CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	December 13, 2013
Reviewer:	Somya Dunn, M.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Reema Mehta, Pharm.D., M.P.H. DRISK
Division Director:	Claudia B. Manzo, Pharm.D. DRISK
Drug Name(s):	Northera™ (Droxidopa)
Therapeutic Class:	Sympathomimetic
Dosage and Route:	100 mg, 200 mg, and 300 mg oral capsules
Application Type/Number:	NDA 203-202
Submission Number:	0044 and 0048
Applicant/sponsor:	Chelsea Therapeutics, Inc.
OSE RCM #:	2013-2027

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1 INTRODUCTION

The purpose of this document is to assess the need for a Risk Evaluation and Mitigation Strategy (REMS) for droxidopa (proposed Tradename Northera™), NDA 203-202. This NDA is under review in the Division of Cardiovascular and Renal Products (DCRP). The Sponsor is Chelsea Therapeutics, Inc. The Sponsor included a proposed REMS in the original NDA submission. However, the submission received a Complete Response (CR) due to inconsistency of data and disproportionate site effects. This submission is the response to the CR and does not include a proposed REMS.

1.1 BACKGROUND

Northera, a produg for norepinephrine, is proposed 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).

Northera is an orally bioavailable, synthetic catecholamine acid prodrug. It is directly metabolized to norepinephrine which increases blood pressure by inducing peripheral arterial and venous vasoconstriction. The proposed dosage form and strengths of Northera are 100 mg, 200 mg, and 300 mg capsules for oral administration. Patients will be titrated to an optimal dosage with individualized doses ranging from 100 to 600 mg three times daily based on the patient's symptomatic response. The maximum total daily dose is 1800 mg.

Currently, the only other approved agent for NOH is midodrine. Midodrine is a prodrug for the active metabolite, desglymidodrine, an α_1-receptor agonist.

1.2 REGULATORY HISTORY

This is a resubmission NDA. The original NDA was submitted on September 28, 2011 and included a proposed REMS, REMS Supporting Document, and a Risk Management Plan to mitigate the risk of supine hypertension. The proposed REMS documents were reviewed by G. Toyserkani in the Division of Risk Management, review dated February 21, 2012. Based on the available data included in the submission, DRISK concluded that a REMS was not needed to ensure the benefits outweighed the risks and labeling was sufficient to manage the drug's benefit-risk profile. Please see her review for further details regarding background, prior regulatory history, clinical program and safety profile as presented in the original NDA submission.

On March 28, 2012 the original NDA received a CR. The Agency cited inconsistency of data and disproportionate site effects. The Sponsor was informed that a second study confirming safety and efficacy would be needed.

The Sponsor submitted a Formal Dispute Resolution Request on December 12, 2012. On February 8, 2013, The Office of New Drugs issued a Formal Dispute Resolution Response upholding the Complete Response. This letter indicated the Sponsor's study, 306B, may have the potential to serve as a basis for a resubmission of the NDA in response to the CR letter's request for at least one additional adequate and well-controlled trial.

On July 3, 2013, the Sponsor submitted a response to the CR, this included data and a study report for Study 306B. However, this response was found inadequate due to statistical issues, missing narratives and a reported discrepancy in study sites. The Sponsor addressed these deficiencies and submitted the remainder of their response on August 28, 2013. The Sponsor's resubmission did not include a proposed REMS.

2 MATERIALS REVIEWED

2.1 MATERIALS INFORMING THIS REVIEW

- Chelsea Therapeutics, Inc. Clinical Overview, Version 2, Submitted July 3, 2013
- Chelsea Therapeutics, Inc. Integrated Summary of Safety Version 2, Submitted July 3, 2013
- Chelsea Therapeutics, Inc. Draft Labeling Text, Submitted July 3, 2013
- G. Toyserkani. DRISK REMS Review, dated February 21, 2012.

3 RESULTS OF REVIEW OF PROPOSED (b) (4) RISK EVALUATION AND MITIGATION STRATEGY

3.1 OVERVIEW OF CLINICAL PROGRAM

The original NDA clinical program was described in Dr. Toyserkani's review. Data for the resubmission NDA included new data from Study 304, 306A, and 306B. Study 306B was the Sponsor's additional study for efficacy as requested in the CR letter. Study 306A and 306B were multi-center, double-blind, randomized, parallel-group, placebo-controlled studies to assess the clinical effect of Northera in the treatment of symptomatic neurogenic orthostatic hypotension in patients with Parkinson's Disease. The primary objective of Study 306A was to evaluate the clinical efficacy of Northera as demonstrated by change in symptom and activity measurements using the Orthostatic Hypotension Questionnaire (OHQ) composite score. The primary objective of Study 306B was to evaluate the clinical efficacy of Northera as demonstrated by improvements in the Orthostatic Hypotension Symptom Assessment (OHSA) Item 1, from Baseline to Visit 4 (Week 1). Study 304 was a multi-center, open-label study to assess the long-term safety of Northera in subjects with primary autonomic failure, dopamine beta hydroxylase deficiency, or non-diabetic neuropathy and symptomatic neurogenic orthostatic hypotension. The purpose of the study was to determine the long-term safety of Northera as measured by the occurrence of treatment-emergent adverse events (AEs) and specific evaluations of blood pressure (BP), heart rate (HR), and laboratory findings across the study.

In total, in the Sponsor's clinical program, 638 patients have been treated with Northera; of which 162 newly exposed patients were included in the resubmission NDA.

3.2 SAFETY CONCERNS

As detailed in Dr. Toyserkani's review, supine hypertension is associated with therapies for NOH. This risk is addressed in labeling for approved products. The overall rate in the

clinical program of supine hypertension, defined as systolic blood pressure greater than 200 mmHg was 3.5% in Northera treated patients versus 0.9% in placebo.

The most common adverse events (AEs) in the clinical program were headache (13.2% in Northera vs. 7.4% in placebo), dizziness (9.6% vs. 4.6%) and nausea (8.8% vs. 4.6%). These rates are from Study 306 which had the longest placebo controlled treatment in the program of 8-10 weeks.

The serious adverse events (SAEs) and patient death rate/profile did not indicate any major differences from the SAE profile in the original NDA. Please see Dr. Shari Targum's review for details and findings regarding the safety profile.

The data in the NDA resubmission did not present an increase in severity of the safety signal of supine hypertension. In addition, no new safety signals that would rise to the level to necessitate a REMS were found in review of this data.

3.3 SPONSOR'S PROPOSED RISK MANAGEMENT PROPOSAL

The Sponsor did not submit a REMS proposal in the NDA resubmission.

4 CONCLUSION/RECOMMENDATIONS

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.

Should DCRP raise further concerns with the risks outlined above or identify additional risks associated with Northera warranting more extensive risk mitigation or a formal REMS, DRISK will revisit this application and/or review the additional data.

This memo serves as the primary DRISK review for Northera under NDA 203-202. Please notify DRISK if you have any questions.

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/s/

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12/13/2013
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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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	February 21, 2012
Reviewer(s):	Gita A. Toyserkani, Pharm.D., MBA, Senior Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Megan Moncur, M.S. DRISK
Division Director:	Claudia B. Karwoski, Pharm.D. DRISK
Drug Name(s):	Northera (droxidopa)
Therapeutic Class:	Sympathomimetic
Dosage and Route:	100 mg, 200 mg, and 300 mg oral capsules
Application Type/Number:	NDA 203202
Submission Number:	000
Applicant/sponsor:	Chelsea Therapeutics, Inc.
OSE RCM #:	2011-3686

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CONTENTS

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review is provided in response to a request by the Division of Cardiovascular and Renal Products (DCRP) to review and comment on Chelsea Therapeutic, Inc.'s Risk Evaluation and Mitigation Strategy (REMS) proposal for Northera (NDA 203202).

The sponsor has voluntarily submitted a REMS proposal for Northera to mitigate the risk of supine hypertension associated with the use of the drug. The REMS proposal consists of a Medication Guide, communication plan, and a timetable for submission of assessments.

This review concludes that based on the current safety information, the risk of supine hypertension can be managed through labeling. Additionally, the proposed Medication Guide can be included as part of the labeling and does not need to be included as part of a REMS. Therefore, a REMS is not warranted at this time.

1 BACKGROUND

1.1 INTRODUCTION

The Agency is reviewing a New Drug Application (NDA) for Northera 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).

Northera (droxidopa) is an orally bioavailable, synthetic catecholamine acid prodrug. It is directly metabolized to norepinephrine which increases blood pressure by inducing peripheral arterial and venous vasoconstriction. Droxidopa crosses the blood brain barrier and therefore, may act both peripherally and centrally.

The proposed dosage form and strengths of droxidopa for commercial distribution are 100 mg, 200 mg, and 300 mg immediate-release capsules. Patients will have their dose titrated to an optimal dosage with individualized doses ranging from 100 to 600 mg three times daily (TID).

1.2 REGULATORY HISTORY

Droxidopa was approved and has been marketed in Japan since January 17, 1989. It is approved in Japan for the following indications, orthostatic hypotension associated with Parkinson's disease, freezing of gait in Parkinson's disease, intradialytic hypotension, and neurogenic orthostatic hypotension (NOH). It should be noted that droxidopa is marketed in Japan at lower doses (100 – 300 mg TID).

On January 17, 2007, droxidopa was granted Orphan Designation in the US, and on August 7, 2008, DCRP granted droxidopa priority review for the treatment of symptomatic NOH. The only drug treatment option for the NOH indication in US at this time is midodrine (accelerated approval in 1996). In 2010 FDA proposed withdrawing

the approval of midodrine as the required confirmatory clinical efficacy trials were not yet completed.

A pre-NDA meeting for droxidopa was held on December 1, 2010. During the pre-NDA meeting, the sponsor stated that they were prepared to implement a REMS that consists of a Medication Guide and a healthcare provider (HCP)-oriented communication plan. The sponsor inquired whether this plan would be adequate in managing the potential risks of droxidopa. The Agency's response was that this would be a review issue that could not be addressed without reviewing the application. (b) (4) the Agency considered this proposal as reasonable, but stated that the entire NDA would need to be reviewed before a decision could be made on the labeling.

The original NDA was received September 28, 2011, and includes a proposed REMS, REMS Supporting Document, and a Risk Management Plan.

1.3 PROPOSED PRODUCT LABELING

The proposed label (received January 26, 2012) contains information about supine hypertension in the following sections:

(b) (4)

The Medication Guide contains the following information about supine hypertension:

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials were reviewed:

- REMS proposal received September 28, 2011

The following materials were referenced:

- Proposed labeling received January 26, 2011
- Clinical Pharmacology Review by Dr. Sreedharan Sabarinath, dated January 25, 2012
- Clinical Review by Dr. Melanie Blank, dated January 27, 2012

3 RESULTS OF REVIEW

3.1 RISK BENEFIT CHARACTERIZATION

3.1.1 Current Therapies

At this time, patients with symptomatic NOH have few therapeutic alternatives. There are currently no available therapeutic options that have been demonstrated to provide clinical benefit.

Midodrine hydrochloride (an alpha1-agonist) is the only medication approved by the FDA (in 1996) for the treatment of symptomatic orthostatic hypotension. The indication is based on midodrine hydrochloride tablet's effect on increases in 1-minute standing systolic blood pressure (SBP), a biomarker that has not been demonstrated to be a valid surrogate marker of treatment benefit. Therefore, at present, the clinical benefits of midodrine, principally improved ability to carry out activities of daily living, have not been established. Since the required confirmatory clinical efficacy trials were not yet completed for midodrine, FDA proposed withdrawing its approval in 2010.

Other vasoconstrictors, such as ephedrine, have not been able to show symptomatic benefit in patients with NOH. Other medications, such as fludrocortisone, are used routinely in patients with symptomatic NOH; however, because of the salt and water retention that it causes, it has limited utility in the elderly. There are other medications that are used off-label; however, most of these drugs carry serious safety concerns, as referenced in the clinical review (see Attachment 1).

3.1.2 Severity of Risk

3.1.2.1 Risk in context of drugs in class, among other drugs used to treat disease prescribers familiarity with risk, monitoring and management

Supine hypertension is associated with the other current therapies for NOH (e.g., midodrine, fludrocortisone, pseudoephedrine/ephedrine, and erythropoietin) and is a treatment-limiting side effect. For example, the midodrine label states that supine hypertension has been reported in 13.4% of patients receiving 10 mg TID.

3.1.2.2 How is the risk managed across other products and/or diseases

Other drug products are associated with supine hypertension, especially those that interact (directly or indirectly) with alpha-adrenergic receptors. At present, this risk is addressed through labeling and no drugs have a REMS to address this risk. The midodrine label includes a boxed warning about the risk of supine hypertension.

3.1.3 Seriousness of 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.[1]

[1] 1The definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *J Auton Nerv Syst* 1996; 58:123-4.

Orthostatic hypotension may be severely incapacitating and substantially impact the quality of life. Some patients become confined to a wheelchair and some become bedridden.

3.1.4 Expected Benefit

The efficacy data were reviewed by the clinical reviewer, Dr. Melanie Blank; there are remaining questions about the magnitude of benefit, as well as concerns about lack of evidence of durability of effect.

3.1.5 Expected Duration of Treatment

Droxidopa is intended as a treatment for a chronic condition. Patients mat be treated indefinitely with droxidopa.

3.2 OVERVIEW OF CLINICAL PROGRAM

There were five clinical trials submitted in this NDA. The first three addressed efficacy and safety (301, 302, and 303), whereas the last two addressed safety only (304 and 305).

Studies 301 and 302 were multi-center, double-blind, randomized, placebo controlled, parallel-group Phase III trials in NOH patients by induction and withdrawal designs, respectively. Study 301 was 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 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.

Studies 303 and 304 were Phase III, multi-center, long-term extension studies to evaluate the long-term safety and efficacy of droxidopa in patients with NOH. There was a 24-hour ambulatory blood pressure monitoring (ABPM) study (305) from a subset of patients originally enrolled in Study 301. There were no dedicated renal or hepatic impairment studies or drug-drug interaction studies in the sponsor's drug development program.

Droxidopa exhibited dose-dependent increases in systolic blood pressure during the open-label dose-titration phase in the Phase III Study 302. The blood pressure effect of droxidopa was further confirmed in the pivotal efficacy trial 301 and in the 24-hour ABPM Study 305. On an average, approximately 8 mmHg and 5 mmHg increases in 24-hour average for systolic (SBP) and diastolic blood pressures (DBP), respectively, were observed in study 305. In Study 301, patients receiving droxidopa experienced a mean increase of 7.3 mmHg ($p<0.001$) in standing SBP compared to placebo. It should be noted that the blood pressure effect of droxidopa was not significant in the double-blind withdrawal phase of Study 302.

According to the clinical reviewer, Dr. Blank, the safety data base for the droxidopa development program was not robust. Total patient exposure in the program was 752 patients with 276 patients exposed ≥ 6 weeks and only 64 of those were exposed to the

maximum dose of 600 mg TID. A total of only 93 patients were exposed over 1 year and only 26 of those were exposed at the maximum dose of 600 mg TID. There was limited Phase III double-blind exposure; only 131 patients received droxidopa with a mean exposure of 11 days during the double-blind Phase III studies.

3.3 FOREIGN POSTMARKET EXPERIENCE (JAPAN)[2]

Postmarketing data have been collected in Japan since the marketing approval of droxidopa in 1989 through the conduct of postmarketing surveys, and through collection of spontaneous adverse events (AEs) reported by health care providers. The surveys were conducted from January 1989 through January 1995.

According to the clinical reviewer, Dr. Blank, a total of 131 patients out of the 1819 (7.2%) patients surveyed reported a total of 194 AEs. The majority of these patients were being treated for Parkinson's disease. The most frequently reported AEs collected during the first 6 years in the postmarketing survey (N=1819) were nausea/vomiting (1.5%); hallucination, BP increased, ALT (SGPT) increased, anorexia, and dizziness/lightheadedness were all reported in <1% of the patients. All of these AEs were expected AEs, based on the precautions section for the approved label in Japan.

Of the 194 AEs reported during the postmarketing survey, one was considered a serious AE (angina pectoris); this AE subsided after discontinuation of droxidopa and was considered possibly related to droxidopa treatment.

Additionally, there were 9 cases of neuroleptic malignant syndrome (NMS) in the Japanese postmarketing experience. The clinical reviewer states that these cases are worrisome and it is unclear from the reports if there is a causal relationship between droxidopa and NMS; the reports do not provide an alternative explanation for the development of NMS. There were no specific AEs attributed to long-term use of droxidopa (please see the clinical review by Dr. Melanie Blank, DARRTS date 27-January-2012 for details).

3.4 SAFETY CONCERNS

3.4.1 Overall Safety

Based on the clinical review, a total of 60 of 476 (12.6%) patients reported 116 SAE across Studies 301, 302, 303, and 304. There were no deaths during the short pivotal trials, Study 301 and Study 302. However, during the longer term open-label phase, there were 18 deaths, as well as SAEs, discontinuations for AEs, and events of hypertensive crisis, strokes and myocardial infarctions; there were also several patients with worsening of their movement disorders (please see the clinical review by Dr. Melanie Blank, DARRTS date 27-January-2012 for details).

3.4.2 Risk of Hypertension and Supine Hypertension

Hypertension was a safety issue that was monitored during the titration phase, as some patients had hypertensive responses and required down titration or discontinuation of

[2] Clinical Review by Dr. Melanie Blank, DARRTS date 27-January-2012

drug. Data from the clinical trials suggest that patients with baseline hypertension are more likely to have worsening hypertension and should be monitored closely for this potential adverse reaction.

One patient in the treatment group, receiving droxidopa 200 mg TID, had a SBP of > 200 (214 mmHg). Dr. Blank opines that it is likely that droxidopa-treated patients will occasionally have hypertensive reactions, and that since SBP is easily monitored, this is not highly concerning safety issue in most cases. However, there were three cases of "hypertensive crisis" in Study 304, fortunately without any permanent sequelae.

According to the sponsor, during the open-label dose-optimization phase, the overall incidence of supine hypertension at any titration visit SBP >200 mmHg was 2.5% and SBP > 180 mmHg was 8.0%. The incidence of supine SBP > 180 mmHg was low in the placebo-controlled phase of clinical trials and slightly higher in droxidopa patients versus placebo patients (3.1% vs. 1.5%). No patients on droxidopa exhibited supine SBP > 200 mmHg during the placebo-controlled phase of the trials. It should be noted, however, that blood pressure was not measured when patients were fully supine.

The potential for supine nighttime hypertension was evaluated in the 24-hour ambulatory blood pressure monitory (ABPM) study (Study 305). There was an overall increase in blood pressure profiles with droxidopa compared to placebo. Changes in mean nighttime blood pressure were comparable to changes in the daytime.

3.5 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

The applicant voluntarily submitted a proposed REMS with the NDA.

3.5.1 Goals

The goals of the REMS are to:

- Inform and educate HCPs about the risk of supine hypertension in patients taking Northera, appropriate patient selection, monitoring, dose optimization, and counseling of patients and/or caregivers.
- Inform and educate patients and/or caregivers about the risk of supine hypertension while taking Northera, the importance of self-monitoring and communicating with their HCP.

3.5.2 Summary of proposed REMS

The sponsor, Chelsea, proposes a REMS comprised of a Medication Guide, a communication plan, and a timetable for submission of assessments. The communication plan consists of a Dear Healthcare Professional (DHCP) Letter. The intended audience for the communication plan is healthcare professionals who are likely to prescribe Northera to treat NOH, and will target those who have written at least one prescription for midodrine or fludrocortisone (excluding endocrinologists) in the past 12 months.

(b) (4)

(b) (4)

3.6 VOLUNTARY RISK MITIGATION MEASURES

(b) (4)

The voluntary tools have not been submitted for review; therefore, DRISK is unable to comment on them.

3.7 PROPOSED POSTMARKETING STUDIES

Chelsea proposes to conduct a Phase IV study to gather more data on exposure to Northera and acute and long-term safety with respect to supine hypertension and cardiac adverse events. The objective of the study is to better characterize the safety of Northera with respect to supine hypertension and cardiac adverse events. The applicant proposes an observational safety registry of 200 to 300 patients with symptomatic NOH and to follow these patients for 4 to 5 years. The applicant states that they will work with the Agency to develop the details of the study protocol.

4 DISCUSSION

REMS are intended to ensure that the benefits of the drug outweigh the risks of the drug. They are also intended to meet specific risk mitigation goals for a product that requires strategies beyond professional labeling to ensure safe use in the postmarketing setting. It

is important to determine if such additional measures are feasible, appropriate, effective, and necessary to mitigate the risks.

Chelsea has proposed a REMS to inform and educate HCPs about the risk of supine hypertension, appropriate patient selection and monitoring, dose optimization, and counseling of patients and/or caregivers, and also to inform and educate patients and their caregivers about the risk of supine hypertension, and the importance of self-monitoring and communicating with their HCP. The proposed REMS consists of a Medication Guide and a one-time DHCP letter.

Given the absence of robust safety data, the questionable magnitude of benefit, as well as the concern about whether the effect of droxidopa diminishes over time, it is difficult to determine if a REMS is necessary to ensure the benefits outweigh the risks and to ensure safe use of the drug.

There are limited safety data in the droxidopa development program to determine the magnitude of effect of droxidopa on supine blood pressure. Given that no patients were allowed to lie flat while on study, it makes it impossible to evaluate the full magnitude of supine hypertension. As pointed out by the clinical reviewer, it would have been helpful to have occasional blood pressure readings when the patients were fully supine to evaluate the magnitude of the effect of droxidopa on supine blood pressure for purposes of safety labeling and risk mitigation strategies.

There are additional limitations to the safety data. It is difficult to properly evaluate the long-term safety of droxidopa, due to the paucity of both long-term exposure and exposure to the highest daily dose. Also, there is a lack of representation of patients who are Hispanic, Asian, or black which is concerning with regards to the generalizability of both the efficacy and safety findings.

Based on the available safety data and our review of the proposed REMS, if droxidopa is approved, we do not recommend a REMS at this time. To date, there has not been a REMS required for the risk of supine hypertension. Other drug products associated with supine hypertension (e.g., levodopa) do not have a REMS and the risk of supine hypertension is addressed through labeling; therefore, there is no precedent to require a REMS. Further, midodrine, another drug for the treatment of OH carries the risk of supine hypertension and does not have a REMS in place.

Although, we believe that supine hypertension is a serious adverse event and can theoretically increase the risk of acute and chronic cerebrovascular disease, it is common in patients with orthostatic hypotension. Patients with NOH have impaired autonomic function, and exhibit OH as well as supine hypertension resulting from either BP dysregulation or following treatment of OH. Other current therapies for NOH carry the risk of supine hypertension. Therefore, physicians treating patients with NOH are most likely familiar with the risk of supine hypertension.

One of the risk management approaches proposed by the sponsor is a one-time DHCP letter. However, there is limited experience on the effectiveness of "education" alone in

improving the safe use of a product. It is unclear if a one-time DHCP letter will have an impact on increasing compliance with monitoring recommendations or mitigating risk.[3]

Furthermore, the purpose of a communication plan would be to emphasize and reinforce the safety messages that are highlighted in the labeling. We believe that if the safety concern does not warrant a boxed warning, a REMS consisting of a communication plan is not warranted. (b) (4) midodrine, which is also indicated for the treatment of symptomatic OH, does include the risk of supine hypertension in a boxed warning, but does not have a REMS.

The sponsor has also proposed a Medication Guide as part of the REMS. A Medication Guide is considered part of the labeling and is also a potential element of a REMS. Based on the risks of a drug and public health concern, the Agency has the authority to require a Medication Guide as part of a REMS if FDA determines that a REMS is necessary to ensure the benefits of the drug outweigh its risks.[4] Under part 208, Medication Guides may be safety-related, addressing serious risk(s) (relative to benefits) of which patients should be made aware, and/or efficacy-related, when patient adherence to directions for use is crucial to the drug's effectiveness.[5] In the case of droxidopa, the Medication Guide can be useful in informing the patient about the risk of supine hypertension. It can also inform the patient about ways to minimize the risk, such as sleeping with the head of the bed elevated (which was done in the clinical trials) and taking the last dose of droxidopa at least 3-4 hours before going to bed. Given that a REMS is not warranted at this time for droxidopa, the Medication Guide can be included as part of the labeling and not part of a REMS.

Finally, a risk management approach as proposed by the sponsor will not be able collect safety data to better characterize the risk of supine hypertension. Therefore, a postmarketing requirement, as proposed by the sponsor, to better elucidate the safety profile of droxidopa may be warranted.

5 CONCLUSION & RECOMMENDATIONS

In summary, there are many factors to weigh in determining the appropriate risk management approach for a particular product and its associated risk(s). This review concludes that 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,

[3] Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact of Wording in "Dear Doctor" Letters and in Black Box Labels.* Clin Pharmacol Ther. 2002;72:735-742.

[4] Guidance - Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS). November 2011.

[5] 21 CFR 208.1(b) and (c).

the sponsor may voluntarily implement a DHCP letter and additional voluntary measures as proposed [redacted] (b) (4)

- 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.

Table 1: Table of Drugs Used for Neurogenic Orthostatic Hypotension

Compound	Contraindications	Main side effects
Desmopressin	Hyponatremia, chronic renal failure Pregnancy Category B	Hyponatremia, water intoxication, headache, nausea, rhinitis
Dihydroergotamine	Myocardial ischemia, uncontrolled hypertension, renal or hepatic failure, hemiplegia or basilar migraine, peripheral artery disease, sepsis, following vascular surgery, pregnancy, nursing mothers Not to be given with vasoconstrictors or ergot-type medications	Myocardial ischemia, stroke, ventricular tachycardia, ventricular fibrillation, vasoconstriction, paresthesias hypertension, headache
Erythropoietin	Uncontolled hypertension, known hypersensitivity Pregnancy Category C	Pure red cell aplasia, infection, congestive heart failure, thrombosis of vascular access, cardiac angina pectoris, arrhythmia and cardiac arrest, hypertension, stroke, increased risk of tumor progression
Fludrocortisone	Systemic fungal infections, known hypersensitivity Pregnancy Category C	Hypertension, edema, hypokalemia, compression fractures hypomagnesaemia, congestive heart failure, headache mental disturbances
Indomethacin	Peripoerative pain in the setting of coronary artery bypass graft, known hypersensitivity, Pregnancy Category C	Myocardial infarction, stroke, pulmonary hypertension, gastrointestinal bleeding, exfoliative dermatitis, aggravation of psychiatric and neurologic conditions including Parkinson's, renal failure
Midodrine	Severe heart disease, acute renal disease, urinary retention, pheochromocytoma, thyrotoxicosis, persistent or excessive supine hypertension Pregnancy Category C	Supine hypertension, paresthesias, pruritus, piloerection, chills, urinary urgency, frequency and retention
Octreotide (somatostatin)	Known hypersensitivity to drug Pregnancy Category B	Nausea, abdominal colic, diarrhea, cholelithiasis, bradycardia, hypthyroidism, goiter, hypertensive crisis, thrombocytopenia
Pyridostigmine	Mechanical intestinal or urinary obstruction, caution with bronchial asthma Safety in pregnancy not established	Abdominal colic and loose stools, muscle cramps, muscle weakness, rash
Yohimbine	No contraindication found in verterinary label	Dogs show apprehensiveness

Sources:

Maule S et al, Orthostatic Hypotension: Evaluation and Treatment, Cardiovascular and Haematological Disorders-Drug Targets, 2007, 7, 63-70.
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GITA A TOYSERKANI
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CLAUDIA B KARWOSKI
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