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Re: New Drug Application for Droxidopa for Neurogenic Orthostatic Hypertension

Dear Commissioner Hamburg, Dr. Woodcock, and Dr. Stockbridge:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing to voice its strong opposition to Food and Drug Administration (FDA) approval of the new drug application (NDA) 203202 for droxidopa (NOTHERA) submitted by Chelsea Therapeutics for the proposed indication of treatment of symptomatic neurogenic orthostatic hypotension (NOH). Droxidopa was the subject of the January 14, 2014, Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting.

Public Citizen strongly opposes approval of droxidopa because the data from the clinical trials presented in the NDA failed to provide substantial evidence that the drug is effective for its proposed indication for use. In particular, two of the four pivotal clinical trials of droxidopa failed to meet their initial pre-specified primary efficacy endpoints, and the other two pivotal

trials met primary efficacy endpoints only after these endpoints were changed near the end of the trials and provided data that were neither robust nor strongly positive. Furthermore, the drug has not been shown to have any durability of effect (beyond one week) even though it would be indicated for treatment of a chronic condition. Indeed, the FDA clinical reviewer has wisely recommended that the agency not approve droxidopa for the treatment of NOH because of inadequate evidence of effectiveness.[1]

The FDA never should have referred the resubmitted NDA for droxidopa to an advisory committee for review in the first place, and we urge the agency to reject the CRDAC's recommendation for approval. FDA approval of droxidopa based on the available data would essentially undermine the integrity and meaningfulness of FDA's standard for approving drugs.

I. Background

A. Drug overview

Droxidopa is being developed to treat symptomatic NOH associated in patients with primary autonomic failure due to Parkinson's disease, Multiple System Atrophy, Pure Autonomic Failure, Dopamine Beta Hydroxylase deficiency, and Non-Diabetic Autonomic Neuropathy.[2] Symptoms of NOH include feeling dizzy, lightheaded, and faint (or like blacking out), as well as actual fainting upon sitting or standing.

The drug is a synthetic amino acid analog that is converted to norepinephrine by the enzyme dopa decarboxylase, the same enzyme that metabolizes levodopa to dopamine.[3] This conversion of the prodrug to norepinephrine can occur peripherally or centrally.[4]

The FDA clinical reviewer noted the following regarding the mechanism of action of droxidopa:[5]

> If symptomatic NOH results from inadequate release or utilization of NE from sympathetic vasomotor neurons, droxidopa treatment is thought to increase central and peripheral levels of NE, increasing blood pressure (BP). However, the exact mechanism of action of droxidopa is not known. In humans, droxidopa treatment results in a transient increase in serum levels of NE; it is possible (though not supported by available data) that NE is rapidly taken up by tissues.

B. Regulatory history overview

[1] Food and Drug Administration. FDA briefing document for the Cardiovascular and Renal Drug Advisory Committee meeting on January 14, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381154.pdf. PDF page 155. Accessed January 30, 2014.
[2] *Ibid*. PDF page 151.
[3] *Ibid*. PDF page 158.
[4] *Ibid*. PDF page 158.
[5] *Ibid*. PDF page 158.

The original NDA for droxidopa was submitted on September 28, 2011, and was considered by the CRDAC on February 23, 2012.[6] Data from three randomized controlled clinical trials — studies 301, 302, and 303 — were included in the original NDA submission to support the effectiveness of droxidopa.[7] As discussed in more detail in section II below, only one of these three studies (study 301) met its primary endpoint, which had been changed from the original pre-specified primary endpoint just prior to completion of the study.[8] Furthermore, FDA reviewers raised significant concerns about the positive efficacy data seen in study 301 due to an unusually homogenous pattern of results from a single study site along with that site's disproportionate contribution to the overall positive results.[9]

At the February 23, 2012, CRDAC meeting, the committee voted 7 to 4 (with one abstention and one member not voting) in favor of approving droxidopa.[10]

On March 28, 2012, the FDA, unconvinced of droxidopa's efficacy, appropriately issued a complete response letter to Chelsea Therapeutics indicating that one additional adequate and well-controlled trial demonstrating "strongly positive" results would be needed to obtain approval.[11] The agency emphasized that this trial "should closely adhere to the criteria specified in the Agency's effectiveness guidance for a single trial."[12]

The sponsor subsequently submitted an amended NDA that included data from one additional study, study 306B, which is discussed in detail below in section III starting on page 11, following the discussion of the earlier studies.

II. Summary of clinical efficacy studies submitted with original NDA

A. Study 302

Study 302, the first of the three pivotal trials for droxidopa presented in the original NDA submission to be completed, was a multicenter, double-blind, randomized, placebo-controlled study to assess the clinical effect of droxidopa in subjects with symptomatic NOH due to primary autonomic failure, dopamine beta hydroxylase deficiency, or non-diabetic neuropathy.[13]

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[6] *Ibid*. PDF page 159.
[7] *Ibid*. PDF page 155.
[8] *Ibid*. PDF page 155.
[9] *Ibid*. PDF page 155.
[10] Food and Drug Administration. Summary minutes of the Cardiovascular and Renal Drugs Advisory Committee. February 23, 2012, meeting. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM298452.pdf. PDF page 6. Accessed January 31, 2014.
[11] Food and Drug Administration. FDA briefing document for the Cardiovascular and Renal Drug Advisory Committee meeting on January 14, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM381154.pdf. PDF pages 155 and 162. Accessed January 30, 2014.
[12] *Ibid*. PDF page 155.
[13] *Ibid*. PDF pages 12 and 68.

The study used an enriched study design. It began with an open-label dose-titration phase in which all subjects[14] were given a starting droxidopa dose of 100 mg three times daily with escalation up to a maximum dose of 600 mg three times daily over a 14-day period.[15] The dose-titration phase was followed by a seven-day open-label treatment period during which subjects continued to take droxidopa at the maximum dose reached during the titration phase.[16] Only subjects who met the following two criteria by the end of the open-label titration phase proceeded to a 14-day double-blind, randomized withdrawal phase in which subjects were randomized to either continue on droxidopa or receive a placebo:

(a) an improvement of at least one point on item 1 of a standard survey instrument for assessing orthostatic hypotension known as the Orthostatic Hypotension Symptom Assessment (OHSA) (item 1 encompasses dizziness, lightheadedness, feeling faint or feeling like you might black out; rated on a scale from 0 to 10 with 0 representing no symptoms and 10 representing the worst possible symptoms); and

(b) an improvement in systolic blood pressure of at least 10 mm Hg at three minutes post standing.[17]

The primary efficacy endpoint was the mean change from baseline at the time of randomization to the end of the study in the score on OHSA item 1.[18]

Of the 181subjects enrolled in the initial open-label dose-titration phase, 101 were randomized to the double-blind, placebo-controlled withdrawal phase, 50 to the droxidopa group and 51 to the placebo group.[19] Of these, only 44 droxidopa subjects and 43 placebo subjects finished the study in accordance with the protocol plan.[20] The failure of treatment was the most common reason subjects did not enter the double-blind withdrawal phase (55 of 80 subjects), followed by adverse events (13 of 80 subjects).[21]

Given the randomized withdrawal design, if the drug were effective, subjects in the droxidopa group should have remained stable or improved further, and those in the placebo group should have gotten worse.[22] However, despite its enrichment design, subjects in both groups worsened considerably, and there was no statistically significant difference between the two study groups on the pre-specified primary efficacy endpoint (see the table below excerpted from the FDA's briefing documents for the January 14, 2014, CRDAC meeting).[23]

[14] *Ibid*. PDF page 12.
[15] *Ibid*. PDF pages 68-69.
[16] *Ibid*. PDF pages 68-69.
[17] *Ibid*. PDF pages 12, 38, and 68-69.
[18] *Ibid*. PDF page 69.
[19] *Ibid*. PDF page 73.
[20] *Ibid*. PDF page 73.
[21] *Ibid*. PDF page 73.
[22] *Ibid*. PDF page 74.
[23] *Ibid*. PDF pages 74-75.

Table 14: Summary of OHSA Item 1 Score[1] (Full Analysis Set with LOCF[2])

	Placebo (N=51)	Droxidopa (N=50)	p-value[3]
Randomization (Visit 4)			
N	51	50	
Mean (SD)	2.1 (2.51)	2.1 (2.19)	
Min, Max	0, 8	0, 8	
End of Study (Visit 5)			
N	51	50	
Mean (SD)	4.0 (3.58)	3.5 (3.17)	
Min, Max	0, 10	0, 10	
Change from Randomization to End of Study			
N	51	50	0.509
Mean (SD)	1.9 (3.16)	1.3 (2.75)	
Min, Max	-4, 9	-6, 9	

LOCF=Last observation carried forward; OHSA=Orthostatic Hypotension Symptom Assessment; Max=Maximum; Min=Minimum; SD=Standard deviation.
1 The OHSA composite score is the average of Items 1-6 with a score of 1 or more at the Baseline Visit.
2 Missing data were imputed using the LOCF method.
3 The change from Randomization was evaluated using the Wilcoxon rank-sum test.
Source: Table 5.1.1.

In addition, study 302 failed to show a benefit with droxidopa on its first secondary endpoint, standing systolic blood pressure at three minutes. The FDA clinical reviewer noted the following regarding these results:[24]

> Study 302 lost on its first secondary endpoint (standing systolic BP at 3 minutes) as shown in Table 15. The patients initially had a substantial rise in standing systolic blood pressure during the titration phase. This initial rise would be a surprising finding with a drug that had no effect on SBP [systolic blood pressure]. Paradoxically, the standing SBP diminished after randomization in both treatment groups [even more so in the droxidopa treatment group than the placebo treatment group (-7.6 compared to -5.2, p=0.680)]. This does cause one to wonder if the effect of droxidopa might diminish over time.

B. Study 301

The second pivotal trial to be completed for the droxidopa NDA submission was study 301, which was ongoing at the same time as study 302. Study 301 used the same enrichment process as study 302 by beginning with a 14-day open-label dose-titration phase to identify responders to the drug using the same two criteria as were used in study 302.[25] Responders then proceeded to a seven-day washout period, followed by a seven-day randomized, double-blind treatment phase in which subjects received either droxidopa or placebo.[26]

[24] *Ibid*. PDF page 75.
[25] *Ibid*. PDF pages 12 and 36-37.
[26] *Ibid*. PDF page 36.

Study 301 initially had the same pre-specified primary endpoint as study 302 — OHSA item 1.[27] However, because study 302 finished first without meeting its pre-specified primary efficacy endpoint, the sponsor, with FDA agreement, changed the primary endpoint of the ongoing study 301, which was practically finished at the time of the change.[28] The new primary efficacy endpoint was the mean change from baseline at the time of randomization to *seven days after randomization* in the score on the Orthostatic Hypotension Questionnaire (OHQ).[29]

The OHQ comprises two questionnaires:

(1) all 6 items of the OHSA (item 2, problems with vision; item 3, weakness; item 4, fatigue; item 5, trouble concentrating; and item 6, head/neck discomfort: as with item 1 discussed above, each of these items is rated on a scale of 0 to 10); and

(2) the Orthostatic Hypotension Daily Activity Scale (OHDAS), which has four items on which the patient rates the perceived degree of interference with standing or walking by the orthostatic hypotension symptoms (item 1, standing short time; item 2, standing long time; item 3, walking short time; item 4,walking long time: each item is rated on a scale of 0 to 10, with 0 representing no interference and 10 complete interference).[30]

To score the OHQ, each subscale is averaged and then the OHSA and OHDAS are averaged.[31] In scoring the scale this way, the OHDAS questions are weighted more heavily than the OHSA questions.

The change in OHQ score was selected as the new primary efficacy endpoint for study 301 because an exploratory analysis of data from study 302 showed a nominally statistically significant improvement in OHQ scores in the droxidopa group compared with the placebo group.[32] Based on the findings of study 302, the sponsor re-determined the sample size for study 301 needed to achieve adequate power.[33]

Of the 263 subjects enrolled in the initial open-label dose-titration phase of study 301, 162 were randomized to the double-blind, placebo-controlled withdrawal phase, 82 to the droxidopa group and 80 to the placebo group.[34] As in study 302, the most common reasons for subjects not entering the randomized withdrawal phase were failure of treatment and adverse events.

Data from study 301 revealed that the droxidopa group had superior results to the placebo group on the OHQ (p=0.003) (see the table below excerpted from the FDA's briefing documents for the January 14, 2014, CRDAC meeting).[35] However, the mean treatment difference between the droxidopa and placebo groups (effect size) was 0.90 units favoring droxidopa on a 10-unit scale, a

[27] *Ibid*. PDF page 12.
[28] *Ibid*. PDF page 12.
[29] *Ibid*. PDF pages 12 and 40.
[30] *Ibid*. PDF pages 40 and 42-43.
[31] *Ibid*. PDF page 40.
[32] *Ibid*. PDF page 12.
[33] *Ibid*. PDF page 40.
[34] *Ibid*. PDF pages 12, 47 and 50.
[35] *Ibid*. PDF page 50.

treatment effect that is quite small and of questionable clinical significance.[36] Study 301 also showed a statistically significant difference in favor of the droxidopa group for the mean change from baseline in the score on OHSA item 1, the original primary efficacy endpoint. However, the difference in the mean change from baseline between groups was only 1.0, which again is small and of questionable clinical significance.

Table 5: Summary of OHQ Composite Score (FAS)

	Placebo (N=80)	Droxidopa (N=82)	ANCOVA[3]
Randomization (Visit 4)			
N[4]	79	81	
Mean (SD)	4.97 (2.41)	5.11 (1.96)	
Min, Max	0.7, 9.8	0.9, 9.1	
End of Study (Visit 5)			
N	79	81	
Mean (SD)	4.04 (2.61)	3.29 (2.20)	
Min, Max	0.0, 9.8	0.0, 8.4	
Change from Randomization to End of Study			
N	79	81	0.003
Mean (SD)	-0.93 (1.69)	-1.83 (2.07)	
Min, Max	-7.5, 2.6	-6.2, 4.4	

ANCOVA=Analysis of covariance; LOCF=Last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; Max=Maximum; Min=Minimum; SD=Standard deviation.

Moreover, the FDA clinical reviewers identified the following key concerns and issues regarding the results of study 301 during the review of the original NDA submission:[37]

> The primary endpoint that was selected for Study 301, the OHQ, was reviewed by the Study Endpoints and Labeling Development (SEALD) team reviewer, Dr. Elektra Papadopoulos, and found to be lacking in content validity. The OHQ questions should have been crafted to measure the symptomatic impact when performing certain functions and/or the functional impact on the symptoms of orthostatic hypotension. It should have included questions that specifically addressed symptoms associated with postural changes and patient's ability to make those postural changes during their daily activities. Instead, it just queried the patients regarding their symptoms or their ability to stand and/or walk without drawing any relationships between these two integral concerns.
>
> Furthermore, the post-hoc OHQ "success" in Study 302 was driven by the benefit on standing which was asked in 2 of 10 OHQ questions (standing briefly; standing for prolonged periods – one is a subset of the other). This was the only question that showed nominally statistically significant improvement in the OHQ of Study 302. "Standing" is not a symptom and therefore cannot be used to support a symptomatic claim. It is also not clear what "standing" means. Does it mean standing up from a seated position or staying standing once you have achieved standing? And how can this positive finding be interpreted as a clinical benefit when the dizziness item (OHSA Item 1) did not show

[36] *Ibid*. PDF page 50.
[37] *Ibid*. PDF pages 17-18.

> improvement? **One might conclude that the post-hoc success of "standing" without improvement on "dizziness" in Study 302 provides additional evidence that the OHQ is not a valid instrument for measuring clinical benefit.**
>
> Study 302 should not be considered to be supportive of approval, not only because 1) it was a hypothesis generating study and 2) it did not show a statistically significant improvement in systolic blood pressure, but also 3**) the lack of validity of OHQ as a measure of symptomatic benefit.** [Emphasis added]

Finally, additional FDA review of study 301 after the February 23, 2012, CRDAC meeting revealed that 6 out of 15 "super responders" (subjects who had ≥ 4-point reduction in the OHQ score) were enrolled at a single study site in Ukraine.[38] The FDA reviewers also observed an unusual pattern of homogeneity in data from this study site, given the large placebo effect and amount of variability observed at other sites in the trial.[39] When this site was removed from the analysis, the results were no longer statistically significant.[40] The FDA clinical reviewer noted the following regarding this analysis of the Ukraine study site in question:

> According to FDA guidance, a single, large, multicenter, adequate and well-controlled study can support effectiveness under certain circumstances. However, "**if analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished**."[Cited source: Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.][41]

C. Study 303

Study 303 was the third efficacy trial submitted with the original NDA.[42] This study, like studies 301 and 302, used a randomized withdrawal design. It was a 3 ½-month extension study of subjects who had had a symptomatic response during studies 301 and 302, with most of the enrolled subjects coming from study 302.[43] The subjects received droxidopa at their titrated dose for three months, after which they were randomized to either continue on droxidopa or switch to placebo for two weeks.[44] The primary efficacy endpoint was the mean change from baseline at randomization to the end of the two-week randomized treatment in OHQ scores.[45] Secondary endpoints included mean changes in scores on the individual elements of the OHSA and changes in blood pressure.[46]

[38] *Ibid*. PDF page 160.
[39] *Ibid*. PDF page 161.
[40] *Ibid*. PDF page 161.
[41] *Ibid*. PDF page 162.
[42] *Ibid*. PDF pages 12 and 82.
[43] *Ibid*. PDF pages 12 and 82.
[44] *Ibid*. PDF pages 12 and 82.
[45] *Ibid*. PDF page 83.
[46] *Ibid*. PDF page 83.

Of the 103 subjects enrolled in the initial three-month open-label phase of study 303, 75 were randomized to the double-blind, placebo-controlled withdrawal phase: 38 to the droxidopa group and 37 to the placebo group.[47]

There were no statistically significant differences between the two groups in the primary endpoint, mean change from baseline in OHQ scores, or in OHSA item 1 or standing systolic blood pressure at the end of the double-blind treatment period.[48]

D. Key additional comments made by FDA reviewers regarding the original NDA submission and FDA action

FDA reviewers made the following additional key comments pertinent to the FDA's decision to issue a complete response letter for the original:

- **It seems clear that NOH is a disease with important morbidity and mortality; however, none of the studies were designed to show effects on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome.** Certainly a 0.9-point improvement in the OHQ is not in this league.[49] [Emphasis added]

- If one were to strictly follow the FDA guidance paraphrased above, it is clear that there would need to be independent substantiation from related study data. The only data to consider for this purpose were the systolic blood pressure data. These data, however, did not provide evidence of consistency of effect. **In fact, there was no difference between placebo and droxidopa treatment groups in either Study 302 or 303 in standing [blood pressure]. If droxidopa affects the symptoms of NOH one would like to be fairly sure that the operative mechanism of action of the improvement in symptoms is an effect on the underlying condition, namely the orthostatic change in systolic blood pressure or the standing systolic blood pressure.**[50] [Emphasis added]

- Shire, the sponsor of midodrine, an approved drug for symptomatic orthostatic hypotension (approved under Subpart H in 1996), is currently being tasked with completing 2 adequate and well controlled trials to demonstrate midodrine's symptomatic benefit. The drug was approved based on a surrogate endpoint of systolic blood pressure because it was felt to be reasonably likely that this endpoint predicted symptomatic benefit. After several failed trials, this has not yet panned out. **It is important to note that we do have strong evidence of a pharmacodynamic effect for midodrine (the increase in [blood pressure]) and yet we are still demanding that they provide us with 2 trials that successfully demonstrate a clinical benefit. We should not apply lesser standards for the approval of droxidopa than we expect for midodrine.**[51] [Emphasis added]

[47] *Ibid*. PDF page 84.
[48] *Ibid*. PDF pages 86-89.
[49] *Ibid*. PDF page 16.
[50] *Ibid*. PDF pages 16-17.
[51] *Ibid*. PDF page 18.

- **There has been no durable effect (i.e., more than 1 week) demonstrated for droxidopa.** Studies 302 and 303, while showing the slightest of favorable trends on OHSA Item 1 (0.6 effect size, p=0.51 for Study 30 2 and 0.4 effect size, p = 0.25 for Study 303), did not demonstrate clinical/ symptomatic benefit for droxidopa after two weeks and 3 months, respectively, of chronic use followed by a 2-week randomized withdrawal period. **These studies also failed to show any durable effect on systolic blood pressure.** The sponsors suggest that there might be a carry-over effect of droxidopa that might obscure benefit in a 2 week randomized withdrawal experience. While this is possible, an alternative explanation could be loss of effect after several weeks of treatment. It is also possible that other study-related effects such as optimization of other aspects of their treatment regimen, including optimization of other medications, increased salt and water intake, increased exercise and elevated head at bed at night may have obscured any additional benefit that droxidopa might have conferred.[52] [Emphasis added]

- **There were numerous concerning safety findings**: 2 deaths in the double blind phase, 17 deaths, 1 stroke on post-mortem examination and 1 other stroke in a patient who survived, 3 AEs of hypertensive crisis, 1 myocardial infarction (resulted in death), 1 case of coronary artery disease that resulted in discontinuation, 33 cases of worsening of underlying movement disorder including 2 SAEs in addition to many other SAEs and discontinuations. Droxidopa is converted into NE which is a vasoactive substance. It is plausible that the cardiovascular adverse events were related to vasoconstriction from NE. Additionally, in the Japanese postmarketing experience, there were 28 reported cases of neuroleptic malignant syndrome, an often fatal condition. A few of these cases appeared to have no likely etiology other than droxidopa for what is considered to be a serious iatrogenic condition. The data that the sponsor provided were insufficient to conclude or exclude causal relationships. It is difficult and imprudent to assign causality to droxidopa because of the mostly open-label design of the study and the nature of postmarketing reporting periods. **Nevertheless, the specter of serious safety issues related to droxidopa has been raised and should not be ignored.**[53] [Emphasis added]

- **The primary reason to not recommend approval is the 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 differently 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,

[52] *Ibid*. PDF page 18.
[53] *Ibid*. PDF page 19.

> 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 caused by 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.[54] [Emphasis added]

Given the results of studies 301, 302, and 303 and the above considerations, the FDA acted appropriately in 2012 by not accepting the CRDAC's recommendation to approve droxidopa and instead choosing to issue a complete response letter to Chelsea Therapeutics indicating that one additional adequate and well-controlled trial demonstrating "strongly positive" results would be needed to obtain approval.[55] Of note, the agency emphasized that the additional requested trial "should closely adhere to the criteria specified in the Agency's effectiveness guidance for a single trial."[56]

III. Summary of additional clinical efficacy and safety data submitted with the resubmitted NDA

A. Study 306B

The NDA resubmission provided one additional pivotal efficacy trial, study 306B.[57] The unacceptable conduct of this trial, as detailed by the FDA clinical reviewer, undermines the integrity and validity of the study's data.

Study 306B (which began as study 306) was a multicenter, randomized, placebo-controlled study to assess the clinical effects of droxidopa in the treatment of symptomatic NOH in patients with Parkinson's disease.[58] Subjects were randomly assigned to receive droxidopa or placebo. Following an initial two-week titration period in which subjects' dosages was increased from 100 mg to a maximum of 600 mg, subjects received their assigned drug or placebo for an eight-week treatment period.[59]

Subject involvement in the study began on June 23, 2010, and ended on October 23, 2012.[60]

The original primary endpoint for study 306B was the change in the OHQ composite score from baseline at randomization to week 8 of treatment.[61] In accordance with the protocol study plan,

[54] *Ibid*. PDF page 21.
[55] *Ibid*. PDF pages 155 and 162.
[56] *Ibid*. PDF page 155.
[57] *Ibid*. PDF page 155.
[58] *Ibid*. PDF page 181.
[59] *Ibid*. PDF page 182.
[60] *Ibid*. PDF page 181.

the data monitoring committee (DMC) conducted an interim analysis after 60 percent of the planned subject enrollment (n=51) had completed the study visit at the end of the eight-week treatment period or had been lost to follow-up.[62] The FDA clinical reviewer noted the following regarding this interim analysis:

> The purpose of this interim analysis was to evaluate safety data and assess assumptions regarding adequacy of the sample size for efficacy assessments. **Based on prespecified criteria, the analysis showed a conditional power of less than 0.1, which met the stopping criteria for futility.** The DMC identified no safety issues of concern.[63] [Emphasis added]

The unblinded statistics team that was part of the DMC had access to all study 306 randomization codes during the time of the interim analysis.[64] This included randomization codes for subjects enrolled at the time of the interim analysis but not included in that analysis; these subjects were included in study 306B.

Rather than stop the study as initially recommended by the DMC, the sponsor split the study into two parts — 306A (the 51 subjects included in the interim analysis) and 306B (all other subjects) — and continued the study. The sponsor used the same study design and patient population, except that it requested the DMC to approve a change in the primary efficacy endpoint for study 306B to the difference in rate of patient-reported falls between the two groups.[65] The DMC granted approval to the sponsor's request on February 1, 2011.[66]

Astonishingly, in a protocol amendment dated November 5, 2012, the primary efficacy outcome was changed to improvement in OHSA item 1, and the difference in patient-reported falls was changed to a secondary efficacy outcome. The study was stopped prematurely with a total enrollment of 174 subjects (89 in the droxidopa group and 85 in the placebo group) based on a new sample size estimate taking into account data from study 301 and the new primary outcome measure for study 306B.[67]

Only after the above changes were implemented did study 306B meet the primary endpoint with an effect size of -0.94 (on the 10-point scale).[68] However, although the result was statistically significant (p=0.028),[69] this result was not robust or strongly positive, as required by the FDA for the additional pivotal trial. Indeed, the FDA clinical reviewer stated the following:

> It is difficult to judge whether the integrity of study 306B was affected by the unblinded interim analysis, along with access by contract research organization statisticians to the treatment codes. The primary endpoint and [systolic blood pressure] effects appear

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[61] *Ibid*. PDF page 184.
[62] *Ibid*. PDF page 184.
[63] *Ibid*. PDF page 184.
[64] *Ibid*. PDF page 184.
[65] *Ibid*. PDF pages 185-186.
[66] *Ibid*. PDF pages 185-186.
[67] *Ibid*. PDF pages 186 and 188.
[68] *Ibid*. PDF page 155.
[69] *Ibid*. PDF page 155.

> reduced after the access to treatment codes was revoked (Table 22). **However, if we give the applicant the benefit of the doubt, and consider study 306B to support efficacy, the results do not meet the criteria as a "robust" or "strongly positive" single study to support a symptom benefit** (see Presubmission Regulatory Activity, section 2.5). This conclusion is based on the small treatment effect, exceeded by the 3-fold higher intra-subject variability. In addition, more patients on droxidopa (vs. placebo) discontinued prior to the first post-randomization OHSA-item 1 (even if patients discontinuing from 306A are counted in discontinuations in 306B), presenting a dilemma in how to interpret the missing OHSA item-1 data.[70]

Moreover, the statistically significant difference in OHSA item 1 at one week of treatment did not persist. The FDA clinical reviewer noted the following in this regard:

> **The results of study 306B, along with results of study 303, support a lack of effect durability in this chronic condition. Study 306B met its primary endpoint at Week 1 after dose titration; however, by Week 2, the next time point, OHSA item-1 results for droxidopa and placebo appeared to merge together** (Figure 8). Results for study 303, where responders received 3 months of open-label droxidopa therapy followed by a randomized, double-blind 2-week withdrawal, showed no significant difference between groups in the primary endpoint (OHQ) or OHSA item-1 and lower standing [systolic blood pressure] for droxidopa compared to placebo.[71] [Emphasis added]

Twenty-five (28.1 percent) droxidopa subjects and 17 (20 percent) placebo subjects discontinued the study. The most common reason for withdrawal in both groups was adverse events (11 percent of droxidopa subjects and 7 percent of placebo subjects).[72]

Also of note, there was an imbalance in the percentage of subjects taking fludrocortisones at or after baseline: 16 placebo (20 percent) and 30 (34 percent) droxidopa patients. This is relevant because fludrocortisone has been used to treat orthostatic hypotension, and this could have confounded the study results.[73]

Regarding patient-reported falls, once the primary endpoint, the FDA statistical reviewer reported the following:

> The sponsor showed that in Study 306B droxidopa patients experienced a lower total number of falls during the treatment period when compared with placebo patients (Table 9). By further examining the data, the reviewer noticed that patient 122013 and patient 146007 in placebo group had 118 and 358 reported falls, respectively. If excluding the two patients, the total number of falls in placebo group reduced to 240 compared with 229 reported falls in droxidopa group. The treatment difference in the total number of falls disappeared.[74]

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[70] *Ibid*. PDF page 156.
[71] *Ibid*. PDF page 156.
[72] *Ibid*. PDF page 189.
[73] *Ibid*. PDF page 189.
[74] *Ibid*. PDF page 232.

Finally, regarding safety data from study 306/306B, the FDA clinical reviewer noted the following:

> **The most common adverse events in study 306 and in the original application were a higher incidence of hypertension, headache, nausea and dizziness in droxidopa-treated patients compared to placebo** (Tables 27, 28; also see prior Clinical Review); in study 306 there was also a higher incidence of insomnia and abnormal dreams (Table 13). While the updated safety database contains more placebo-controlled and long-term experience, there remains limited long-term exposure at the highest doses and no long-term controlled studies.[75] [Emphasis added]

B. Key additional comments made by FDA reviewers regarding the NDA resubmission

The FDA clinical reviewer made the following additional key comments regarding the resubmitted NDA for droxidopa:

- In summary, the applicant submitted 4 studies (301, 302, 303 and 306) in the droxidopa application; two of these studies, 301 and 306B, met their primary endpoint. Although studies 301, 302 and 303 were enriched populations (e.g., enrolling responders), studies 302 and 303, both randomized withdrawal studies, failed to meet their respective primary endpoints, and 306A (not enriched, but with a primary endpoint measured at Week 8) met the criteria for futility. Of the two studies (301, 306B) that succeeded in meeting their amended primary endpoints, one site with unusually homogeneous positive results (507) contributed disproportionately to the positive result (301); the other study (306B), created after an unblinded interim analysis, met its amended primary endpoint with a statistically significant treatment effect at a single early time point. Additional issues affecting the interpretability of study 306B results include: the imbalance in premature discontinuations and missing data (more in the droxidopa-treated group); the small treatment effect in the face of larger intra-subject and inter-subject variability; lack of durability beyond the Week 1 time point; and the inconsistent OHQ, OHSA item-1 and standing [systolic blood pressure] curves between study 306A and 306B. **Collectively, these concerns undermine this reviewer's confidence in study 306B as a "strongly positive" trial supporting a benefit with droxidopa**.[76]

The FDA clinical reviewer made the following recommendation:

> **This reviewer recommends a Complete Response action for droxidopa in the treatment of symptomatic neurogenic orthostatic hypotension (NOH), because of inadequate evidence of effectiveness.**[77] [Emphasis added]

The FDA statistical reviewer made the following additional key comments regarding study 306B and the resubmitted NDA for droxidopa:

[75] *Ibid*. PDF page 156.
[76] *Ibid*. PDF page 157.
[77] *Ibid*. PDF page 155.

- Although statistically significant, **the treatment effect on OHSA Item 1 at Week 1 seemed small at the presence of intra-subject variability, which was 2.9** based on reviewer's calculation.[78] [Emphasis added]

- The treatment effect at later weeks in the study was not so consistent. The treatment effect on OHSA Item 1 almost completely diminished at Week 2 and was also less at Week 4 and Week 8. The treatment effect in standing [systolic blood pressure] did not sustain through the 8-week treatment period. This made it questionable whether droxidopa has any long term treatment effect.[79]

- **Droxidopa group had more dropouts during the titration phase. 20 droxidopa patients were excluded from the primary analysis compared with only 7 placebo patients.** Except for three untreated patients, the rest of these patients had missing OHSA Item 1 score at Week 1. Even if excluding 8 patients who enrolled earlier before the interim analysis, Study 306B still had 4 patients treated with placebo and 12 patients treated with droxidopa discontinued study prior to Week 1. The imbalance remained. **It is concerning to see such imbalance of dropouts between treatment groups, especially if the data were not missing at random. The treatment effect of OHSA Item 1 became -0.45 with 95% confidence interval (-1.2, 0.3) if imputing missing data by carrying forward baseline observation (BOCF).**[80] [Emphasis added]

The FDA statistical reviewer made the following conclusion:

> **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.**[81] [Emphasis added]

IV. Summary and conclusions

In summary, the data from the four pivotal randomized clinical trials summarized above clearly fail to provide sufficient evidence that droxidopa is effective for treating symptomatic NOH.

In 2012, following review of the original NDA submission, the FDA concluded, correctly, that droxidopa could not be approved based on the data from studies 301, 302, and 303 because there was a lack of evidence that the drug was effective for its proposed indication. The FDA required that the sponsor submit data from one additional randomized, well-controlled trial. The FDA emphasized in its complete response letter to the sponsor that this additional trial would need to demonstrate "strongly positive" results to obtain agency approval for the drug.

According to the FDA review, study 306B undoubtedly fell well short of providing the "strongly positive" results regarding effectiveness required for FDA approval. Even if the design and conduct of study 306B had been impeccable, the results would have failed to provide strongly

[78] *Ibid*. PDF page 237.
[79] *Ibid*. PDF page 237.
[80] *Ibid*. PDF page 237.
[81] *Ibid*. PDF page 238.

positive evidence of effectiveness. The overall difference on the final primary efficacy outcome measure, although statistically significant, was quite small — the difference between the droxidopa and placebo groups in the mean change from baseline to one week on the OHSA item 1 was only -0.94 on a 10-point scale in the context of a high intra-subject variability of 2.9 — and of questionable clinical significance. Moreover, the effect of droxidopa on the primary efficacy outcome, as well as blood pressure on standing, in study 306B was not durable beyond one week. Such a lack of durability for a drug intended for treatment of a chronic condition essentially renders the drug useless, even if it had significant effectiveness at one week.

But the design and conduct of study 306B was clearly far from being acceptable. First, the primary efficacy endpoint was changed once after a pre-specified interim analysis by the DMC resulted in a recommendation to terminate the study for reasons of futility with respect to the likelihood of finding a difference on the initially pre-specified primary efficacy outcome. Second, the sponsor rejected the DMC's recommendation, and the primary efficacy endpoint was changed a second time near the completion of the study. Third, at the time of the interim analysis, the DMC statistical team gained access to unblinded subject data for some subjects included in study 306B. Fourth, the study was stopped prematurely based on a new projected sample size calculation using the newly selected primary efficacy outcome measure. Fifth, there was a substantial imbalance in subject dropouts during the titration phase, with more subjects from the droxidopa group than from the placebo group being excluded from the primary analysis. These and other issues identified by the FDA reviewers undermine the validity and reliability of the results from study 306B. Therefore, the results from study 306B were not "strongly positive."

In conclusion, the sponsor has failed to demonstrate that droxidopa is effective and, thus, that the risks of the drug are outweighed by its benefits. Despite the vote of the CRDAC, the FDA is obligated to disapprove the drug based on the agency's own expert review of the evidence. Therefore, the only appropriate action for the FDA to now take is to follow the reasonable recommendation of its medical reviewer and issue a complete response letter for the resubmitted NDA for droxidopa. FDA approval of droxidopa based on the available data would essentially undermine the integrity and meaningfulness of FDA's standard for approving drugs and cause immeasurable harm to the agency's reputation.

Thank you for considering our comments on this very important matter.

Sincerely,

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