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Testimony Before the FDA's Endocrinologic and Metabolic Drugs Advisory Committee Regarding New Drug Application 022517 for NOCDURNA (desmopressin)

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I am Dr. Michael Carome, Director of Public Citizen's Health Research Group. Public Citizen and I have no financial conflicts of interest. Before joining Public Citizen, I was a practicing board-certified nephrologist with a scope of practice that included evaluating and managing patients with hyponatremia.

We strongly oppose Food and Drug Administration (FDA) approval of Nocdurna (desmopressin) — a drug already twice rejected by the FDA — for treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void because the drug:

(1) offers meager clinically meaningful benefit relative to placebo for the proposed indication; and
(2) causes severe, potentially life-threatening hyponatremia, a risk that far outweighs the drug's benefits.

We urge the committee to recommend that the FDA reaffirm its prior decision and not approve Nocdurna.

Efficacy Assessment: Meager Clinical Benefit

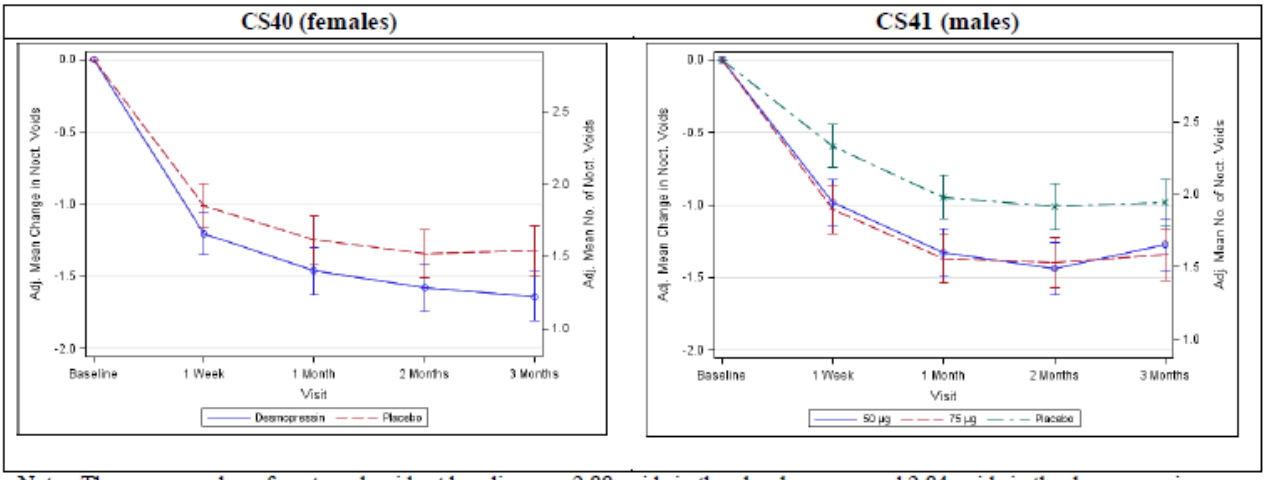
The sponsor's first new drug application (NDA) submission for Nocdurna included data from a single randomized, placebo-controlled pivotal trial (CS29) comparing four different doses of Nocdurna (10, 25, 50, and 100 micrograms [µg]) administered daily before bedtime for 28 days.[1] The trial had two co-primary endpoints: (1) change from baseline in mean number of nocturnal voids; and (2) proportion of subjects with a 33 percent reduction from baseline in the mean number of voids. A statistically significant difference favoring the Nocdurna-treated subjects compared to placebo-group subjects on both co-primary endpoints was seen only at the 100 µg dose, a dose with a high incidence of hyponatremia.[2]

The sponsor's second NDA submission included data from two additional randomized, placebo-controlled pivotal clinical trials (CS40 in women, comparing 25 µg of Nocdurna to placebo daily at bedtime over three months; and CS41 in men, comparing 50 µg and 75 µg to placebo daily at bedtime over three months).[3] These two trials used the same co-primary endpoints as CS29. While

[1] Food and Drug Administration. Briefing document for the Endocrinologic and Metabolic Drugs Advisory Committee meeting on January 12, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM429353.pdf. Accessed January 8, 2015. Pages 27-30, 41.
[2] *Ibid.* Page 41.
[3] *Ibid.* Pages 42-43, 47.

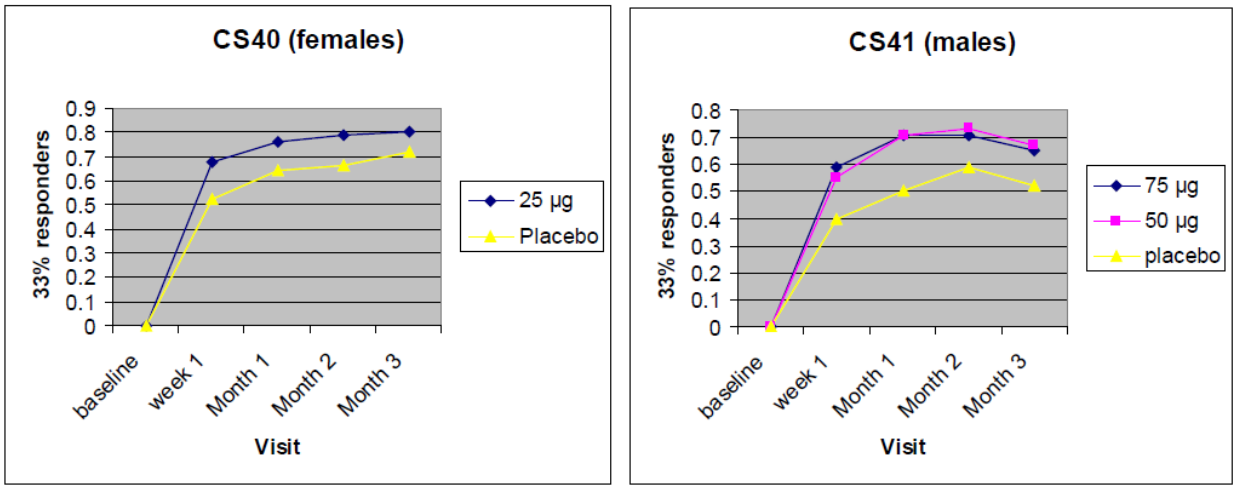
statistically significant differences favoring Nocdurna were seen for both co-primary endpoints in both trials, the differences were small (see Figures 1 and 2 below). For the change from baseline in mean number of nocturnal voids averaged over a three-month period, the difference versus placebo was -0.22 voids per night for women in CS40 and -0.41 and -0.37 for men at doses of 50 and 75 µg, respectively, in CS41.[4]

Figure 1: Adjusted Change From Baseline During Three Months of Treatment in Mean Number of Nocturnal Voids (Trials CS40 and CS41)[5]



Note: The mean number of nocturnal voids at baseline was 2.88 voids in the placebo group and 2.84 voids in the desmopressin group in CS40 [CS40, Table 3.4] and was 2.90 voids in the placebo group, 2.88 voids in the desmopressin 50 µg group, and 2.99 voids in the desmopressin 75 µg group in CS41 [CS41, Table 3.5]. Although treatment-by-visit interaction was not significant, the adjusted mean changes from baseline depicted in this figure are based on the model including the treatment-by-visit interaction, to demonstrate numerical changes of treatment contrasts in time.
Cross-reference: [CS40, Figure 6.1.1.1] and [CS41, Figure 6.1.1.1]

Figure 2: Proportion of 33% Responders by Visit (Trials CS40 and CS41)[6]



[4] *Ibid.* Page 51.
[5] *Ibid.* Page 52.
[6] *Ibid.* Page 55.

The FDA's Division of Metabolic and Endocrine Products (DMEP) concluded the following regarding the efficacy results from trials CS40 and CS41:[7]

> **[R]elative to placebo, the treatment effect size associated with Nocdurna in the currently studied patient population with nocturia was modest and of unclear benefit.** The 0.22 reduction of nocturnal voids relative to placebo observed in study CS40 in females amounts to an average reduction of 1 nocturnal void every 5 days. Similarly, the 0.4 placebo-subtracted reduction in voids seen in males in study CS41 is equivalent to reduction of 1 nocturnal void every 2-3 days. … [Emphasis added]
>
> The Nocdurna clinical program did not provide convincing evidence of clinical benefit beyond the above mentioned reduction in nocturnal voids.

Reviewers from the FDA's Division of Bone, Reproductive and Urologic Products who were consulted by DMEP also provided the following assessment of the efficacy data for Nocdurna:[8]

1. The demonstrated effect of NOCDURNA on the frequency of nocturia in patients with nocturnal polyuria is small when compared to placebo. **The clinical meaningfulness of this small effect is not interpretable in the absence of a validated measure of the clinical benefit of reduction of nocturia episodes**. [Emphasis added]
2. In the pivotal studies, homogenous urologic populations were not studied, making the efficacy study results difficult to interpret.

In seeking to have FDA reverse its decision not to approve Nocdurna, the sponsor emphasized data from the clinical trials demonstrating that Nocdurna caused improvements on quality-of-life measures and increased time of undisturbed sleep prior to first night time awakening. However, an FDA Study Endpoints Consult Review assessing the data on quality-of-life measures concluded: [9]

> [T]he clinical trial evidence submitted by the applicant is **inadequate to support labeling claims** on the basis of the [Nocturia Impact Diary] or [Nocturia Quality-of-Life questionnaire] because of the exploratory nature of the data. Therefore, **these clinical trial results do not meet standards for inclusion in labeling claims**. [Emphasis added]

Likewise, a reviewer with the FDA's Division of Psychiatry Products who was consulted by DMEP concluded the following regarding the sleep data: [10]

> It is important to note that **the sponsor's submission does not provide new clinical trial data.** Rather, the sponsor provides post-hoc analyses of existing trial data in the context of selected literature, ostensibly contributing additional "benefit" considerations to the benefit-risk evaluation. … [Emphasis added]

[7] *Ibid.* Page 72.
[8] *Ibid.* Page 97.
[9] *Ibid.* Page 85.
[10] *Ibid.* Pages 107-108.

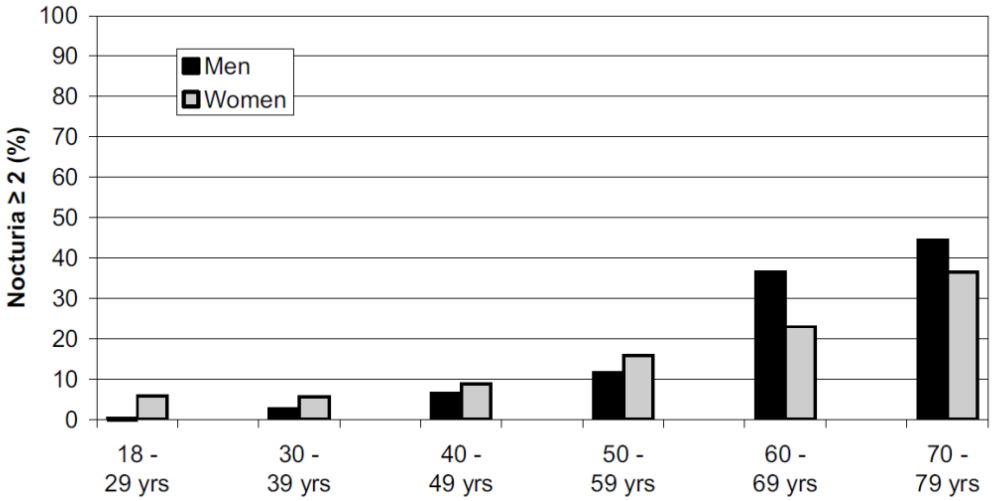
> Although there is some face validity to the sponsor's argument that a placebo-subtracted increase of 39-49 minutes in FUSP [first uninterrupted sleep period] may improve health-related quality of life, the means by which that conclusion is reached requires several inferential steps, each based on limited direct evidence. **The sponsor is making an argument based on a proxy in the absence of objective evidence.** The argument would be more compelling if the sponsor had polysomnographic data to support the claim that improvements in FUSP are related to increases in [slow wave sleep]; even in that case, there would still be an additional inferential leap required before one could conclude that Nocdurna improves health-related quality of life or reduces the risk of long-term consequences of chronic sleep disturbance. [Emphasis added]

Major Risk: Severe Hyponatremia

The major concerning risk of Nocdurna is hyponatremia. Desmopressin, given its mechanism of action in blocking water excretion by the kidneys, has long been known to cause acute hyponatremia. Acute severe hyponatremia is a medical emergency because it can cause cerebral edema, which can result in loss of consciousness, seizure, coma, respiratory arrest, and death. In addition, FDA reviewers noted that mild chronic hyponatremia may be associated with neurocognitive impairment, gait disturbances and predisposition to falls, osteoporosis and fractures in elderly patients.[11]

The majority of patients who would be candidates for Nocdurna under its proposed indication would already have one or more of the following factors predisposing to hyponatremia: advanced age, female gender, use of concomitant medications (e.g., thiazide and loop diuretics, nonsteroidal anti-inflammatory drugs [NSAIDs], anti-depressants), and specific disease states (e.g., renal impairment, congestive heart failure, nephrotic syndrome). Figure 3 below shows that nocturia is most prevalent in patients age 60 or older.

Figure 3: Prevalence of Nocturia by Age and Sex[12]



[11] *Ibid.* Page 6.
[12] *Ibid.* Page 5.

Combined data from the pivotal clinical trials of Nocdurna show a clear dose-related increase in the incidence of hyponatremia.[13] In CS40, three women (2 percent) developed moderate hyponatremia (serum sodium from 126 to 129 millimoles/liter[mmol/L]), and in CS41, six men (2 percent) developed severe hyponatremia (serum sodium ≤ 125 mmol/L; two on 50 µg and four on 75 µg).[14]

The sponsor proposes to mitigate the risk of hyponatremia with Nocdurna by including in the product labeling a description of a recommended sodium monitoring plan that includes:[15]

- Stipulating that all patients should have a baseline serum sodium level ≥ 135 mmol/L prior to initiation of Nocdurna.
- For all patients age 65 or older and patients with an increased risk of hyponatremia due to concomitant medications, checking a serum sodium during the first week (days 4 to 8) of Nocdurna and again after one month of treatment.

Such monitoring is not sufficient to mitigate the risk of hyponatremia because the absence of hyponatremia during the initial month of treatment fails to guarantee that patients will not develop hyponatremia during later chronic use. Many patients without hyponatremia during the first month of Nocdurna use will develop any number of factors predisposing to hyponatremia at a later time — such as renal impairment, heart failure, or new concomitant use of prescription and over-the counter NSAIDs or other drugs — which could lead to acute severe hyponatremia when combined with long-term Nocdurna use. Indeed, during one clinical trial, a 78-year old subject developed severe hyponatremia after contracting a pulmonary infection on day 327 of Nocdurna use at a dose of only 10 µg.[16]

The FDA also correctly noted that:[17]

> [A]lthough the risk of severe hyponatremia has been reduced considerably once the Nocdurna doses have been reduced in both males and females[,] there is still **a persistent risk for hyponatremia which may become more apparent if the drug is used in a larger and more diverse population** with additional comorbidities and risk factors under clinical practice conditions that differ considerably from the relatively controlled environment of a clinical trial. [Emphasis added]

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[13] *Ibid.* Page 66.
[14] *Ibid.* Pages 66-67.
[15] Ferring Pharmaceuticals. NOCDURNA, Desmopressin orally disintegrating tablet for the treatment of nocturia due to nocturnal polyuria in adults: Briefing document for Endocrinologic and Metabolic Drugs Advisory Committee. January 12, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM429354.pdf. Accessed January 8, 2015. Page 206.
[16] Food and Drug Administration. Briefing document for the Endocrinologic and Metabolic Drugs Advisory Committee meeting on January 12, 2015. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM429353.pdf. Accessed January 8, 2015. Page 71.
[17] *Ibid.* Pages 72-73.

Furthermore, in the real-world setting, there is certain to be off-label use in patients more susceptible to developing hyponatremia, failures by health care providers and patients to comply with the recommended initial monitoring scheme, and use of doses higher than those recommended in the drug label. All of these factors undoubtedly will lead to cases of severe hyponatremia in patients using Nocdurna.

Conclusion

Given the meager clinical benefit of Nocdurna seen in the pivotal clinical trials, no risk mitigation strategy will reduce the risk of severe hyponatremia sufficient to make the case that the benefits outweigh the risks of this drug. In the interest of protecting public health, we urge the committee to recommend that the FDA reaffirm its prior decision and not approve Nocdurna.