), Visit 5 (n=103), and Visit 6 (n=127)**

Criterion Measure	OHQ composite Score (Baseline)	OHQ composite Score (Visit 5)	OHQ composite Score (Visit 6)
<b>Clinical Global Impression – Symptom Severity</b>			
Clinician-scored	0.43	0.50	0.51
Patient-scored	0.61	0.67	0.58
<b>SF-36 Domains*</b>			
Physical functioning	-0.34	-0.48	-0.54
Role-Physical	-0.43	-0.60	-0.59
Bodily pain	-0.20	-0.25	-0.26
General health	-0.29	-0.40	-0.52
Vitality	-0.43	-0.46	-0.58
Social functioning	-0.42	-0.54	-0.62
Role-Emotional	-0.21	-0.37	-0.40
Mental health	-0.22	-0.28	-0.47
Physical Health Summary	-0.37	-0.46	-0.52
Mental Health Summary	-0.26	-0.35	-0.49

\*Note: scoring conventions in SF-36 scale and summary measure scores invert the direction of improvement; the negative (-) sign in the correlation coefficient reflects the empirical relationship among scores though it should be interpreted as a positive relationship among the underlying concept of measurement (i.e., as OH improves, so does the referenced HRQoL domain).

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*Reviewer's comments: It is unclear whether these expected relationships were pre-specified, because a statistical analysis plan for the validation of the OHQ was not provided. Further, construct validity cannot be interpreted without first establishing content validity.*

### **Construct Validity-Known-Groups Validity**

Known-groups validity is based on the ability of scores to discriminate between groups of subjects thought to be clinically distinct. For the OHQ, known-groups validity was examined in two ways: (1) by comparing the OHQ, OHSA, and OHDAS scores by NOH disease severity status as determined by the patient (using the patient CGI-S), and (2) by comparing the OHQ, OHSA, and OHDAS scores by NOH disease severity status as determined by the clinician (using the clinician CGI-S). Baseline data were used and one-way analyses of variance (ANOVAs) were conducted to test for differences in the composite scores across the defined groups.

**Table 6 Mean differences in OHQ, OHSA, and OHDAS composite scores across clinician and patient rated Clinical Global Impression of Severity categories at Baseline**

Measure	Little/no symptoms			Moderate/most extreme symptoms			F-value
	N	LSMean	SE	N	LSMean	SE	
Clinician CGI-S <sup>1</sup>							
OHQ	24	4.42	0.33	113	5.38	0.20	6.07*
OHSA	24	4.13	0.36	113	5.24	0.22	6.97*
OHDAS	24	4.71	0.37	113	5.49	0.23	3.23
Patient CGI-S <sup>1</sup>							
OHQ	29	3.96	0.31	107	5.83	0.22	26.63*
OHSA	29	3.92	0.33	107	5.45	0.24	15.17*
OHDAS	28	3.97	0.34	106	6.24	0.24	30.71

<sup>1</sup>Patients were categorized into the "Little or no symptoms" group by ratings on the CGI-S of 1 to 3 and "moderate or extreme symptoms" by ratings greater than 3.

\*p<0.05

### **Ability to Detect Change:**

The PRO dossier presented the following figure demonstrating change in OHQ, OHSA and OHDAS scores in relation to predefined change categories determined by the patient Clinical Global Impression of Severity. Note, again, that these results are derived from clinical trial data outside of the droxidopa clinical development program.

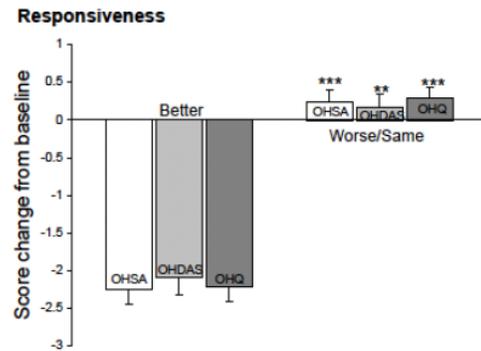
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**Figure 3 Average Change in OHQ Composite, OHSa and OHDAS from Baseline to Visit 6 by CGI-S Categories**



<sup>1</sup> Patients were categorized as "Better" if they endorse either "very much improved," "much improved," or "slightly improved" and "Worse/Same" if they endorsed "no change," "slightly worse," "much worse," or "very much worse" on the CGI-S.

\*\* p<0.01

\*\*\* p<0.001.

*Reviewer's comment: An instrument's ability to detect change cannot be interpreted without first establishing content validity.*

## 6 INTERPRETATION OF SCORES

Consistent with the advice in the FDA PRO Guidance, the sponsor should use both anchor- and distribution-based methods to determine what might be a clinically important intra-patient change in the instrument. One anchor-based approach to defining responders makes use of patient ratings of change administered at different periods of time or upon exit from a clinical trial. These numerical ratings range from *worse to the same* and *better*. The difference in the PRO score for persons who rate their condition *the same* and *better* or *worse* can be used to define responders to treatment.

The PRO Guidance document also states that distribution-based methods (e.g.,  $\frac{1}{2}$  SD benchmark) for determining clinical significance of particular score changes should be considered as supportive and are not appropriate as the sole basis for determining a responder definition.

The minimal important different (MID) estimates for the OHQ were provided in Table 18 of the OHQ PRO evidence dossier; these estimates were drawn from data collected in a clinical trial to assess the clinical benefit of midodrine hydrochloride in patients with NOH conducted by a company other than Chelsea. The PRO dossier used both anchor-based as well as distribution-based methods. For the anchor-based method, the patient had an opportunity to rate global changes in OH symptoms (in relation to baseline) on a 7-point scale (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5= minimally worse, 6=much worse, 7=very much worse).

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The following table from the sponsor's PRO dossier describes the results for both anchor-based and distribution-based methods derived from the midodrine hydrochloride clinical trial.

[**Note:** Table 6 below is reproduced from the original OHQ PRO evidence Dossier, which mis-specifies the CGI-I as CGI-S.]

**Table 7 Minimal Important Difference Estimates Using Anchor-based and Distribution-based Methods**

Scale	Anchor-Based Method Patient CGI-S						Distribution-Based Method	
	Visit 5							
	N	No Change		Minimal Improvement			½ SD <sup>2</sup>	SEM <sup>3</sup>
Mean CFB <sup>1</sup>		SD	N	Mean CFB <sup>1</sup>	SD			
OHSA composite score	18	0.23	1.00	32	-0.82	1.25	0.98	0.78
OHDAS composite score	18	0.20	1.09	33	-0.71	1.47	1.04	0.83
OHQ composite score	18	0.21	0.75	33	-0.83	1.39	0.94	0.62
Visit 6								
Scale	N	No Change		Minimal Improvement			½ SD <sup>2</sup>	SEM <sup>3</sup>
		Mean CFB <sup>1</sup>	SD	N	Mean CFB <sup>1</sup>	SD		
OHSA composite score	24	-0.47	1.69	28	-1.26	1.62		
OHDAS composite score	23	-0.16	1.45	28	-0.89	1.55		
OHQ composite score	24	-0.31	1.37	29	-1.16	1.36		

<sup>1</sup>Mean change from Baseline<sup>2</sup>Standard deviation of the entire sample at Baseline<sup>3</sup>SEM calculated as the standard deviation of the Baseline measure multiplied by the square root of 1-reliability (internal consistency).Appears  
this way  
on original

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Based on these data, and using the anchor-based method corresponding to a change of “minimally improved” on the 7-point scale, the sponsor suggested that a minimal inpatient change of -0.83 on the OHQ composite score (which has a theoretical range from 0-10) represents the minimal inpatient change on that scale that is meaningful from the patient perspective.

The PRO dossier also describes the results of two distribution-based methods for PRO interpretation also using the midodrine hydrochloride study data (Table 6). First, the one-half SD (0.5 x SD) method for generating an MID estimate was used and yielded a result of 0.94. Second, the MID was also estimated using the standard error of measurement (SEM), which is calculated as the (baseline standard deviation x  $\sqrt{(1-\text{reliability})}$ ), using the internal consistency reliability (0.89). This yielded a result of 0.62.

*Reviewer's comments: Using data drawn from a previous study using midodrine hydrochloride, the minimal clinically important inpatient difference in the OHQ score was estimated by taking into consideration both the anchor-based as well as the two-distribution based methods described above. However, these results are not the most appropriate estimates for use in interpretation of the current droxidopa clinical trials. The current droxidopa studies (Study 301 and 302) are the preferable source of data for the estimation of the inpatient change in score that is considered meaningful in those studies.*

*The droxidopa clinical trials used four different global impression scales; two of these were clinician-reported and the other two were patient-reported. Given that only patients can validly report their symptoms, this reviewer recommends that only the patient-reported scales be considered as anchors. The patient-reported CGI-I asks subjects to compare their current state with Visit 2 (baseline, prior to the dose titration period). The patient-reported CGI-S is simply measured at a single point in time and does **not** require any comparison to another timepoint. The relatively simple task of reporting on a discreet timepoint (as with the CGI-S) is likely more valid than a more complex task that requires comparison to a previous timepoint. Additionally, given that the trial included two treatment periods separated by a washout period, there is even greater risk of error and potential misunderstanding in what patients should use as the reference point when evaluating their change. Therefore, this reviewer recommends that the anchor-based methods using changes on the patient-reported CGI-S should be given the most weight for interpretation of meaningful intra-patient changes on OHDAS Item 1 (dizziness, lightheadedness feeling faint or feeling like you might black out).*

The PRO Guidance recommends presenting the entire distribution of responses for treatment and control group using a cumulative distribution display. Such cumulative distribution displays show a continuous plot of the percent change from baseline on the X-axis and the percent of patients experiencing that change on the Y-axis.

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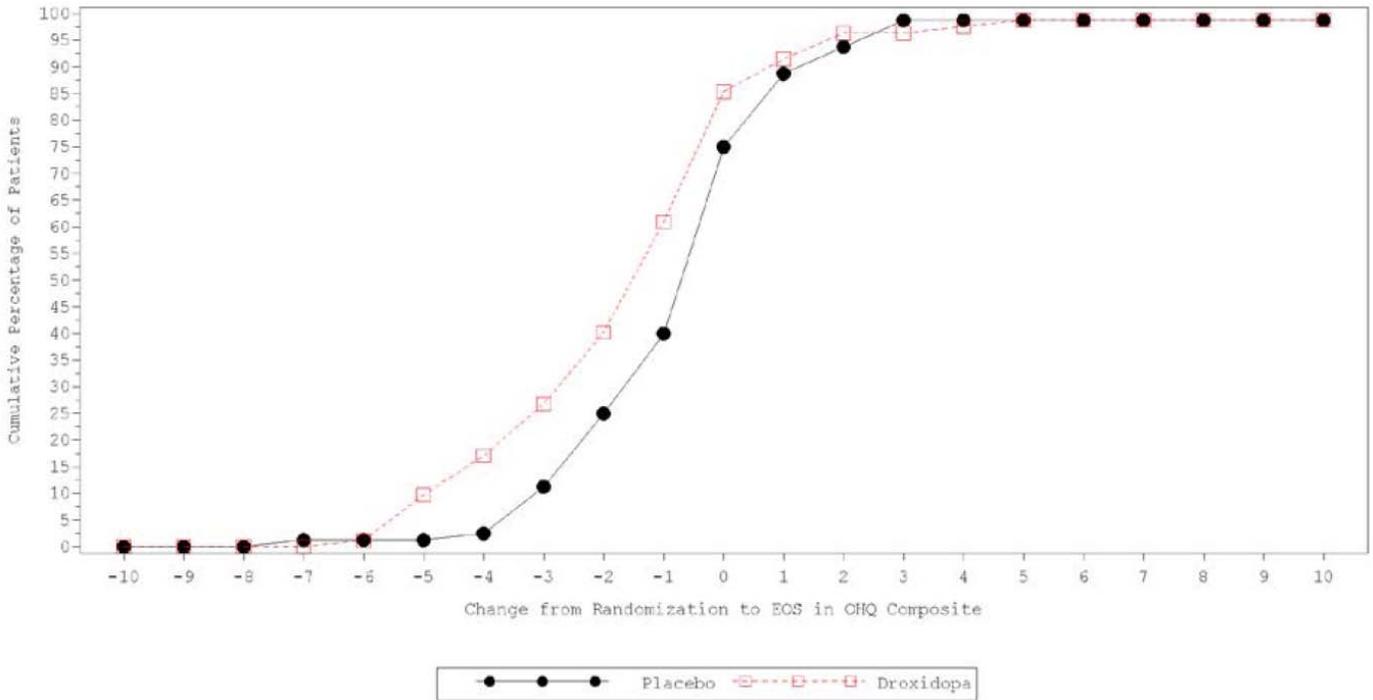
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Figures 2, 3, and 4 show the cumulative distribution function for Study 301 for the OHQ overall score, OHSA score and OHDAS score, respectively.

**Figure 4 OHQ Total Score Cumulative Distribution Function (Study 301)**



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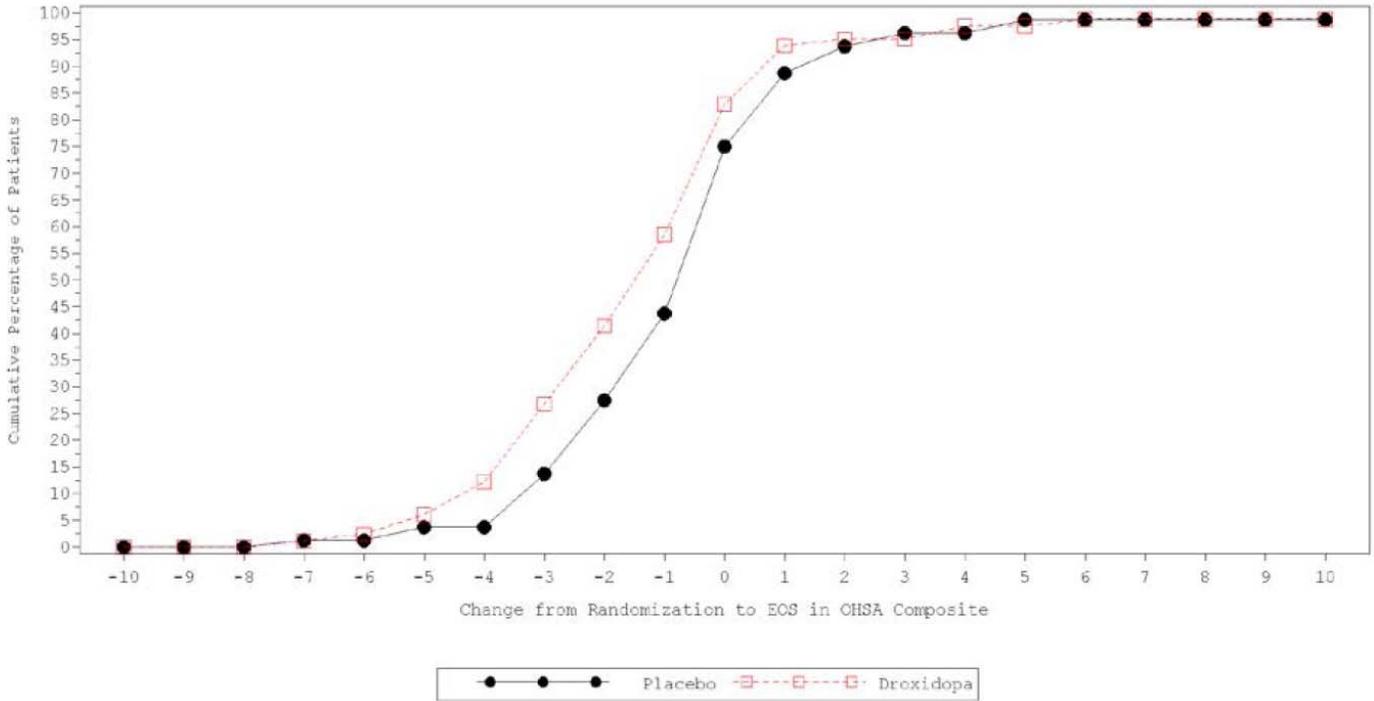
Elektra J. Papadopoulos, MD, MPH

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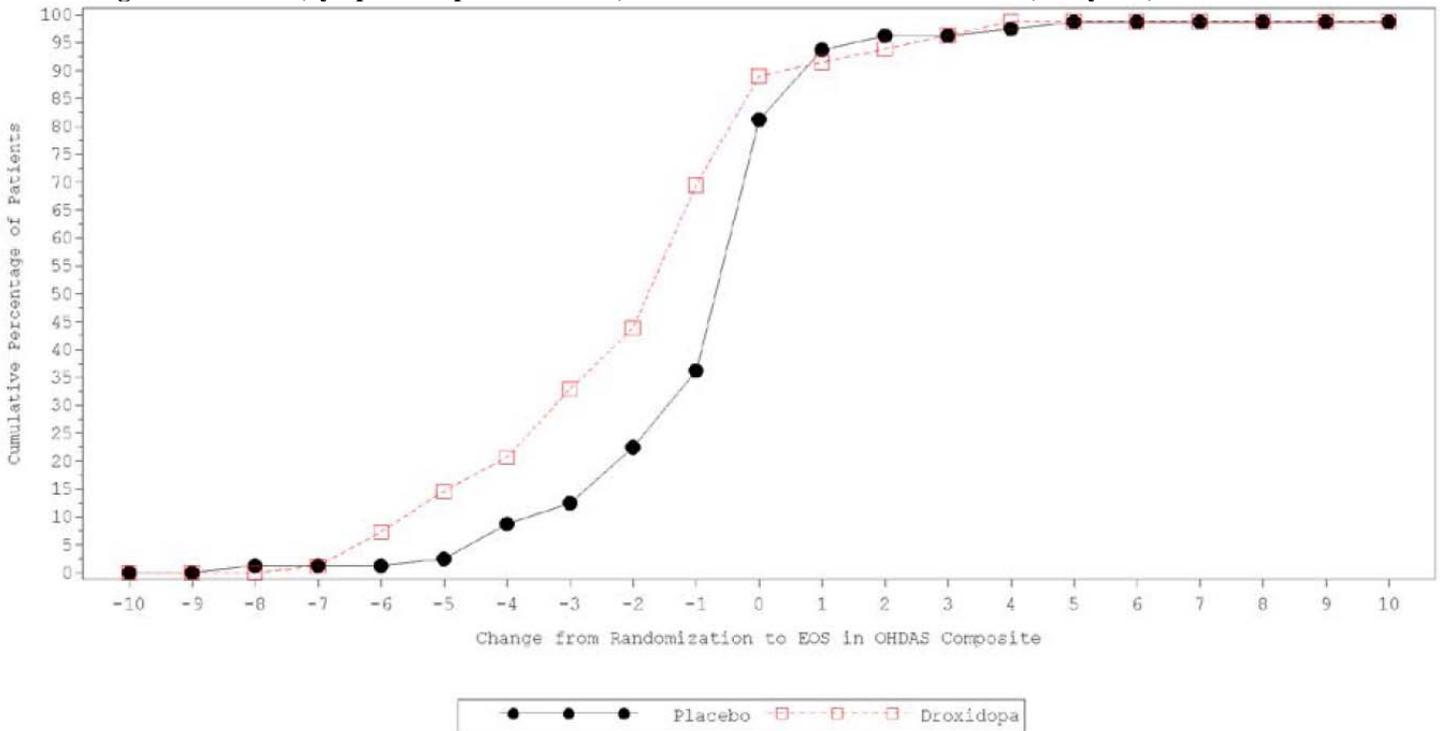
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**Figure 5 OHSA (Symptom Subscale) Cumulative Distribution Function (Study 301)**



**Figure 6 OHDAS (Symptom Impacts Subscale) Cumulative Distribution Function (Study 301)**



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*Reviewer's comments: Given concerns with the content validity of the OHSA, OHDAS and the OHQ composite score, we recommend that none of these scores be represented in product labeling. Instead, if the product is approved, we recommend describing the study results using Item 1 of the OHSA (dizziness, lightheadedness, feeling faint or feeling like you might black out) using a cumulative distribution function curve similar to those shown above. Additionally, the responder definition that is derived from the appropriate studies (i.e., Study 301 and 302) and agreed upon with the Agency should be applied to the CDF curve to aid in interpretation of these results.*

## 7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

According to the PRO dossier, in the phase 3 clinical trial, Study 301, the OHQ was administered in the following five languages:

- (1) US English;
- (2) French (for Canada);
- (3) German (for Austria);
- (4) Russian (for Ukraine); and
- (5) Ukrainian.

The OHQ instructions, items, and response options were translated and linguistically validated by the vendor (PharmaQuest Ltd.) from US English into the target languages following procedures described by the International Society for Pharmacoeconomic and Outcomes Research (ISPOR) Task Force for Translation and Cultural Adaptation of PRO measures.

This process involves the following elements:

- (1) Concept elaboration;
- (2) Two forward translations (by an in-country investigator and a certified translator fluent in English and the target language);
- (3) Reconciliation by the in-country investigator;
- (4) Back translation of the reconciled version by two certified translators who are English speakers fluent in the target language;
- (5) Review of the back translation by bilingual clinical experts in order to identify discrepancies and evaluate the semantic and conceptual equivalence of the translations;
- (6) Pilot testing (cognitive debriefing was done in French, Russian and Ukrainian);
- (7) Pilot testing review; and
- (8) Proofreading.

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The instructions, items, and response options in French (Canada) and Russian and Ukrainian (for Ukraine) were cognitively debriefed with patients (n=5 for each language) in order confirm the validity of the translations.

The PRO dossier provided a comprehensive report detailing the translation methodology and results. Additionally, it provided copies of the translated versions of the questionnaire (not shown in this review).

The PRO Guidance document states that we will review evidence to demonstrate comparability of the content validity and other measurement properties between versions. The evidence was provided in a comprehensive report (October 2008) of methodology and results appended to the PRO dossier.

Examples of the qualifications of the in-country investigator are described follow:

- One of the French investigators obtained her qualification in medical and pharmaceutical translation from the Université de Lyon.
- The Ukrainian investigator (for Ukrainian language) had 15 years of part-time experience as a translator and 4 years of full-time experience specializing in the areas of medicine and pharmaceuticals and had worked on projects such as the Brief Fatigue Inventory (BFI) and Visual Analogue Scale (VAS) for arthritis.
- The Ukrainian investigator (for Russian language) worked as a professor of English at the university level in Russia and had also done freelance translation and interpretation specializing in legal and medical translations.
- The Italian investigator was a psychologist with experience in the development, validation and cultural adaptation into Italian of numerous measures assessing health-related quality of life (HRQoL) over the previous 10 years.

*Reviewer's comment: The qualifications of the persons conducting the translations appeared adequate with many of them having degrees in languages and literature and previous experience with freelance translation projects. Others had backgrounds in psychology with experience in development, validation and cultural adaptation of instruments (e.g., HRQoL instruments).*

## **8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION**

Not applicable.

## **9 PROTOCOL AND ANALYSIS PLAN (STUDIES 301 AND 302)**

### **Study 301**

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Study 301 was a pivotal Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel-group, induction-design study in patients with symptomatic NOH and Parkinson's Disease, Multiple System Atrophy, Pure Autonomic Failure, dopamine beta hydroxylase deficiency or non-diabetic autonomic neuropathy.

The study was composed of an initial open-label dose optimization period; a 7-day washout period; and a 7-day, double-blind, randomized treatment period in which patients were treated with either droxidopa or matching placebo.

Study 301 included 162 patients randomized to receive placebo (N=80) or droxidopa (N=82).

Patients entering the study were required to have a drop of at least 20 mmHg in systolic or 10 mmHg in diastolic blood pressure upon standing along with symptoms associated with NOH.

The primary efficacy endpoint was change in the OHQ composite score from randomization to end of study; the two subcomponents of the OHQ, the Orthostatic Hypotension Symptom Assessment (OHSA) and the Orthostatic Hypotension Daily Activity Scale (OHDAS), were secondary efficacy endpoints.

### **Primary Analysis of the Primary Endpoint (Study 301)**

According to the sponsor's study report, the mean change in the OHQ composite score from Baseline to End of Study favored droxidopa. Droxidopa-treated patients had a mean decrease of 1.83 units in their OHQ composite score (indicating improvement in symptom severity and daily activity) compared with a 0.93 unit decrease in the placebo patients, resulting in a difference between placebo and droxidopa of 0.90 units favoring droxidopa ( $p=0.003$ ).

The baseline mean OHQ composite scores were 5.62 (range 1.2-9.8) for the placebo-treated group and 5.96 (range 2.0-9.6) for the droxidopa-treated group.

### **Secondary Analysis of the OHSA (Study 301)**

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OHSA Item Symptom	Placebo, Mean (SD) N=80			Droxidopa, Mean (SD) N=82			ANCOVA <sup>2</sup>
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #1 (n) Dizziness	80 5.4 (2.88)	80 4.3 (3.10)	80 -1.1 (2.58)	82 5.4 (2.46)	82 3.0 (2.67)	82 -2.4 (3.20)	<0.001
Item #2 (n) Vision	80 3.8 (3.14)	80 3.0 (3.15)	80 -0.7 (2.25)	82 3.4 (2.58)	82 1.9 (2.28)	82 -1.6 (2.81)	0.013
Item #3 (n) Weakness	80 5.0 (3.02)	80 4.1 (2.93)	80 -0.9 (2.34)	82 5.2 (2.23)	82 3.3 (2.29)	82 -1.9 (2.54)	0.007
Item #4 (n) Fatigue	80 5.5 (2.81)	80 4.3 (2.88)	80 -1.2 (2.51)	82 5.3 (2.35)	82 3.4 (2.48)	82 -1.9 (2.57)	0.030
Item #5 (n) Concentration	80 4.1 (2.86)	80 3.2 (2.80)	80 -0.9 (2.15)	82 3.5 (2.44)	82 2.6 (2.38)	82 -0.9 (1.89)	0.355
Item #6 (n) Head/Neck Discomfort	80 3.5 (3.06)	80 2.7 (2.74)	80 -0.8 (2.36)	82 3.6 (2.69)	82 2.6 (2.47)	82 -1.0 (2.28)	0.975
Composite (n) Items 1-6	79 4.70 (2.379)	79 3.75 (2.520)	79 -0.95 (1.901)	81 4.60 (2.013)	81 2.93 (2.084)	81 -1.68 (2.125)	0.010

*Reviewer's comments: No effect was shown on item #5 (concentration) or on item #6 (head and neck discomfort). This finding could result from an inadequacy of the instrument to assess these symptoms or from a lack of effect of the treatment on these symptoms. Overall, these findings suggest that a general claim of improvement in symptoms of NOH is not warranted. This reviewer recommends that only item #1 of the OHSA be described in labeling, without reference to the OHQ composite score, the OHSA or the OHDAS.*

### Secondary analysis of the OHDAS (Study 301)

OHDAS Item Symptom	Placebo, Mean (SD) N=80			Droxidopa, Mean (SD) N=82			ANCOVA <sup>2</sup>
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #1 (n) Standing Short Time	80 4.6 (2.99)	80 3.8 (2.94)	80 -0.8 (2.60)	82 5.0 (2.68)	82 3.1 (2.59)	82 -1.9 (2.75)	0.003
Item #2 (n) Standing Long Time	79 5.9 (3.19)	79 4.9 (3.40)	79 -1.0 (2.11)	81 6.4 (2.54)	81 4.0 (2.79)	81 -2.3 (2.58)	0.001
Item #3 (n) Walking Short Time	80 4.4 (3.08)	80 3.8 (2.98)	80 -0.6 (2.37)	82 4.7 (2.71)	82 3.0 (2.74)	82 -1.7 (2.55)	0.009
Item #4 (n) Walking Long Time	78 5.8 (3.41)	78 4.8 (3.49)	78 -1.1 (2.19)	78 5.8 (2.52)	78 4.0 (3.00)	78 -1.8 (2.52)	0.007
Composite (n) Items #1-4	79 5.24 (2.844)	79 4.33 (2.976)	79 -0.92 (1.816)	81 5.62 (2.296)	81 3.65 (2.577)	81 -1.98 (2.310)	0.003

*Reviewer's comments: Although Study 301 demonstrated statistically significant findings on the OHQ composite score, as well as its subscales (OHSA and OHDAS), the interpretation of these results is hampered by the content validity concerns with the instrument as outlined earlier in this review.*

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### Study 302

The second phase 3 study, Study 302, was a multi-center, multi-national, double-blind, randomized withdrawal, placebo-controlled, parallel-group study with an initial open-label dose-titration period, followed by 7 days of open-label treatment, followed by a 14-day randomized-withdrawal period in patients with symptomatic NOH.

The primary efficacy variable was the mean change from Randomization to End of Study in the OHSA Item 1 Score. Study 302 failed to show a difference between droxidopa and placebo for Item 1 of the OHSA from Randomization to End of Study.

A post-hoc, exploratory analysis showed a difference between droxidopa and placebo in the mean change in the OHQ composite score from Randomization to End of Study.

### Efficacy Results

In Study 302, the hierarchy of efficacy endpoints was prospectively defined in the SAP; the results (change from Randomization to End of Study) are presented below and were not adjusted for multiple comparisons.

#### 1. Primary efficacy endpoint:

OHSA Item 1(dizziness, lightheadedness, feeling faint or feeling like you might black out): Treatment Difference 0.6 units favoring droxidopa (p=0.509).

#### 2. Secondary efficacy endpoints:

- i. OHSA Item 4 (fatigue): Treatment Difference 0.8 units favoring droxidopa (p=0.233);
- ii. OHSA Item 3 (weakness): Treatment Difference 0.9 units favoring droxidopa (p=0.214);
- iii. OHSA Item 2 (vision): Treatment Difference 0.3 units favoring **placebo** (p=0.833);
- iv. OHSA Item 5 (concentration): Treatment Difference 0.8 units favoring droxidopa (p=0.113);
- v. OHSA Item 6 (head and neck discomfort): Treatment Difference 1.3 units favoring droxidopa (p=0.097);
- vi. OHDAS composite: Treatment Difference 1.15 units favoring droxidopa (p=0.038);
- vii. OHSA composite: Treatment Difference 0.75 units favoring droxidopa (p=0.160);

3. Systolic blood pressure (SBP) during orthostatic challenge: Treatment Difference 2.4 mmHg favoring **placebo** (p=0.680).

*Reviewer's comment: It is unexpected that in Study 302, the SBP during orthostatic challenge numerically favored the placebo group.*

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*Additionally, in Study 302, OHSa Item 2 (vision) numerically favored placebo, though the difference was a very modest 0.3 units. However, the fact that the treatment effect on OHSa Item 2 went in the opposite direction from the other OHSa items suggests that the use of an overall OHSa score is not empirically justified.*

*Finally, the treatment effect on the OHDAS (1.15 units) was somewhat larger than that seen on the OHSa (0.75 units); thus, the OHDAS response may unduly influence the overall OHQ composite score. Given this concern and other concerns with the OHQ's content validity, we do **not** recommend presenting study results in terms of an overall OHQ composite score in either Study 301 or Study 302.*

## 10 KEY REFERENCES FOR MEASURE

Malamut, R., Freeman, R., Gilden, J., Tulloch, J., and Kaufmann, H. A multicenter, double-blind, randomized, placebo controlled, cross-over study to assess the clinical benefit of midodrine in patients with neurogenic orthostatic hypotension. Clin Auton.Res 15(5), 337. 2005.

Kaufmann, H., Malamut, R., • Norcliffe-Kaufmann, L., Rosa, K., and • Freeman, R. The Orthostatic Hypotension Questionnaire (OHQ): validation of a novel symptom assessment scale. Clin Auton.Res 02 Nov 2011.

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**APPENDIX A: ORTHOSTATIC HYPOTENSION QUESTIONNAIRE**

## Patient Instructions

We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease).

Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after lying down. Some people have symptoms that improve only after sitting or lying down for quite some time.

Please answer the questions on [the following pages](#) keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

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<b>VISIT:</b> _____	<b>Subject Int:</b> _____
<b>Protocol No. Droxidopa 302</b>	<b>Screening No.:</b> _____
	<b>Visit Date:</b> ____/____/____ dd      mmm      yyy

**I. The Orthostatic Hypotension Symptom Assessment (OHSA)**

Please circle the number on the scale that best rates how severe your symptoms from low blood pressure have been *on the average* over the past week. Please respond to every symptom. If you do not experience the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

**1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

**2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

**3. Weakness**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

**4. Fatigue**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

**5. Trouble concentrating**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

**6. Head/neck discomfort**

None	0	1	2	3	4	5	6	7	8	9	10	Worst Possible
------	---	---	---	---	---	---	---	---	---	---	----	----------------

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**VISIT:** \_\_\_\_\_

**Protocol No. Droxidopa 302**

**Subject Int:** \_\_\_\_\_

**Screening No.:** \_\_\_\_\_

**Visit Date:** \_\_\_ / \_\_\_ / \_\_\_  
                  dd      mmm      yyyy

**II. The Orthostatic Hypotension Daily Activity Scale (OHDAS)**

We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by circling the number that best represents how much the activity has been interfered with *on the average* over the past week by the low blood pressure symptoms you experienced.

If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

<b>1. Activities that require standing for a short time</b>	<b>CANNOT DO FOR OTHER REASONS</b>
No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference	<input type="checkbox"/>
<b>2. Activities that require standing for a long time</b>	<b>CANNOT DO FOR OTHER REASONS</b>
No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference	<input type="checkbox"/>
<b>3. Activities that require walking for a short time</b>	<b>CANNOT DO FOR OTHER REASONS</b>
No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference	<input type="checkbox"/>
<b>4. Activities that require walking for a long time</b>	<b>CANNOT DO FOR OTHER REASONS</b>
No Interference 0 1 2 3 4 5 6 7 8 9 10 Complete Interference	<input type="checkbox"/>

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**Appendix B: Clinical Global Impressions-Patient (Case Report Form)**

Clinical Global Impressions-Patient (PGLO)

1. Was assessment performed?

List: YES\_NO ▾

\*\*2. Reason not performed:

**Severity of Illness**

\*\*3. How severe is your Orthostatic Hypotension (OH) at this time?

List: SEVERE ▾

Global Improvement ? Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to your condition at your Baseline Visit 2, how much has your orthostatic hypotension changed?

\*\*4. Select

List: IMPROVE ▾

\*\* Conditional Question

List:YES_NO	
Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE	
Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

List:IMPROVE	
Label	Value
[Blank]	
Not Assessed	0
Very much improved	1
Much improved	2
Slightly improved	3
No change	4
Slightly worse	5
Much worse	6
Very much worse	7

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELEKTRA J PAPADOPOULOS  
01/23/2012

LAURIE B BURKE  
01/23/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: January 23, 2012

Reviewer(s): Ray Ford, RPh, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader(s): Lubna Merchant, PharmD, MS, Team Leader  
Division of Medication Error Prevention and Analysis  
Irene Z. Chan, PharmD, BCPS, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Division Director  
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Northera (Droxidopa) Capsules, 100 mg, 200 mg, and  
300 mg

Application Type/Number: NDA 203202

Applicant/sponsor: Chelsea Therapeutics Inc.

OSE RCM #: 2011-3918

\*\*\* This document contains proprietary and confidential information that should not be released to the public. \*\*\*

## 1. INTRODUCTION

This review evaluates the proposed container labels, carton labeling, and insert labeling for Northera (droxidopa) 100 mg, 200 mg, and 300 mg capsules (NDA 203202), in response to a request from the Division of Cardiovascular and Renal Products (DCRP).

### 1.1 PRODUCT INFORMATION

The following product information is provided in the October 13, 2011 submission.

- Established Name: Droxidopa
- Indication of Use: The treatment of neurogenic symptomatic orthostatic hypotension in patients with primary autonomic failure, including multiple system atrophy (Shy-Drager syndrome), pure autonomic failure, Parkinson's disease (cerebrovascular parkinsonism), dopamine- $\beta$ -hydroxylase deficiency and nondiabetic autonomic neuropathy (amyloid and autoimmune)
- Route of administration: Oral
- Dosage form: Capsule
- Dose: 300 mg to 900 mg per day (minimum dose 300 mg/day, 100 mg three times daily; usual dose is 900 mg/day, 300 mg three times daily). The maximum recommended dose in a 24-hour period is 1800 mg (600 mg three times per day).
- Strengths: 100 mg, 200 mg, and 300 mg
- How Supplied: 9 count, 21 count, and 90 count bottles
- Storage: 25° C (77° F); excursions to 15° C to 30° C (59° F to 86° F) are permitted [see USP Controlled Room Temperature]
- Container and Closure systems: 100 mg , 200 mg, and 300 mg 9-count: 40 cc high density polyethylene bottles (b) (4)  
100 mg , 200 mg, and 300 mg 21-count: 60 cc high density polyethylene bottles (b) (4)  
100 mg and 200 mg, 90-count: 90 cc high density polyethylene bottles (b) (4)  
300 mg, 90-count: 120 cc high density polyethylene bottles (b) (4)  
100 mg, 200 mg, (b) (4) Foil blister packs, 9 capsules per card containing 10 Blister Packs.

## **2. METHODS AND MATERIALS REVIEWED**

Using Failure Mode and Effects Analysis<sup>1</sup>, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Professional Sample Container Label submitted December 8, 2011 (Appendix A)
- Trade Container Labels submitted December 8, 2011 and January 5, 2012 (Appendix B)
- Insert Labeling submitted December 8, 2011

## **3. RESULTS**

The following section describes the deficiencies identified in our assessment of the label and labeling.

### **A. PROFESSIONAL SAMPLE AND TRADE CONTAINER LABEL**

1. The label contains a graphic in front of the proprietary name that might be misread as 'i.'
2. The proprietary name font is displayed using two colors giving unequal emphasis on the first syllable of the name.
3. The strength is not located with the proprietary and established name.
4. The established name does not contain a dosage form.
5. The primary display panel does not contain a medication guide statement.

### **B. BLISTER PACK CARTON AND BLISTER FOIL PACK LABEL**

1. See A1 through A5 above.
2. Lower one-third of principle display panel is cluttered and not easy to read.
3. NDC numbers have not been provided for evaluation.
4. Blister Pack Back strengths not well differentiated.

### **C. INSERT LABELING**

1. Use of dangerous symbols that may lead to medication errors.
2. Incomplete directions for the administration of Northera.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

#### 4. CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling introduce vulnerability that can lead to medication errors. We found the container and carton labeling had an inadequate prominence of the established name, strength, and medication guide statement. In addition, use of error-prone abbreviations, symbols, acronyms are used throughout the labeling. We advise that the following recommendations be implemented prior to approval:

- A. Professional Sample Container Label (100 mg, 200mg, 300 mg-9 count and 21 count)
  1. The graphic design in front of the proprietary name is too prominent and distracting. The graphic can be misread as an upper case 'I' or bold font lower case 'i' before the proprietary name Northera. Remove this graphic from the label or relocate and minimize this graphic so that it does not appear with the proprietary name.
  2. Revise the presentation of the proprietary name so that it is presented in a single color. Select a color for the proprietary name that is unique and not previously used in the strength differentiation.
  3. We note that the established name is ½ the size of the proprietary name however, lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast and other printing factors in accordance with 21 CFR 201.10 (g)(2).
  4. The established name includes the active ingredient but lacks the finished dosage form. We request that you add the dosage form "Capsules" to appear after "Droxidopa" on the primary display panel.
  5. The primary display panel does not have a Medication Guide statement to ensure that a medication guide is dispensed to every patient by every dispenser of Northera. Revise to include medication guide statement on the primary display panel in a prominent and conspicuous manner in accordance with 21 CFR 208.24 (d).
  6. The strength statement is not prominently displayed on the primary display panel. Relocate the strength statement directly below the proprietary name and established name.
  7. Revise the strength statement to read 100 mg per capsule, 200 mg per capsule, or 300 mg per capsule.
  8. Decrease the prominence of the "Rx Only" statement on the primary display panel.

9. Revise Usual dosage statement from (b) (6) to read “See Prescribing Information” to decrease clutter on the side display panel.
  10. Remove “ (b) (4) statement to decrease clutter on the left display panel.
  11. Revise “ (b) (4) to read “Store at 25 °C (77 °F): excursions permitted from 15 °C to 30 °C (59 °F to 86 °F); Dispense in a tight, light-resistant container.” Use the same prominence of the Usual Dosage statement on the side display panel to increase readability.
  12. Relocate the “Patient Samples-Not for Sale” to the area under the “Rx Only” statement at the lowest portion of the label.
- B. Trade Container Labels (100mg , 200 mg, and 300 mg 90 capsules count)
1. See comment in A 1 through A 6 and A8 through A 11 above.
  2. Move the medication guide statement to the primary display panel per above in accordance with 21 CFR 208.24 (d).
  3. Remove “ (b) (4),” statement from the side display panel to decrease clutter and increase readability.
- C. Blister Pack Outer Carton, Blister Pack Front and Back Label (100 mg, 200 mg, (b) (4) Unit of Use-9 Capsules each containing Ten Blister Packs)
1. See comment in A 1 through A 6.
  2. Remove the “ (b) (4) and “ (b) (4) from the Outer Carton and the Blister Pack Front.
  3. Place net quantity statement in top left area of primary display panel.
  4. Decrease the prominence of the “Rx Only” statement and relocate to the bottom left of the primary display panel.
  5. Increase the font size or use color for the strength statement on the Blister Pack Back foils to differentiate the 100 mg, 200 mg, (b) (4) capsule.
- D. Insert Labeling
1. General Comments:

The applicant has used throughout the HIGHLIGHTS OF PRESCRIBING INFORMATION, and FULL PRESCRIBING INFORMATION error prone abbreviations. The symbols <, ≤, >, ≥ were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used

as the incorrect symbol. As part of a national campaign to decrease the use of dangerous symbols<sup>2</sup>, the FDA agreed not to use such error-prone symbols in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore, DMEPA recommends that < be replaced with “less than,” ≤ be replaced with “less than or equal to,” > be replaced with “greater than,” and ≥ be replaced with “greater than or equal to.”

2. Define all abbreviations and acronyms for clarity. For example in table 1 reads “...Adverse Events...” and in table 2 “...AEs...” Revise table 1 to “...Adverse Events (AE)...” for consistency throughout the insert labeling.
3. When writing numbers with symbols or units, insert a space between the number, symbol, or unit for better readability. For example in section 5.1 Supine Hypertension revise “2.5%” to read “2.5 %.”
4. Provide each unit of measure with each number. In section 8.1 Pregnancy revise “60, 200, and 600 mg/kg/day” to read “60 mg/kg/day, 200 mg/kg/day, and 600 mg/kg/day.”
5. Consider stating numbers greater or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100.” In section 10.1 Symptoms revise “...7700 mg...” to read “...7,700 mg...”
6. In the DOSAGE AND ADMINISTRATION section 2 does not state that Northera (droxidopa) can be opened and sprinkled on food or that it should be taken whole. Revise to include information on whether the capsules should be taken whole or other directions consistent with the intended use of Northera (droxidopa).
7. In the DOSAGE FORMS AND STRENGTHS section 3, the capsules are imprinted with (b) (4). The imprint (b) (4) on the capsule body implies the name of the drug is (b) (4) and is misleading. Remove (b) (4)” from the capsule body

If you have further questions or need clarifications, please contact OSE Regulatory Project manager, Phuong Nina Ton, at 301-796 1648-.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>2</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010

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/s/  
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FOREST R FORD  
01/23/2012

LUBNA A MERCHANT  
01/23/2012

IRENE Z CHAN  
01/23/2012

CAROL A HOLQUIST  
01/23/2012

<b>OSI Consult</b>	
<b>Request for Biopharmaceutical Inspections</b>	
Date	October 28, 2011
Subject	Request for Biopharmaceutical Inspections (BE)
Addressed to	Sam H. Haidar, Ph.D., R.Ph. Chief, Bioequivalence Investigations Branch Division of Bioequivalence and GLP Compliance Office of Scientific Investigations
Consulting Office/Division	Division of Cardiovascular and Renal Products
Project Manager	Anna Park
Application Type	PEPFAR? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
	<input checked="" type="checkbox"/> NDA <input type="checkbox"/> BLA <input type="checkbox"/> ANDA
Application Number	203202
Drug Product	Droxidopa
Sponsor Name	Chelsea Therapeutics, Inc.
Sponsor Address	3530 Tarringdon Way Charlotte, NC 28277
US Agent (if applicable)	
US Agent Address	
Electronic Submission	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
PDUFA Due Date	March 28, 2012
Action Goal Date	January 14, 2012
OSI Review Requested By	Sreedharan Nair Sabarinath

<b>Inspection Request Detail</b> (All fields should be fill out completely)	
<b>Study #1</b>	
Study Number	<b>Study # 101</b>
Study Title	A Randomized, Open-Label, Three-Period, Three-Sequence, Single-Dose Crossover and Separate Three-Daily-Dose Treatment Period Study Comparing the Pharmacokinetic Profiles Following Oral Dosing of 300 mg of Droxidopa in the Fed versus Fasted State, the Bioequivalence of Three 100 mg Capsules of Droxidopa versus a Single 300 mg Capsule of Droxidopa, and 300 mg of Droxidopa Given Three Times at Four Hour Intervals in Healthy, Elderly Subjects. <b>Study Site:</b> Cetero Research Address:, 4801 Amber Valley Parkway, Fargo, ND, 58104  <b>Bioanalysis Site:</b> Validated LC/MS/MS methods by <span style="background-color: gray; color: gray;">(b) (4)</span>
Study Type	<input checked="" type="checkbox"/> In vivo BE <input type="checkbox"/> In vitro BE <input type="checkbox"/> Permeability <input type="checkbox"/> Others (specify)

OSI 08/05/11

<input checked="" type="checkbox"/> Inspection Request - <b>Clinical Site</b>	<input checked="" type="checkbox"/> Inspection Request - <b>Analytical Site</b>
Facility #1 Name: <b>Cetero Research</b> <b>Address: 4801 Amber Valley Parkway, Fargo, ND, 58104</b> (Tel) (Fax)	Facility #1 Name: (b) (4) <b>Address:</b> (b) (4) (Tel) (Fax)
Clinical Investigator: <b>Gregory M. Haugen, M.D.</b>  (email)	Principal Analytical Investigator: (b) (4)  (email)
Facility #2 Name: (if applicable) Address: (Tel) (Fax)	Facility #2 Name: (if applicable) Address: (Tel) (Fax)
Clinical Investigator: (email)	Principal Analytical Investigator: (email)
Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause	Check one: <input checked="" type="checkbox"/> Routine inspection <input type="checkbox"/> For cause
<i>(please include specific review concerns or items to be addressed during the inspection in the appendix below)</i>	
<input checked="" type="checkbox"/> Study Report: 5.3.1.2.3	<input checked="" type="checkbox"/> Validation Report: (5.3.1.4) <input checked="" type="checkbox"/> Bioanalytical Report: (5.3.1.4)

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, OSI.**

## ***I. Appendix***

<b>Specific Items To be Addressed During the Inspection</b>
<p>The sponsor intends to market three capsule strengths: 100 mg, 200 mg and 300 mg. Capsules 100 mg and 200 mg strengths were used in the phase III efficacy trial. Capsule 300 mg strength was not studied in the phase III trial and was tested for BE in study # 101 (Part 1) for 3 x 100 mg capsules vs 1 x 300 mg capsule. This makes it the pivotal BE study for the 300 mg capsule. We request you to have an in vivo BE site inspection as well as inspection of the bioanalysis site for part 1 of the study # 101. Since the BE between the 1x300 mg strength and 3x100 mg is the focus of Part 1 of study 101, the bioanalysis inspection should focus on droxidopa as the analyte.</p>

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/s/  
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ANNA J PARK  
12/07/2011

# DSI CONSULT: Request for Clinical Inspections

**Date:** November 17, 2011

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Sharon Gershon, PharmD  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Melanie Blank, M.D., Clinical Reviewer, Division of Cardio-Renal Products  
Shari Targum, M.D., Cross-Discipline Team Leader, DCRP  
Norman Stockbridge, M.D. Division Director, DCRP

**From:** Anna Park, Regulatory Health Project Manager,DCRP

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA- 203202

Applicant/ Applicant contact information (to include phone/email):

Chelsea Therapeutics, Inc.  
POC: Rex Horton  
Director, Regulatory Affairs  
3530 Tarringdon Way  
Charlotte, NC 28277  
(704) 973-4248 office  
(704) 458-7616 cell  
horton@chelsearx.com

Drug Proprietary Name: Northera

NME or Original BLA (Yes/No): NME

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of symptomatic neurogenic orthostatic hypotension (NOH)

PDUFA: March 28, 2012

Action Goal Date: March 28, 2012

DSI Consult

version: 5/08/2008

Preliminary Inspection Summary Goal Date: February 13, 2012

## **II. Protocol/Site Identification**

A DSI consult is requested for several reasons:

- 1) This is a new drug never approved before in the U.S.
- 2) There is no approved treatment for symptomatic orthostatic hypotension in the U.S.
- 3) This is considered an orphan designation and therefore, this is a priority review and there will be special exclusivity provisions if approved

4) Study 301 was the only successful study of 3 efficacy studies and the primary efficacy endpoint was changed after nearly all of the originally planned patients to be enrolled had completed the study. Not only was the primary efficacy endpoint changed, but the trial was resized based on results from another study (302) according to the sponsor. The rationale for resizing is not obvious from the information that the sponsor has heretofore provided. Therefore, we are questioning the sponsor further about why they decided to resize Study 301. The approvability of droxidopa hinges on the credibility of Study 301 and the change in SAP and study size are troubling signs.

5) There are concerns about the study conduct in this multinational multisite trial (study 301) that employed a patient reported outcome (PRO) measurement tool as the primary efficacy endpoint. It is important to be reassured that the PRO measurement tool was appropriately administered and that the results were properly documented at the highest risk sites, determined primarily by considering site enrollment and site performance on the primary efficacy endpoint. It is important to note that patients could be eliminated at different time points during the run-in to the double blind period in both trials. A high proportion of patients were eliminated prior to randomization. 95/259 of the screened patients were not randomized. It would be interesting to know if "borderline" performers were or were not randomized and if there was a pattern for such decisions. It would be especially interesting to know how data values would be determined and entered if patients provided answers to questions on the OHQ that were between different integers. Did investigators elicit AEs before or after the questionnaires were administered? Did that vary? Did investigators take BP readings before or after the questionnaires were administered? Did that vary? Was the number and time of the BP readings documented? How close to the 3 hour mark after drug dosing were the questionnaires done? Were concomitant medications captured at each visit?

6)  (b) (4), (b) (6)

 (b) (4), (b) (6)

Please consider investigating the following sites:

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
507; Prof. Lyudmyla Dzyak; Dnipropetrovs'k State Medical Academy, Chair of Nervous Disease and Neurosurgery of the Faculty of Post- Diploma Education (FPE) 9, Dzerzhynskogo Str.; Dnipropetrovsk,49044, Ukraine	301	19	Symptomatic neurogenic orthostatic hypotension
505; Dr. Yanosh E. Sanotsky; L'viv Regional Clinical Hospital of the MoH of Ukraine Neurology Department; 6 Nekrasova Str. Lviv 79010 Ukraine	301	12	Symptomatic neurogenic orthostatic hypotension
513; Prof. Valeryi Bitenskyy; Odessa Regional Clinical Psychiatric Hospital #1 Males and Females Departments; Odessa State Medical University Cathedra of Psychiatry 9, Ac. Vorobyeva Str. Odessa 65006 Ukraine	301	7	Symptomatic neurogenic orthostatic hypotension
103; Brent Goodman, MD Replaced by: Erika D. Driver-Dunckley, MD; Mayo Clinic Arizona Department of Neurology 13400 East Shea Boulevard Scottsdale, AZ 85259	301	8	Symptomatic neurogenic orthostatic hypotension
105; Joseph Jankovic, MD Baylor College of Medicine 6550 Fannin, Suite 1801 Houston, TX 77030	301	8	Symptomatic neurogenic orthostatic hypotension

### **III. Site Selection/Rationale**

Rationale for site choices:

- Sites 507 and 505 had relatively large enrollment and treatment effect. Site 513 was smaller but also had a relatively large treatment effect
- Site #103 in the U.S. had a better treatment effect in the placebo arm with eight subjects
- Site #105 in the U.S. had a high number of protocol violations and enrolled nine subjects

**Domestic Inspections:**

Reasons for inspections:

- Enrollment of large numbers of study subjects
- High treatment responders
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections:

- The treatment effect in the foreign sites was in general higher than in the domestic sites
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and a large part of the limited experience with this drug has been at foreign sites. Therefore, it would be desirable to include foreign sites in the DSI inspections to verify the quality of conduct of the study.

**Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *Please see section III.*

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**IV. Tables of Specific Data to be Verified (if applicable)**

Please verify all questionnaire and vital sign data that is available.

Page 5-Request for Clinical Inspections

Should you require any additional information, please contact Anna Park, R.Ph. at 301-796-1129 *or* Melanie Blank, M.D. at 301-796-1330.

Concurrence: (as needed)

Shari Targum, M.D. Cross-Discipline Team Leader

Melanie Blank, M.D. Medical Reviewer

Norman Stockbridge, M.D., Ph.D. Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/  
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ANNA J PARK  
11/29/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: November 23, 2011

TO: Director, Investigations Branch  
Minneapolis District Office  
212 3rd Ave, South  
Minneapolis, MN 55401

Director, Investigations Branch  
Detroit District Office  
300 River Place, #5900  
Detroit, MI 48207

From: Sam H. Haidar, Ph.D., R.Ph. \_\_\_\_\_  
Chief, Bioequivalence Investigations Branch  
Division of Bioequivalence and GLP Compliance (DBGC)  
Office of Scientific Investigations (OSI)

SUBJECT: FY 2012, **High Priority User Fee NDA, Pre-Approval Data  
Validation Inspection** Bioresearch Monitoring, Human  
Drugs, CP 7348.001

RE: NDA 203202  
DRUG: Droxidopa (Northera®)  
100 mg, 200 mg, 300 mg Capsule  
SPONSOR: Chelsea Therapeutics, Inc.  
Charlotte, NC 28277

This memo requests that you arrange for inspections of the clinical and analytical portions of the following bioequivalence study. **A DBGC, OSI scientist with specialized knowledge may participate in the inspection of the analytical site to provide scientific and technical expertise. Please contact DBGC upon receipt of this assignment to arrange scheduling of the inspections. These inspections should be completed before December 31, 2011.**

**Study Number:** 101

**Study Title:** "A randomized, open-label, three-period, three-sequence, single-dose crossover and separate three-daily-dose treatment period study comparing

the pharmacokinetic profiles following oral dosing of 300 mg of Droxidopa in the fed versus fasted state, the bioequivalence of three 100 mg capsules of Droxidopa versus a single 300 mg capsule of Droxidopa, and 300 mg of Droxidopa given three times at four hour intervals in healthy, elderly subjects."

**Clinical Site:** Cetero Research  
4801 Amber Valley Parkway  
Fargo, ND 58104  
TEL: 701-239-4750; 701-277-7227

**Clinical Investigator:** Gregory M. Haugen, M.D.

Please have the records of all study subjects audited. The subject records in the NDA submission should be compared to the original documents at the site. The protocol and actual study conduct, IRB approval, drug accountability, as well as the source documents and case report forms for dosing, clinical and laboratory evaluations related to the primary endpoint, adverse events, concomitant medications, inclusion/exclusion criteria and number of evaluable subjects should be examined. The SOPs for the various procedures need to be scrutinized. Dosing logs must be checked to confirm that correct drug products were administered to the subjects. Please verify that the subjects were compliant with the trial regimen and confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in the EIR. In addition to the standard investigation involving source documents, the correspondence files should be examined for sponsor-requested changes, if any, to the study data or report. Relevant exhibits should be collected for all findings, including discussion items at closeout, to assess the impact of the findings. Please check the batch numbers of the test and reference products used in these studies with the descriptions in documents submitted to FDA. Please confirm whether reserve samples were retained as required by 21 CFR Parts 320.38 and 320.63. The site conducting the above bioequivalence study is responsible for randomly selecting and retaining reserve samples from the shipments of drug product provided for subject dosing. Please refer to CDER's guidance document "Handling & Retention of BA and BE Testing Samples" that clarifies the requirements for reserve samples (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126836.pdf>). Samples of the test and reference products should

be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening at the following address:

Center for Drug Evaluation and Research  
Division of Pharmaceutical Analysis (DPA)  
Center for Drug Analysis (HFH-300)  
US Courthouse and Custom house Bldg.  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Also, obtain a written assurance from the clinical investigator (CI) or the responsible person at the CI's site that the reserve samples are representative of those used in the specific bioequivalence study, and that they were stored under conditions specified in accompanying records. Document the CI's signed and dated statement (21 CFR 320.38(d, e, g) on the facility's letterhead, or Form FDA 463a, Affidavit. Include the written statement in Sample Collection Report (CR) as a DOC sample. Examine the surveillance drug samples collected and shipped them to DPA under current program directives. Please see the IOM and/or contact your district or DFFI for assistance with the Sample Collection Report.

**Analytical Site:**

(b) (4)

**Bioanalytical Investigator:**

(b) (4)

**Methodology:**

**LC-MS/MS** [L-*threo*-DOPS (droxidopa);  
3-OM-DOPS (methylated droxidopa)]  
**LC-EC** [Norepinephrine]

Droxidopa is converted partly to norepinephrine and methylated droxidopa in the body.

For Study 101, the (b) (4) project number is 0542-10201. All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data provided in the NDA submission should be compared with the original documents at the site. The method validation and the actual assay of the subject plasma samples, as well as the variability between and within runs, QC, stability, the number of repeat assays of the subject plasma

Page 4 - BIMO Assignment, NDA 203202, Droxidopa (Northera®)  
100 mg, 200 mg, 300 mg Capsule

samples, and the reason for such repetitions, if any, should be examined. **The SOP(s) for repeat assays and other relevant procedures must also be scrutinized.** In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following the identification of the investigator, background materials will be forwarded directly.

Headquarters Contact Person: Jyoti B. Patel, Ph.D.  
(301) 796-4617

CC:

CDER OSI PM TRACK

OSI/DBGC/Salewski/Haidar/Skelly/Patel/Dejernet/CF

OND/ODEI/DCRP/Anna Park

OTS/OCP/DCPI/Sreedharan Sabarinath

HFR-CE750/Keith Jasukaitis (DIB)/Nancy Bellamy (BIMO)

HFR-CE850/Cheryl Bigham (DIB)

HFR-CE8590/Constance Richard-Math (BIMO)

Draft: JBP 11/15/2011

Edit: MFS 11/23/11

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FACTS: 1360323

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/s/  
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JYOTI B PATEL  
11/23/2011

MICHAEL F SKELLY  
11/23/2011  
Skelly signing on behalf of Dr. Haidar

# **REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW**

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 203202

**Name of Drug:** NORTHERA (Droxidopa) Oral Capsules

**Applicant:** Chelsea Therapeutics

## **Labeling Reviewed**

**Submission Date:** September 23, 2011

**Receipt Date:** September 28, 2011

## **Background and Summary Description**

Chelsea Therapeutics, Inc. submitted a 505(b)(1) NDA for Droxidopa, an orally administered, synthetic catecholamine acid pro-drug that is converted to NE. The proposed indication for Droxidopa is for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease [PD], Multiple System Atrophy [MSA] and Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (DBH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

Droxidopa was granted Orphan Designation on January 17, 2007 and Fast-Track Designation on August 7, 2008 for the treatment of symptomatic NOH.

The sponsor's clinical development program included 3 studies, Study 301, 302 and 303, to assess the efficacy of Droxidopa. Study 301 is the pivotal efficacy trial in the Droxidopa development program, and the efficacy results from this study are the predominant focus of this NDA.

This NDA is an electronic submission which follows the eCTD guidance. Draft labeling was submitted for the Package Insert (PI) and Carton and Container. The PI was submitted in PLR format. Electronic Content of Labeling was submitted in SPL format.

## **Review**

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an "X."

In addition, the following labeling issues were identified:

1. Highlights (HL):
  - a. Paragraphs need to be summarized and referenced to sections of FPI.
  - b. Use bullets throughout HL to decrease text and increase readability.
  - c. Bolding is reserved for section and subsection. For titles throughout the label, use italic or underline.
  - d. Under “Drug Interaction”, each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
2. When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
4. Under “Adverse Reactions”:
  - a. The correct title is “Clinical Trials Experience”. For the “Clinical Trials Experience” subsection, the following verbatim statement should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
  - b. References must be formatted appropriately per regulations.
6. Please move “Effects of QTc interval” to Section 12.
7. Under “Clinical Trials”, avoid using company study titles as subsection titles. (What did study show? Why is this important?)

## **Recommendations**

All labeling issues identified on the following pages with an “X” will be conveyed to the applicant in the 60-day letter. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by December 9, 2011. The resubmitted labeling will be used for further labeling discussions.

Anna Park, R.Ph.  
Regulatory Project Manager

November 16, 2011  
Date

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# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

### • Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

### • Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANNA J PARK  
11/21/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203202	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: <b>NORTHERA</b> Established/Proper Name: <b>Droxidopa</b> Dosage Form: <b>oral capsules</b> Strengths: <b>100 mg, 200 mg, and 300 mg</b>		
Applicant: <b>Chelsea Therapeutics, Inc.</b>		
Date of Application: <b>September 23, 2011</b> Date of Receipt: <b>September 28, 2011</b> Date clock started after UN:		
PDUFA Goal Date: <b>March 28, 2012</b>		Action Goal Date (if different):
Filing Date: November 16, 2011		Date of Filing Meeting: <b>October 27, 2011</b>
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>1</b>		
Proposed indication(s)/Proposed change(s): treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's Disease [PD], Multiple System Atrophy [MSA] and Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i><b>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</b></i>		
Review Classification:  <i><b>If the application includes a complete response to pediatric WR, review classification is Priority.</b></i>  <i><b>If a tropical disease priority review voucher was submitted, review classification is Priority.</b></i>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i><b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b></i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 77248				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	x			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	x			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	x			
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		x		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	x			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid  <input checked="" type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>																				
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>																				
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  <b>Check the Electronic Orange Book at:</b>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p><b>Exclusivity</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a></p>		<p>x</p>																		

<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		x		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>			x	
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?<sup>1</sup>            If not, explain (e.g., waiver granted).</p>	x			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	x			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	x			

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?				
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	x			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	x			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	x			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	x			
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	x			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	x			

<p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>		<b>x</b>		<b>CSS was consulted on 11/1/11 due to concerns of abuse potential.</b>

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		<b>x</b>		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	x			
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>	x			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	x			
Is the PI submitted in PLR format? <sup>4</sup>	x			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	x			October 27, 2011
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	x			October 13, 2011
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	x			October 13, 2011
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	x  x			OSE – Proprietary Name Review – sent 10/7/11  Division of Biometrics 6 (Applications in

	x			Pharmacology/ Toxicology)- sent 10/13/11
	x			SEALD Endpoints – 10/16/11
	x			DDMAC – sent 10/27/11
	x			DSI Bioequivalence – sent 10/28/11
	x			DSI Inspection – sent 11/17/11
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s): September 20, 2007</b> <i>If yes, distribute minutes before filing meeting</i>	x			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s): December 17, 2010</b> <i>If yes, distribute minutes before filing meeting</i>	x			
Any Special Protocol Assessments (SPAs)? <b>Date(s): November 28, 2007</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	x			

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** October 27, 2011

**BLA/NDA/Supp #:** 203202

**PROPRIETARY NAME:** Northera

**ESTABLISHED/PROPER NAME:** droxidopa

**DOSAGE FORM/STRENGTH:** 100 mg, 200 mg, and 300 mg oral capsules

**APPLICANT:** Chelsea Therapeutics, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's Disease [PD], Multiple System Atrophy [MSA] and Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (DBH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

**BACKGROUND:** Droxidopa is an orally administered, synthetic catecholamine acid pro-drug that is converted to NE through a single step of decarboxylation by the endogenous enzyme 3,4-dihydroxyphenylalanine (DOPA) decarboxylase, an enzyme found in many tissues including autonomic nerve terminals.

On January 17, 2007, droxidopa was granted Orphan Designation and on August 7, 2008, the Division granted Droxidopa Fast-Track Designation for the treatment of symptomatic NOH.

The sponsor's clinical development program included 3 studies, Study 301, 302 and 303, to assess the efficacy of Droxidopa. Study 301 was a pivotal, Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose-titration period (up to 14 days) prior to a 7-day washout period, followed by a 7-day double-blind randomized treatment period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo. A total of 162 patients were included in the Full Analysis Set (FAS). The FAS included patients who were randomized and received at least 1 dose of double-blind study medication: 80 patients randomized to placebo and 82 patients randomized to droxidopa. Study 301 is the pivotal efficacy trial in the droxidopa development program, and the efficacy results from this study are the predominant focus of this NDA.

Study 302 was a supportive, Phase 3, multi-center, double-blind, randomized, placebo controlled, parallel-group, withdrawal-design study that included an initial open-label dose-titration period (up to 14 days), a 7-day open-label treatment period, and a 14-day randomized-withdrawal period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo. A total of 101 patients were included in the FAS: 51 patients randomized to placebo and 50 patients randomized to droxidopa. Study 302 failed to meet its primary endpoint and, as a result, the efficacy data from this trial are supportive in nature. Of note, the Division met with the sponsor on November 18, 2009 in light of the results of the failed study and the sponsor was allowed to modify the primary outcome variable in Study 301.

Study 303 was a Phase 3, multi-center, long-term extension study to evaluate the long-term safety and efficacy of droxidopa in patients with NOH. The study had an initial 12-week open-label phase, followed by 2 weeks of treatment with droxidopa or placebo in a randomized-withdrawal phase, and then an open-label, long-term extension period in which patients were again treated with their individualized dose of droxidopa for up to 2 years. All patients entered this study from a prior study with droxidopa (Studies 301 or 302). A total of 103 patients were enrolled into Study 303 (102 patients received at least a single dose of droxidopa); 75 patients participated in the double-blind, placebo-controlled withdrawal period of the study (37 patients randomized to placebo and 38 patients randomized to droxidopa).

A Pre-NDA meeting was held on December 1, 2010. Since the primary endpoint was changed after 124 subjects had been enrolled and 165 subjects have been randomized, Dr. Stockbridge recommended the sponsor be as thorough as possible in providing the full documentation for the basis of that decision in their complete study report. The sponsor agreed and would provide the documentation to show that they remained blinded to the study results at the time.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Anna Park	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Shari Targum		Y
Clinical	Reviewer:	Melanie Blank	Y
	TL:	Aliza Thompson	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sreedharan Sabarinath	Y
	TL:	Rajnikanth Madabushi	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	James Hung	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Donald Jensen	Y
	TL:	Tom Papoian	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Lyudmila Soldatova	Y
	TL:	Kasturi Srinivasachar	Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Forest Ford	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:	Barbara Fuller	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Sharon Gershon	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: February 23, 2012 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b> Determined need for CSS consult at the Filing Meeting for possible tolerance potential.</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Ellis Unger, M.D.	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):	
Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

<input type="checkbox"/>	<ul style="list-style-type: none"> <li>notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Anna Park, R.Ph.  
Regulatory Project Manager

November 17, 2011  
Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANNA J PARK  
11/21/2011