

**Food and Drug Administration
Center for Drug Evaluation and Research**

**Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting
October 19, 2016**

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503),
10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committee discussed the safety and efficacy of new drug application (NDA) 201656
(desmopressin) 0.75 mcg/0.1 mL and 1.5 mcg/0.1 mL nasal spray, submitted by Serenity
Pharmaceuticals, LLC, for the proposed treatment of adult onset nocturia.

These summary minutes for the October 19, 2016, meeting of the Bone, Reproductive and Urologic
Drugs Advisory Committee of the Food and Drug Administration were approved on December 21,
2016.

I certify that I attended the October 19, 2016, meeting of the Bone, Reproductive and Urologic Drugs
Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what
transpired.

_____/S/
Kalyani Bhatt, BS, MS
Designated Federal Officer
Bone, Reproductive and Urologic Drugs
Advisory Committee (BRUDAC)

_____/S/
Vivian Lewis, MD
Chairperson, BRUDAC

**Summary Minutes of the
Bone, Reproductive and Urologic Drugs Advisory Committee Meeting**
October 19, 2016

The following is the final report of the Bone, Reproductive Urologic Drugs Advisory Committee held on October 19, 2016. A verbatim transcript will be available in approximately six weeks, sent to the Division of Bone, Reproductive and Urologic Products and posted on the FDA website at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm507639.htm>

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

The Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 19, 2016 from 8:15 am to 5:00 pm at the FDA White Oak Campus, Building 31, the Great Room (Rm. 1503) White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided background materials from the FDA and from Serenity Pharmaceuticals, LLC. The meeting was called to order by Vivian Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately 150 persons in attendance.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 201656 (desmopressin) 0.75 mcg and 1.5 mcg nasal spray, submitted by Serenity Pharmaceuticals, LLC, for the proposed treatment of nocturia in adults who awaken two or more times per night to void.

Attendance:

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Voting): Douglas C. Bauer, MD; Matthew T. Drake, MD, PhD; Stuart S. Howards, MD; Vivian Lewis, MD (Chairperson); Sarah E. Sorscher, JD, MPH (Consumer Representative)

Bone, Reproductive and Urologic Drugs Advisory Committee Members Not Present (Voting): Ann E. Burke, MD, MPH; Toby Chai, MD; Kathryn M. Curtis, PhD; Roger T. Dmochowski, MD; Amy H. Herring, ScD

Bone, Reproductive and Urologic Drugs Advisory Committee Members Present (Non-Voting): Gerard G. Nahum, MD, FACOG (Industry Representative)

Temporary Members (Voting): G Caleb Alexander, MD, MS; Barbara Berney (Patient Representative); David Cella, PhD; Michael Chancellor, MD; Daniel Coyne, MD; Brian Erstad, Pharm D; Walid Gellad, MD, MPH; Philip Hanno, MD, MPH; Theodore Johnson, MD, MPH; Kevin McBryde, MD; James D. Neaton, PhD; Christian Pavlovich, MD; Ashley Wilder Smith, PhD, MPH; Robert J. Smith, MD

FDA Participants (Non-Voting):

Hylton Joffe, MD, MMSc; Suresh Kaul, MD; Olivia Easley, MD; Martin Kaufman, DPM, MBA; Jia Guo, PhD; Sarrit Kovacs, PhD

Designated Federal Officer: Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Stephanie Fox-Rawlings, PhD (National Center for Health Research); Howard Lavine (University of Minnesota Law School Center for the Study of Political Psychology); Laurence Z. Rubenstein, MD, MPH, FACP (University of Oklahoma College of Medicine); Diane K. Newman, DNP FAAN BCB-PMD (University of Pennsylvania Penn Center for Continence and Public Health); Eboni Green RN, PhD (Caregiver Support Services); Benjamin M. Brucker, MD (New York University Langone Medical Center)

The agenda was as follows:

Call to Order and Introduction of Committee

Vivian Lewis, MD
Chairperson, BRUDAC

Conflict of Interest Statement

Kalyani Bhatt, BS, MS
Designated Federal Officer, BRUDAC

FDA Opening Remarks

Hylton V. Joffe, MD, MMSc
Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Office of Drug Evaluation III (ODE III)
Office of New Drugs (OND), CDER, FDA

APPLICANT PRESENTATIONS

Serenity Pharmaceuticals, LLC

Introductory Remarks

Seymour Fein, MD
Chief Medical Officer
Serenity Pharmaceuticals, LLC

Nocturia - An Unmet Medical Need

Alan J. Wein, MD, PhD (Hon)
Founder Professor and Chair of Urology
Perelman School of Medicine
University of Pennsylvania

Clinical Pharmacology and Efficacy

Seymour Fein, MD

Patient Treatment Benefit Patient Reported-Outcomes

Kristin M. Khalaf, PharmD, PhD
Assistant Director
Global Health Economics and Outcomes Research
Xcenda, LLC

Integrated Summary of Safety

Seymour Fein, MD

Benefit-Risk Assessment/Risk Mitigation Strategy

Annette Stemhagen, DrPH, FISPE
Senior Vice President
Safety, Epidemiology, Registries and Risk Management – UBC

Concluding Remarks

Steven Kaplan, MD
Professor of Urology
Icahn School of Medicine at Mount Sinai

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Efficacy

Olivia Easley, MD
Medical Officer
DBRUP, ODE III, OND, CDER, FDA

An Exploratory Analysis of Clinical
Meaningfulness

Jia Guo, PhD
Biostatistician
Division of Biometrics III
Office of Biostatistics, OND, CDER, FDA

Impact of Nighttime Urination (INTU)
Instrument

Sarrit Kovacs, PhD
Reviewer
Clinical Outcome Assessments (COA) Staff OND,
CDER, FDA

Efficacy Summary

Olivia Easley, MD
Medical Officer
DBRUP, ODE III, OND, CDER, FDA

Clinical Review of Safety

Martin Kaufman, DPM, MBA
Clinical Analyst
DBRUP, ODE III, OND, CDER, FDA

Clarifying Questions to FDA

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions to Applicant or FDA

BREAK

Questions to the Committee/Committee Discussion

ADJOURN

Questions to the Committee:

1. **DISCUSSION:** The Applicant's trials limited enrollment to adults at least 50 years of age, had numerous exclusion criteria, and had no restrictions on fluid intake.

Discuss whether the Applicant studied desmopressin in the appropriate patient population.

Committee Discussion: *Most advisory committee members did not express concerns with the age restriction or the absence of restriction on fluid intake. One member raised concerns about some causes of nocturia being different in a younger population and the lack of efficacy and safety data in those settings, such as nocturia related to pregnancy. Another advisory committee member would have preferred greater enrollment of the very elderly (>85 years of age) in the trials. A majority of the committee members expressed concern that the numerous exclusion criteria in the clinical trials limit the generalizability of the data. Members noted that, if approved, use of the drug is likely to occur in patients who have nocturia attributable to multiple causes and who may be taking many of the medications that were excluded in the trials. One member observed that the racial demographics of the study population did not reflect the affected population, as African Americans are disproportionately affected by nocturia. Please see the transcript for details of the committee's discussion.*

2. **DISCUSSION:** Discuss the clinical significance of the observed treatment effects of desmopressin on nocturia compared to placebo.

Committee Discussion: *Most of the committee members agreed that the SER120 1.5 mcg dose produced a clinically meaningful, albeit modest, effect. They noted the 18-19% absolute difference between the SER120 1.5 mcg and placebo groups in the percentage of patients with at least a 50% reduction in nightly nocturia episodes. Some members also noted the effects of SER120 1.5 mcg on some of the prespecified secondary efficacy endpoints, such as percentage of nights with one or less episodes of nocturia. Some members stated that the Impact of Nighttime Urination (INTU) mean change scores did not show a meaningful separation between the SER120 1.5 mcg and placebo groups. Most of the members stated that the 0.75 mg dose did not produce a meaningful effect. Please see the transcript for details of the committee's discussion.*

3. **DISCUSSION:** Discuss whether the safety of desmopressin has been adequately characterized, and whether additional safety data are needed.

Committee Discussion: *There was general agreement that safety in the population studied had been adequately characterized although some advisory committee members stated that there were insufficient safety data beyond one year of use and that the safety database was too small to observe rare events. One member had concerns about the timing of the serum sodium testing and whether the protocol used measurements that were too late in the day to capture the nadir sodium concentration following the evening dose of study medication. Some committee members raised concerns that, if approved, the drug will likely be prescribed to patients who would have been excluded from the clinical trials (e.g., nursing home patients and those at increased risk for hyponatremia) and that monitoring of serum sodium will not be as frequent with real-world use. Some committee members expressed concern with the numerical excess of deaths observed in the SER120 dose groups. Please see the transcript for details of the committee's discussion.*

4. **DISCUSSION:** Nocturia is a symptom that can be caused by many conditions, some of which may co-exist in the same patient.

Discuss whether the Applicant's proposed broad indication for the treatment of nocturia that does not specify the underlying etiology is clinically appropriate. If it is, discuss the adequacy of the Applicant's data to support this proposed indication, or whether additional data are necessary. If additional data are necessary, discuss what data would be needed to support the broad indication.

Committee Discussion: *There was general consensus that the broad indication of nocturia is not supported by the clinical trial population in which the drug was tested. There were also concerns that the drug would be used to treat the symptom of nocturia without patients undergoing diagnosis and treatment of the underlying cause(s). The majority of the panel members recommended "nocturnal polyuria" as the indication. However, one member acknowledged that the definition of nocturnal polyuria (currently defined as producing more than 33% of total 24-hour urine volume at night) may change in the future.*

Some members were interested in a study limited to patients with nocturnal polyuria, because this population was a subgroup of the randomized patients in the clinical trials. One member recommended studying a larger number of African American patients to determine if there are additional concerns in that group.

Please see the transcript for details of the committee's discussion.

5. **VOTE:** Is there sufficient evidence to conclude that at least one of the desmopressin doses is effective?

Provide rationale for your answer. If you voted "Yes", specifically comment on which dose(s) are effective and whether the data support the proposed regimen of starting with 0.75 mcg nightly then titrating to 1.5 mcg nightly, if needed, after 2-4 weeks.

Vote: Yes: 17 No: 1 Abstain: 0 No-Voting: 1

Committee Discussion: *One committee member was not present to vote as noted for the record. Seventeen of the eighteen voting committee members agreed that there is sufficient evidence that the SER120 1.5 mcg dose is effective. Most agreed that there was insufficient evidence to show that the SER120 0.75 mcg dose is effective, and did not endorse the proposed regimen of titrating the dose upward from 0.75 mcg. Some members liked the option of having the 0.75 mcg dose available because it appears to have a lower risk of hyponatremia, although they acknowledged the efficacy data did not clearly support this approach. The one committee member who voted "No" to this question explained that she did not believe the evidence supported a clinically meaningful effect of either SER120 dose in treating the broad indication of nocturia. Please see the transcript for details of the committee's discussion.*

6. **VOTE:** Do the benefits of desmopressin outweigh the risks and support approval?

Provide rationale for your answer. If you voted “Yes,” specify the indication that is supported by your benefit/risk assessment. If you voted “No,” include recommendations for additional data that might support a favorable benefit/risk assessment.

Vote: **Yes: 14** **No: 4** **Abstain: 0** **No-Voting: 1**

Committee Discussion: *One committee member was not present to vote as noted for the record. Fourteen of the eighteen voting committee members agreed that the benefits of desmopressin outweigh the risks and supported approval. Thirteen of the 14 members who voted “Yes” opposed a general indication of nocturia and recommended instead an indication for nocturnal polyuria. Other comments included that the label should reflect the trials’ exclusion criteria, that the product should not be recommended in institutionalized patients and that use should be carefully monitored in patients older than 65 years of age.*

Those who voted “No” were concerned that the benefits were modest compared to the risks and that the product may be used inappropriately in clinical settings (e.g., in the very elderly patients, without adequate monitoring for hyponatremia, or by practitioners who do not understand the seriousness of hyponatremia or the underlying conditions that predispose to nocturia). Another concern was that the trials did not limit enrollment only to patients with nocturnal polyuria.

Some members recommended additional strategies to mitigate the risk of hyponatremia, such as a Boxed Warning and Risk Evaluation and Mitigation Strategies.

Please see the transcript for details of the committee’s discussion.

The meeting was adjourned at approximately 4:30 p.m.