

**Summary Minutes of the Endocrinologic and Metabolic Drugs
Advisory Committee Meeting
January 12, 2015**

The following is the final report of the Endocrinologic and Metabolic Drugs Advisory Committee meeting held on January 12, 2015. A verbatim transcript will be available in approximately six weeks, sent to the Division of Metabolism and Endocrinology Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm426278.htm>.

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on January 12, 2015, at the College Park Marriott Hotel & Conference Center, Potomac Ballroom, 3501 University Blvd. East, Hyattsville, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Ferring Pharmaceuticals, Inc. The meeting was called to order by Robert J. Smith, MD (Chairperson). The conflict of interest statement was read into the record by Stephanie L. Begansky, PharmD (Acting Designated Federal Officer). There were approximately 115 people in attendance. There were 7 Open Public Hearing (OPH) speaker presentations.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 022517, proposed trade name NOCDURNA (established name: desmopressin), orally disintegrating sublingual tablets submitted by Ferring Pharmaceuticals, Inc. The proposed indication is treatment of nocturia due to nocturnal polyuria in adults who awaken two or more times each night to void.

Attendance:

EMDAC Members Present (Voting): Brendan M. Everett, MD, MPH; Diana Hallare, MPH (Consumer Representative); Susan R. Heckbert, MD, PhD; William R. Hiatt, MD, FACP, FAHA; James D. Neaton, PhD; Robert J. Smith, MD (Chairperson); Peter W.F. Wilson, MD

EMDAC Member Present (Non-Voting): Mads F. Rasmussen, MD, PhD (Industry Representative)

EMDAC Members Not Present (Voting): David W. Cooke, MD; Ed J. Hendricks, MD; Charles A. Stanley, MD

Temporary Members (Voting): Diane M. Biskobing, MD; Daniel Budnitz, MD, MPH; Toby C. Chai, MD; Jonathan Emens, MD; Stuart S. Howards, MD; John Lavelle, MD; Kevin D. McBryde, MD; Martha Nason, PhD; Shirley Miller (Patient Representative); Christian Pavlovich, MD

FDA Participants (Non-Voting): Jean-Marc Guettier, MD; Mark Hirsch, MD; William Lubas, MD, PhD; Roger Wiederhorn, MD

Open Public Hearing Speakers: Roger Beyer, MD, CPI; Michael A. Carome, MD (Health Research Group, Public Citizen); Steven G. Gregg, PhD (National Association For Continence); Walt Hennessee; Monica Liebert, PhD (Simon Foundation for Continence); Nancy Mueller; Allen Wales

The agenda was as follows:

Call to Order and Introduction of Committee	Robert J. Smith, MD Chairperson, EMDAC
Conflict of Interest Statement	Stephanie L. Begansky, PharmD Acting Designated Federal Officer, EMDAC
FDA Introductory Remarks	Jean-Marc Guettier, MD Director, Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation (ODE) II Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATION	
Nocturia Overview	Jerry G. Blaivas, MD, FACS Clinical Professor of Urology Weill Cornell Medical College Cornell University Adjunct Professor of Urology SUNY Downstate Medical School Chairman The Institute for Bladder and Prostate Research
Clarifying Questions	
APPLICANT PRESENTATIONS	
Introduction	Ferring Pharmaceuticals, Inc. Brenda Marzi, PharmD Vice President US Regulatory Affairs Ferring Pharmaceuticals, Inc.
Nocturia due to Nocturnal Polyuria	Eric Rovner, MD Professor of Urology Medical University of South Carolina

APPLICANT PRESENTATIONS (CONT.)

Efficacy Results	Jens Peter Norgaard, MD, DMSc Professor of Urology Global Scientific Affairs Ferring Pharmaceuticals
Additional Clinical Relevance/Sleep	Donald Bliwise, PhD Professor of Neurology Emory University School of Medicine
Patient Reported Outcomes/Quality of Life	Ray Rosen, PhD Chief Scientist New England Research Institutes, Inc.
Safety	Vladimir Yankov, MD Vice President Reproductive Health & Urology Ferring Pharmaceuticals
Hyponatremia	Joseph Verbalis, MD Professor and Chief Division of Endocrinology and Metabolism Georgetown University
Conclusion	Eric Rovner, MD
Clarifying Questions	

BREAK

FDA PRESENTATIONS

Clinical Review of Efficacy	William Lubas, MD, PhD Medical Officer DMEP, ODE II, OND, CDER, FDA
Urologic Considerations for the Evaluation and Treatment of Nocturia in Patients with Nocturnal Polyuria	Roger Wiederhorn, MD Medical Officer Division of Bone, Reproductive and Urologic Products (DBRUP) Office of Drug Evaluation III (ODE III) OND, CDER, FDA
Clinical Review of Safety	William Lubas, MD, PhD
Clarifying Questions	

LUNCH

Open Public Hearing

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Comment on whether the applicant has adequately identified and evaluated the intended population (adults with nocturia due to nocturnal polyuria) for the proposed indication. Explain your answer.

Committee Discussion: A number of committee members expressed that this was an appropriate target population because a high percentage of patients in the pivotal trials met the definition of nocturnal polyuria. The panelists generally accepted that nocturia is associated with multiple and heterogeneous etiologies. There was some discomfort expressed amongst the committee regarding the use of a targeted therapy in a disease with diverse etiologies. Overall, the committee voiced that there were only a small number of subjects enrolled in the studies relative to the size of the population for whom this drug would be used if it were approved. One committee member commented on the large proportion of screening failures apparently due to the extensive exclusion criteria. The committee also noted the large impact of lifestyle/behavioral change on the endpoint variable (i.e., number of nocturnal voids). The committee further stated that the lifestyle/behavioral change effect on the population enrolled was not well understood and had not been well characterized. Finally the committee noted that the large placebo effect suggested that an inadequate run-in period had been used in the pivotal trials. It was noted that the large placebo effect was likely the result of concurrently starting study drug while implementing one or more lifestyle/behavioral intervention(s). Please see the transcript for details of the committee discussion.

2. **DISCUSSION:** Discuss the observed placebo-adjusted effect size at NOCDURNA doses of 25 mcg in women and 50 mcg in men and comment on whether you believe an effect of this size represents a meaningful clinical benefit. In your answer and if appropriate, identify findings in the briefing document and presentations that substantiate your position.

Committee Discussion: There was general agreement expressed by the committee that differences in responses for mean number of nocturnal voids between placebo and Nocdurna were real and statistically significant. However, the majority of the committee members stated that the difference between active treatment and placebo was small for mean number of nocturnal voids and lacked support for clinical meaningfulness from validated patient-reported outcome (PRO) measures, acceptable sleep disturbance or wakefulness-related parameters, or actual rates of falls. Some members commented that the correlation between the changes in number of nocturnal voids and clinical benefit was still unknown. One member commented that a final decision that Nocdurna was associated with clinical benefit

would require a “leap of faith” at this time. Therefore, the current efficacy results were viewed as only suggestive of a clinical benefit. The impact of the large placebo effect on potentially masking an important actual treatment effect was discussed extensively. Again use of a run-in period to eliminate patients who improve on things other than treatment (i.e., life-style and behavioral changes, regression to the mean) was suggested.

Committee members expressed divergent opinions and many struggled with regard to interpreting the clinical meaningfulness of the demonstrated impact of Nocturna over placebo. Some committee members stated that from a patient perspective, any increase in sleep or decrease in number of awakenings to urinate, could be construed as clinically relevant. While other committee members were reluctant to accept this and commented that larger decreases in number of voids in a more severely affected population might be needed to demonstrate clinical relevance. In general, committee members stated that more studies should be required. Some members recommended use of a more fully developed and validated PRO instrument to capture the impact of reduction in nighttime void on an outcome important to patients. Some members recommended that subsequent studies include more robust measures of sleep disturbance. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** In light of the overlap between the population at risk for hyponatremia and the population at risk for nocturia, discuss your level of concern with regard to the risk of acute and chronic hyponatremia in clinical practice. In your discussion please include:
 - a. Whether the CS-40 and CS-41 trials can reliably inform the risk in patients who are likely to be prescribed NOCDURNA, if approved.
 - b. Whether this risk can be adequately mitigated through proper patient selection, serum sodium monitoring and communications to patients and prescribers through labeling.
 - c. Additional suggestions, if appropriate.

Committee Discussion: A number of committee members expressed that the study data itself provides some reassurance that the risk of severe hyponatremia was not high and could be monitored. Members were in agreement that the additional proposed monitoring strategies proposed for product initiation were sensible and could further mitigate, though not completely eliminate, this risk. A few members were concerned that the proposed strategies had not been tested prospectively and were “fit” to the data. Many committee members stated that they had trouble translating the study results to the care setting because of generalizability issues, relatively limited long-term controlled safety data in at risk patients and uncertainty with regard to predicting compliance with implementation of the proposed the monitoring strategy in practice.

One obstacle noted was whether the proposed labeling would be effective at excluding patients that may be subject to a higher risk of hyponatremia including those with concomitant diseases, such as congestive heart failure or liver disease, or those taking concomitant drugs or having intercurrent illness. In addition members questioned whether labeling would be adequate to mitigate risk across the full spectrum of patients and uses,

especially patients who may not fully understand how to manage their nocturia during an intercurrent illness episode (e.g., pneumonia), and the elderly. One member questioned whether labeling would suffice for risk mitigation.

Additionally, the overall understanding of the adverse health effects of chronic mild hyponatremia was felt to be limited and was expressed as another obstacle. For example, one member expressed concerns that mild hyponatremia may itself be associated with an increased risk of all-cause mortality. Others commented that the risks of hyponatremia may be worse in patients over 65 years of age. The panel stated that hyponatremia was a concern for this drug proposed for long-term use in patients who will use the drug as they age. The committee stated that the risk of hyponatremia in other populations at high risk such as those with low glomerular filtration rate (GFR) or kidney disease, needs to be addressed. Please see the transcript for details of the committee discussion.

4. **VOTE:** Does the demonstrated benefit of NOCDURNA outweigh the risks and support approval for nocturia due to nocturnal polyuria?
 - a. Provide a rationale for your vote. If you believe additional studies are needed, explain whether these studies are needed pre-approval or whether they can be conducted post-approval. Provide specific recommendations on ways to identify patients who may be candidates for this drug in clinical practice or in additional trials.

Vote: Yes = 5 No = 10 Abstain = 2

Committee Discussion: *The majority of the committee voted “No” and most committee members who voted “No” along with the two members that abstained from the vote, stated that while both co-primary endpoints achieved statistically significant differences from placebo in the two Phase III trials, the clinical benefit of the observed treatment effect remained unclear, particularly given the large placebo effect seen in the trials. One committee member stated that the sponsor is heading in the right direction exploring the time to first awakening (time to first nocturnal void), but more objective clinical efficacy data, such as data from a validated PRO instrument and/or polysomnography (e.g., slow wave sleep), is needed in pre-approval studies. Others also stated that pre-approval trials linking the currently demonstrated effect on nocturnal voids to a clinically meaningful outcome should be completed. The committee members that voted “Yes” expressed that while the benefit was not that impressive over placebo, it was in fact present and with proper labeling the benefit outweighs the risks, in their opinions. Additionally, some committee members expressed that the risk of hyponatremia was still a concern. One member stated that a postmarketing risk mitigation program may be an appropriate way to address the risk of hyponatremia. One member stated that additional prospective studies may be needed to validate the proposed serum sodium monitoring strategy. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:04 p.m.