CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201656Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA #	NDA 201656
Applicant Name	Serenity Pharmaceuticals, LLC
Date of Submission	February 4, 2016
PDUFA Goal Date	March 4, 2016
Proprietary Name / Established (USAN) Name	Noctiva (desmopressin acetate) nasal spray
Dosage Forms / Strength	0.83 mcg desmopressin acetate per 0.1 mL spray 1.66 mcg desmopressin acetate per 0.1 mL spray
Proposed Indication(s)	Treatment of nocturia in adults who awaken at least two times per night to urinate
Action	Approval, but for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to urinate

Material Reviewed/Consulted Action Package, including:	**Names of discipline reviewers**
Cross-Discipline Team Leader	Suresh Kaul, M.D., M.P.H.
Medical Officer Review	Olivia Easley, M.D. and Martin Kaufman, D.P.M., M.B.A.
Pharmacology Toxicology Review	Deepa Rao, D.V.M., Ph.D., D.A.B.T., D.A.C.V.P., Mukesh Summan, Ph.D., D.A.B.T., and Abigail Jacobs, Ph.D.
Office of Pharmaceutical Quality	Mark Seggel, Ph.D., Benjamin Stevens, Ph.D., M.P.H., Donna Christner, Ph.D., Hong Cai, Ph.D., Moo-Jhong Rhee, Ph.D., Li-Shan Hsieh, Ph.D., Nallaperumal Chidambaram, Ph.D., Juandria Williams, Ph.D., Brian Ryan, John Arigo, Ph.D., Yarery Smith, Ph.D., Anjanette Smith, Michael Hadwiger, and David Keire
Clinical Pharmacology Review	Jihong Shon, M.D., Ph.D., Luning (Ada) Zhuang, Ph.D., Doanh Tran, Ph.D., Jeffry Florian, Ph.D., and Capt. E. Dennis Bashaw, Pharm.D.
Clinical Outcome Assessments Staff	Sarrit Kovacs, Ph.D., Selena Daniels, Pharm.D., M.S., and Elektra Papadopoulos, M.D., M.P.H.
Center for Devices and Radiological Health Review	Kathleen Fitzgerald, Alan Stevens, Christopher Brown, LT Viky Verna, Sarah Mollo, and Keisha Findley
Biostatistics	Jia Guo, Ph.D. and Mahboob Sobhan, Ph.D.
Division of Medication Error Prevention and Analysis	Denise Baugh, Pharm.D., B.C.P.S., Lolita White, Pharm.D., QuynhNhu Nguyen, M.S., Walter Fava, R.Ph., M.S.Ed., Danielle Harris, Pharm.D., B.C.P.S., Irene Chan, Pharm.D., B.C.P.S., and Todd Bridges, R.Ph.
Division of Risk Management	Somya Dunn, M.D., Leah Hart, Pharm.D., and Jamie Wilkins Parker, Pharm.D.
Division of Medical Policy Programs	Karen Dowdy, R.N., B.S.N., Marcia Williams, Ph.D., and LaShawn Griffiths, M.S.H.S.-P.H., B.S.N., R.N.
Office of Prescription Drug Promotion	Jina Kwak, Pharm.D.
Office of Scientific Investigations	Roy Blay, Ph.D., Janice Pohlman, M.D., M.P.H., and Kassa Ayalew, M.D., M.P.H.

Signatory Authority Review

1. Introduction

Serenity Pharmaceuticals, LLC submitted this New Drug Application (NDA) for SER120, a desmopressin acetate nasal spray (tradename Noctiva) proposed for the treatment of nocturia in adults who awaken at least twice per night to urinate. Currently, there are no drugs that are FDA-approved for the treatment of nocturia.

The Applicant is seeking approval through the 505(b)(2) pathway, relying, in part, on FDA's finding for DDAVP nasal spray (an FDA-approved desmopressin indicated for the treatment of central diabetes insipidus) and on published literature to abbreviate aspects of the nonclinical pharmacology/toxicology and clinical pharmacology programs.

This document serves as FDA's decisional memorandum on the application.

2. Background

Nocturia, which is defined as wakening at night to urinate, is a symptom that can be caused by various underlying conditions, some of which may co-exist in the same patient. Causes include edema-associated states (e.g., peripheral edema, congestive heart failure, and nephrotic syndrome), poorly controlled diabetes mellitus, diabetes insipidus, drugs (e.g., diuretics), excessive fluid intake, and nocturnal polyuria (overproduction of urine at night, which may be idiopathic or result from other conditions such as edema-associated states). Intrinsic bladder conditions can also cause nocturia, such as bladder outlet obstruction (e.g., benign prostatic hyperplasia), bladder detrusor overactivity (overactive bladder), and low bladder capacity.

Desmopressin is a 9-amino acid synthetic analog of the pituitary hormone, vasopressin that stimulates reabsorption of water in the kidneys, leading to more concentrated urine and less water excretion. The Applicant is seeking approval of its nasal formulation for a broad, general indication for nocturia, regardless of underlying etiology, and is proposing two doses, containing either 0.75 mcg or 1.5 mcg of desmopressin. The Applicant proposes starting with 0.75 mcg administered 30 minutes before bedtime, which can be increased, if needed and if tolerated, after 2-4 weeks, to 1.5 mcg nightly.

Noctiva is not approved in any country, although there are other desmopressin formulations approved outside the United States for the treatment of nocturia due to nocturnal polyuria. The FDA has approved other intranasal, oral and injectable desmopressin formulations for the treatment of central diabetes insipidus, primary nocturnal enuresis in children,[1] and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgery.[2] The

[1] In 2007, FDA removed the primary nocturnal enuresis indication for the intranasal desmopressin formulations because of the risk of severe hyponatremia and seizures.
[2] Desmopressin increases plasma concentrations of factor VIII activity in patients with hemophilia and von

proposed Noctiva doses are lower than the approved dose of DDAVP nasal spray (10 mcg desmopressin acetate per spray). However, it is unclear how the pharmacokinetic profiles of Noctiva and DDAVP compare because the Applicant did not conduct a comparative bioavailability study with the two products and Noctiva includes a novel excipient, cyclopentadecanolide (CPD), intended to increase its absorption.

Desmopressin products have traditionally been managed by the Division of Metabolism and Endocrinology Products, in light of that division's experience with desmopressin for the treatment of central diabetes insipidus. However, the Office of New Drugs determined in 2015 that drugs intended to treat nocturia should instead be managed by the Division of Bone, Reproductive and Urologic Products. Shortly thereafter, the Noctiva Investigational New Drug Application was transferred to our division. The Phase 3 trials were nearing completion at the time of transfer.

During our review of the NDA, we determined that the Applicant's proposed broad indication for the treatment of nocturia is not appropriate and requested efficacy and safety analyses in the subgroup of patients with nocturnal polyuria. We determined that these data constituted a Major Amendment, which extended the goal date by three months. The rationale for narrowing the indication is discussed further in the Recommendations section.

3. CMC/Device

The Office of Pharmaceutical Quality and the Center for Devices and Radiological Health recommend approval. See their reviews for details.

Noctiva is a drug-device combination product containing desmopressin formulated as a sterile oil-in-water emulsion in a metered-dose nasal spray. The device portion consists of a mechanical, multidose pump and a 3.5 mL amber glass bottle. The bottle contains enough drug for up to 30 doses in addition to the amount required for priming. Five priming actuations are needed prior to the first dose to ensure that the full 0.1 mL spray is delivered. Re-priming with two actuations is needed when the pump has not been used for more than three days.

Two strengths are proposed for marketing:

- 0.75 mcg desmopressin (equivalent to 0.83 mcg desmopressin acetate) per 0.1 mL spray
- 1.5 mcg desmopressin (equivalent to 1.5 mcg desmopressin acetate) per 0.1 mL spray.[3]

(b) (4) It is unknown whether two sprays of 0.75 mcg are bioequivalent to one spray of 1.5 mcg.

Ordinarily, strength in labeling would be reported for desmopressin, not desmopressin acetate, based on the USP Salt Nomenclature Policy. However, for Noctiva, we will be labeling the

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Willebrand's disease type I.

[3] For the remainder of this memorandum, I will refer to Noctiva doses based on desmopressin content (0.75 mcg, 1 mcg, and 1.5 mcg), not content of desmopressin acetate.

strength for desmopressin acetate because of medication error concerns with the overlap of the Noctiva 1.5 mcg dose with the 0.15 mg per spray dose of Stimate, another FDA-approved desmopressin product that is not indicated for the treatment of nocturia.

Noctiva's other ingredients include CPD (a permeation enhancer to enhance absorption of desmopressin through the nasal mucosa), water for injection, cottonseed oil, polysorbate 20, sorbitan monolaurate, and citrate buffer.

The Applicant has provided adequate data to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product, and has acceptable manufacturing processes. Drug Master Files and required manufacturing inspections were acceptable. Specification tests and acceptance criteria for the drug product were also acceptable, including emulsion particle size distribution, spray content uniformity, spray droplet size, and spray pattern. Leachables and extractables testing of the drug-contacting components of the nasal spray raised no concerns.

The Center for Devices and Radiological Health reviewed the device component, including design, functionality, biocompatibility, and materials, and found it to be acceptable.

Nasal sprays are not typically required to be sterile. Noctiva is manufactured under aseptic conditions but becomes non-sterile once in use. The device adequately prevents ingress of bacteria, which is important because the product does not contain a preservative and bacterial contamination could degrade desmopressin.

Before opening, Noctiva is stable for 24 months when stored upright at 2-8 degrees Celsius. The Chemistry reviewers concluded that the patient can store Noctiva upright at room temperature of 20-25 degrees Celsius for 60 days after opening.

The Chemistry reviewers agree with the Applicant's request for a categorical exclusion from environmental assessment, because the estimated introduction concentrations are below the 1 parts per billion threshold with no extraordinary circumstances.

Human Factors: The Division of Medication Error Prevention and Analysis (DMEPA) identified deficiencies with the Applicant's first Human Factors validation study, related to patients not performing critical tasks correctly when using the nasal spray (e.g., patients failing to prime upon initial use, patients priming with daily, repeated use, and patients having incorrect positioning of the head and device during dosing). The reviewers determined that revisions are needed to the Instructions for Use, and that these revisions should be assessed in a new Human Factors validation study to confirm that the changes have adequately addressed the critical task use errors without introducing new errors. The Applicant submitted a protocol for the new study during the review cycle and completed the study after incorporating DMEPA's recommendations in the protocol design. DMEPA reviewed the results from this second Human Factors study and determined that further changes to the Instructions for Use are needed, but that those revisions do not require additional Human Factors testing for support. These revisions have been adequately incorporated into labeling. See the DMEPA review for further details.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers recommend approval. See their reviews for details.

The Applicant abbreviated the nonclinical pharmacology/toxicology program by bridging to FDA's finding for DDAVP Nasal Spray, which also contains desmopressin acetate as its active ingredient. This 28-day bridging toxicology study in rats compared intranasal administration of SER120 and DDAVP. There were no remarkable findings. This study did not assess serum sodium concentrations; however, hyponatremia is a well-known risk with desmopressin products and was adequately assessed in the clinical trials.

In nonclinical toxicology studies, the Applicant adequately demonstrated the safety of three excipients – CPD, cottonseed oil and sorbitan monolaurate – that have not been used in any FDA-approved, nasally administered products. With regard to CPD, intranasal administration in a 39-week dog study caused minimal to slight hyperplasia of the nasal epithelium and mixed cell inflammation at doses over 5000-times the maximum recommended clinical dose, based on nasal surface area. The nonclinical pharmacology/toxicology reviewers concluded that these CPD-related findings were consistent with an irritant response. There were no CPD-related findings in the 26-week rat study at doses over 9000-times the maximum recommended clinical dose.

We granted the Applicant's request for a waiver from conducting carcinogenicity studies for CPD because of negative genotoxicity findings, limited systemic exposures, absence of accumulation and no concerning histopathology findings.

There have been no long-term studies in animals to assess the effects of Noctiva on carcinogenicity, mutagenicity or fertility. This will be noted in labeling.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers recommend approval. See their review for details.

The Applicant conducted a pharmacokinetic assessment of Noctiva in a subset of patients enrolled in Study DB3, which was one of the pivotal Phase 3 trials that compared Noctiva doses of 0.75 mcg, 1 mcg, and 1.5 mcg to placebo. Data from this subgroup showed:

- The median time to reach maximal plasma concentrations of desmopressin (Tmax) was 15 minutes for the 0.75 mcg dose and 45 minutes for the 1.5 mcg dose. This supports the Applicant's proposal to administer Noctiva about 30 minutes before bedtime.

- The mean half-life of desmopressin was 1.9 hours for the 0.75 mcg dose and 2.8 hours for the 1.5 mcg dose. For 85% of patients, desmopressin concentrations were below the lower limit of quantification within 6 hours post-dose.

- There were slightly greater than dose-proportional increases in desmopressin maximal plasma concentrations (Cmax) and area under the concentration-time curve (AUC) between the 0.75 mcg and 1.5 mg doses, but less than dose-proportional increases from 0.75 mcg to 1 mcg.

- There was large inter-individual variability in systemic exposure to desmopressin. For the 0.75 mcg dose, the coefficient of variation was 96% for Cmax and 146% for AUC. For the 1.5 mcg dose, the coefficient of variation was 76% for Cmax and 82% for AUC. Data were too limited to reliably assess exposure-response because of this large inter-individual variability, as well as small sample sizes in the pharmacokinetic subset, and undetectable desmopressin concentrations in some blood samples.

- Sex and age (<65 vs. ≥65 years old) did not have a significant impact on systemic exposures to desmopressin.

Desmopressin is a peptide so it may undergo degradation by non-specific proteases, although the extent to which this occurs in humans is unknown. Desmopressin is mainly excreted in the urine. In a pharmacokinetic study, eight patients with moderate or severe renal impairment (with an estimated glomerular filtration rate of 22-43 mL/min/1.73 m^2) had a three-fold increase in systemic exposure to desmopressin compared to a control group with normal or mildly impaired renal function (with an estimated glomerular filtration rate of 69-103 mL/min/1.73 m^2). The terminal half-life was also increased three-fold compared to the controls, although these data were more limited because of smaller sample sizes (n=3-4) and some undetectable desmopressin concentrations. Because of concerns that the increased exposures and half-life of desmopressin in patients with more advanced renal impairment could lead to severe hyponatremia, the Applicant proposes a contraindication for patients with a glomerular filtration rate below 50 mL/min/1.73 m^2, consistent with the existing contraindication for DDAVP nasal spray. This is reasonable. Of note, the Phase 3 trials excluded patients with an estimated glomerular filtration rate less than 50 mL/min/1.73 m^2.

Although the Applicant is seeking approval of both the 0.75 and 1.5 mcg doses, the Clinical Pharmacology reviewers recommend approving only the 1.5 mcg dose, noting that the 0.75 mcg dose was not superior to placebo on both co-primary efficacy endpoints in the Phase 3 trials. This issue is discussed further in the Efficacy and Benefit/Risk Assessment sections.

The Clinical Pharmacology reviewers recommend risk minimization strategies to reduce the risk of hyponatremia such as limiting fluid intake before and after dosing, monitoring of serum sodium starting within the first week of therapy (instead of after two weeks, as proposed by the Applicant), and more frequent sodium monitoring in the elderly. The recommendation for fluid restriction is based on the results from a Phase 1 study in water-loaded healthy volunteers given single intranasal desmopressin doses of 0.5, 1, and 2 mcg. In this study, the serum sodium nadir occurred 2-4 hours after dosing, with return to baseline sodium concentrations by six hours post-dose. These recommendations have been incorporated into labeling and are discussed further in the Benefit/Risk Assessment section.

The Clinical Pharmacology reviewers also recommend restricting use of Noctiva to adults at least 50 years of age because younger patients were not included in the pivotal Phase 3 trials. As noted in the Labeling section, there will be a Limitation of Use stating that Noctiva has not been studied in patients younger than 50 years of age.

The Applicant did not conduct drug-drug interaction studies with other nasally administered products. In the absence of these data, labeling will state that the use of Noctiva is not recommended in patients using other nasally administered products. Labeling will also include a Warning against use in patients with coexisting intranasal conditions (e.g., acute or chronic rhinitis, atrophy of the nasal mucosa) that could potentially increase absorption of desmopressin, because this could increase the risk for hyponatremia.

Lastly, if we approve both the 0.75 and 1.5 mcg doses, the Clinical Pharmacology team recommends that we require a postmarketing clinical pharmacology trial to compare the bioavailability of two sprays of 0.75 mcg to one spray of 1.5 mcg. Until those results are available, they recommend an explicit statement in labeling that two sprays of 0.75 mcg are not interchangeable with one spray of 1.5 mcg. The concern is that two separate sprays of 0.75 mcg could potentially increase desmopressin exposures beyond that achieved with one spray of 1.5 mcg, which could increase the risk for hyponatremia. This scenario could potentially occur when patients prescribed 0.75 mcg are uptitrated to 1.5 mcg, and consider using remaining drug from the 0.75 mcg bottle to deliver the 1.5 mcg dose. The hyponatremia risk may be increased (b) (4) Also, in a pharmacokinetic study, a 1 mcg dose given as one 0.5 mcg spray in each nostril led to about a two-fold higher systemic exposure compared to two sprays of 0.5 mcg in one nostril. This postmarketing requirement is reasonable.

6. Clinical Microbiology

See the Chemistry section of this memorandum.

7. Clinical/Statistical-Efficacy

In this section, I focus on the key design features and results of the two pivotal Phase 3 trials (DB3 and DB4). See the clinical efficacy review, the statistical review, and the Cross-Discipline Team Leader Memorandum for further details.

DB3 and DB4 were randomized, double-blind, placebo-controlled trials, conducted in the United States and Canada. Neither was conducted under Special Protocol Assessment. Both trials had a two-week screening period, a two-week double-blind, placebo lead-in period and a 12-week treatment period. DB3 randomized patients to Noctiva 0.75 mcg (n=188), 1.0 mcg (n=188), or 1.5 mcg (n=186) or placebo (n=188). DB4 randomized patients to Noctiva 0.75 mcg (n=270) or 1.5 mcg (n=266) or placebo (n=270). Study drugs were administered intranasally every night, approximately 30 minutes prior to bedtime. Neither trial restricted fluid intake. The Applicant is

not seeking approval for the 1.0 mcg dose. The 0.75 mcg and 1.5 mcg formulations used in the Phase 3 trials are identical to those proposed for marketing.

Both trials restricted enrollment to patients 50 years of age or older. During Phase 3 development, the FDA advised the Applicant to limit enrollment to this older age group to better assess the risk of hyponatremia, a known side effect of desmopressin that occurs more commonly in older patients.

Patients were required to have a history of at least two nocturia episodes per night for at least six months, which was confirmed using two 3-day voiding diaries during screening. Data from these six voiding diary days were averaged to calculate baseline parameters.

The trials had numerous exclusion criteria, including severe daytime lower urinary tract symptoms secondary to benign prostatic hyperplasia, overactive bladder or severe stress urinary incontinence, symptomatic congestive heart failure, nephrotic syndrome, history of urinary retention, hepatic or renal impairment, more than 2+ pretibial edema on physical exam, neurogenic detrusor overactivity, obstructive sleep apnea, prohibited medications (loop diuretics and systemic glucocorticoids), and several restricted medications (allowed only if on a stable dose for at least two months).

The trials defined a nocturic episode as a non-incontinent urinary void during the normal hours of sleep following an initial period of sleep and, thereafter, preceded and followed by sleep or an attempt to sleep. During the treatment period, patients completed three-day voiding diaries weekly for the first two weeks then every other week until the end of the trial.

Both trials had the same co-primary efficacy endpoints:

- Change from screening in the mean number of nocturia episodes per night
- Percentage of patients achieving at least a 50% reduction from screening in the mean number of nocturia episodes per night

Secondary efficacy endpoints included the following, shown in order of hierarchical testing:

- Change from screening in the Overall Impact Score of the Impact of Nighttime Urination (INTU) questionnaire (DB4 only)
- Change from screening in the time from going to sleep to first nocturic void
- Change from screening in the percentage of nights with no nocturic voids
- Change from screening in the percentage of nights with at most one nocturic void
- Change from screening in nocturic urine volume

In DB4, the first ranked secondary endpoint was the Overall Impact Score from a 10-item patient-reported outcome instrument known as the INTU questionnaire. This instrument was developed to measure the nighttime and daytime impacts of nocturia on some aspects of daily living, such as tiredness, sleep disruption, bother with getting out of bed at night to urinate, difficulty concentrating, and irritability. The score has a range from 0-100, with higher scores representing greater impact. Patients completed this questionnaire during the screening period and during weeks 6 and 12 of the treatment period. The Clinical Outcome Assessments staff determined that the INTU had acceptable content validity, measurement properties and

performance, and that, while acceptable, it could be further optimized because some items appear to have high floor effects that could lead to insensitivity in detecting treatment effects. An item has a floor effect when a high percentage of patients select the least severe response indicating that many of the patients were not experiencing those particular impacts from nocturia and, therefore, would not be able to show improvement on those impacts.

The Applicant defined the Intent-to-Treat (ITT) population as patients who received study drug and had at least three days of post-randomization efficacy data. The ITT population comprised 97-98% of randomized patients in DB3 and DB4. Missing data for the co-primary efficacy endpoints were not imputed in DB3, and were imputed using a multiple imputation method in DB4. There was no imputation of missing data for the secondary efficacy endpoints.

The modified Intent-to-Treat population (mITT) was limited to the subgroup of patients in the ITT population who were placebo non-responders during the two-week placebo lead-in period. The Applicant considered patients to be placebo responders during the two-week placebo lead-in period if they had at least a 50% reduction in the mean number of nocturic episodes compared to screening, or if the mean number of nocturic voids was less than 1.8. The mITT population in DB3 and DB4 comprised about 70% of the randomized population.

The Applicant specified the mITT as the primary statistical population for the key efficacy analyses in DB3. The FDA recommended the mITT also be used as the primary statistical population for DB4 because the treatment effect in DB3 was slightly greater for placebo non-responders compared to placebo responders, suggesting that an enrichment strategy could be useful. However, after the Application was transferred to our division, and after both DB3 and DB4 were completed and the results were known, we chose to focus on the ITT population. We view the ITT as more appropriate because it is the typical statistical population for efficacy analyses. Also, the mITT population is essentially a subgroup analysis of placebo non-responders because both trials randomized patients to the treatment arms regardless of placebo-responder status.

Co-Primary Efficacy Endpoints: At baseline, patients had about three nocturic voids per night, on average. As shown in Table 1, the 1.5 mcg dose was statistically superior to placebo on both co-primary efficacy endpoints in both trials. The mean reduction in nightly nocturic episodes with the 1.5 mcg dose was 0.3-0.4 compared to placebo. Across the two trials, 47-52% of patients treated with the 1.5 mcg dose at least halved their nightly nocturic voids compared to 29-33% of patients in the placebo group, with a corresponding treatment effect of 18-20%.

In DB3, the 1.0 mcg dose failed to achieve statistical significance on one of the co-primary efficacy endpoints. Statistical testing then stopped and did not proceed to the 0.75 mcg dose, according to the prespecified, hierarchical testing procedure. Therefore, p-values shown for the 0.75 mcg dose for DB3 in Table 1 are nominal.

In DB4, the 0.75 mcg dose was statistically superior to placebo for the change from baseline in mean nocturic episodes per night, but not for the percentage of patients with at least a 50% reduction from baseline in nocturic episodes per night (treatment effect 7%; p=0.09).

The trials defined nocturnal polyuria as nighttime urine production exceeding one-third of the 24-hour urine production. As shown in Table 1, an exploratory analysis in the subgroup of patients with nocturnal polyuria yielded essentially identical results for the co-primary efficacy endpoints compared to the overall population. This is not surprising because most randomized patients (about 80%) had nocturnal polyuria.

Table 1. Co-Primary Efficacy Endpoints for DB3 and DB4 (Intent-to-Treat Population) Adapted from Tables 8, 12, 17 and 18 in the Statistical Review

	Study DB3				Study DB4		
	Noctiva 0.75 mcg	**Noctiva 1.0 mcg**	**Noctiva 1.5 mcg**	**Placebo**	**Noctiva 0.75 mcg**	**Noctiva 1.5 mcg**	**Placebo**
OVERALL POPULATION	**N=186**	**N=183**	**N=179**	**N=186**	**N=262**	**N=260**	**N=260**
Mean Nocturic Episodes Per Night							
Baseline	3.4	3.3	3.2	3.3	3.3	3.3	3 3
Change from Baseline	-1.4	-1.4	-1.6	-1.2	-1.4	-1.5	-1.2
Treatment Effect 95% Confidence Interval p-value	-0.2 (-0.4, -0.06) <0.01[1]	-0.2 (-0.4, -0.01) 0.04	-0.4 (-0.6, -0.2) <0.0001		-0.2 (-0.4, -0.1) <0.01	-0.3 (-0.4, -0.1) <0.001	
≥50% Reduction in Nocturic Voids Per Night							
Percentage of Patients	41%	40%	52%	33%	36%	47%	29%
Difference from Placebo[2] 95% Confidence Interval[2] p-value	10% (-0.2%, 19%) 0.09[1]	8% (-2%, 18%) 0.16	20% (9%, 29%) <0.001		7% (-1%, 15%) 0.09	18% (10%, 26%) <0.0001	
NOCTURNAL POLYURIA SUBGROUP	**N=145**	**N=146**	**N=143**	**N=145**	**N=209**	**N=199**	**N=204**
Mean Nocturic Episodes Per Night							
Baseline	3.4	3.3	3.2	3.3	3.4	3.4	3 3
Change from Baseline	-1.4	-1.4	-1.5	-1.1	-1.5	-1.5	
Treatment Effect 95% Confidence Interval p-value[3]	-0.3 (-0.5, -0.1) <0.01	-0.2 (-0.4, -0.04) 0.02	-0.4 (-0.6, -0.2) <0.0001		-0.2 (-0.4, -0.1) 0.01	-0.3 (-0.5, -0.1) <0.01	
≥50% Reduction in Nocturic Voids Per Night							
Percentage of Patients	41%	37%	49%	29%	35%	47%	27%
Difference from Placebo[2] 95% Confidence Interval[2] p-value[3]	12% (1%, 23%) 0.03	8% (-3%, 19%) 0.14	21% (10%, 32%) <0.001		9% (-0.4%, 17%) 0.08	21% (11%, 30%) <0.0001	

[1] Nominal p-values (not controlled for type 1 error) because the prespecified hierarchical testing procedure stopped when the 1.0 mcg dose failed on both co-primary efficacy endpoints
[2] Difference and 95% confidence interval obtained from stratified Cochran-Mantel-Haenszel analysis
[3] Nominal p-values (not controlled for type 1 error) because the nocturnal polyuria subgroup analysis was post-hoc

Key Secondary Efficacy Endpoints: The 1.5 mcg dose was statistically superior to placebo on all secondary endpoints that were controlled for type 1 error, including changes from baseline in the INTU Overall Impact Score (discussed separately below), the time from going to sleep to first

nocturic void, the percentage of nights with no nocturic voids, the percentage of nights with at most one nocturic void, and nocturic urine volume. Key results are shown in Table 2.

Table 2. Selected Secondary Efficacy Endpoints for DB3 and DB4 (Intent-to-Treat Population) Adapted from Tables 9, 13, 19 and 22 in the Statistical Review

	Study DB3				Study DB4		
	Noctiva 0.75 mcg	**Noctiva 1.0 mcg**	**Noctiva 1.5 mcg**	**Placebo**	**Noctiva 0.75 mcg**	**Noctiva 1.5 mcg**	**Placebo**
OVERALL POPULATION	**N=186**	**N=183**	**N=179**	**N=186**	**N=262**	**N=260**	**N=260**
Percentage of Nights with No Nocturic Episodes							
Baseline	0	0	0	0	0	0	0
Change from Baseline	9	9	12	6	8	10	5
Treatment Effect	3	3	6		3	5	
95% Confidence Interval	(-1, 7)	(-1, 7)	(2, 10)		(-0.4, 6)	(2, 9)	
p-value	0.11[1]	0.12[1]	<0.01		0.09[2]	<0.01	
Percentage of Nights with at Most One Nocturic Episode							
Baseline	2	2	2	1	1	1	1
Change from Baseline	39	48	42	33	40	45	34
Treatment Effect	6	9	16		6	11	
95% Confidence Interval	(-1, 14)	(2, 16)	(8, 23)		(-1, 12)	(4, 17)	
p-value	0.09[1]	0.02[1]	<0.0001		0.07[2]	0.001	
NOCTURNAL POLYURIA SUBGROUP	**N=145**	**N=146**	**N=143**	**N=145**	**N=209**	**N=199**	**N=204**
Percentage of Nights with No Nocturic Episodes							
Baseline	0	0	0	0	0	0	0
Change from Baseline	8	7	9	4	7	11	5
Treatment Effect	4	3	5		2	6	
95% Confidence Interval	(0.4, 8)	(-1, 7)	(1, 9)		(-1, 6)	(2, 10)	
p-value[3]	0.03	0.16	<0.01		0.19	<0.01	
Percentage of Nights with at Most One Nocturic Episode							
Baseline	2	1	1	1	1	1	1
Change from Baseline	40	40	45	30	40	44	34
Treatment Effect	9	9	16		6	9	
95% Confidence Interval	(1, 18)	(1, 18)	(6, 23)		(-1, 13)	(2, 17)	
p-value[3]	0.03	0.03	<0.001		0.12	0.01	

[1] Nominal p-values (not controlled for type 1 error) because the prespecified hierarchical testing procedure stopped when the 1.0 mcg dose failed on both co-primary efficacy endpoints
[2] Nominal p-values (not controlled for type 1 error) because the prespecified hierarchical testing procedure stopped when the 0.75 mcg dose failed on both co-primary efficacy endpoints
[3] Nominal p-values (not controlled for type 1 error)

As shown in Table 2, essentially no patients had zero or one nocturic episode per night at baseline. Across the two trials, about 10-12% of nights were nocturia-free among the patients treated with the 1.5 mcg dose compared to 5-6% of nights treated with placebo (treatment effect

5-6%; p-value <0.01). With the 1.5 mcg dose, about 45% of nights had at most one nocturic episode compared to about one-third of nights among placebo-treated patients (treatment effect 11-16%; p≤0.001).

Secondary efficacy endpoint results for the 0.75 mcg dose are descriptive because this dose was not tested statistically in DB3 after the 1.0 mcg dose failed on one of its co-primary efficacy endpoints, and because the 0.75 mcg dose did not meet both of its co-primary efficacy endpoints in DB4.

As with the primary efficacy endpoints, an exploratory analysis in the subgroup of patients with nocturnal polyuria yielded essentially identical results for the key secondary efficacy endpoints compared to the overall population.

INTU: At baseline, the mean Overall Impact Score on the INTU was about 30 in all treatment groups. The 1.5 mcg dose reduced the score by 14 points, on average, and placebo reduced the score by 12 points, on average. The treatment effect of 3 points (on a scale of 0-100), while statistically significant, is of unclear clinical relevance because it is numerically small. As seen with the co-primary efficacy endpoints and other key secondary endpoints, an exploratory analysis in the subgroup of patients with nocturnal polyuria yielded essentially identical results compared to the overall population.

The results shown for the 0.75 mcg dose are descriptive because this dose did not meet both co-primary efficacy endpoints in DB4.

Table 3. INTU Overall Impact Score (DB4 Only)
Intent-to-Treat Population
Adapted from Tables 13 and 22 in the Statistical Review

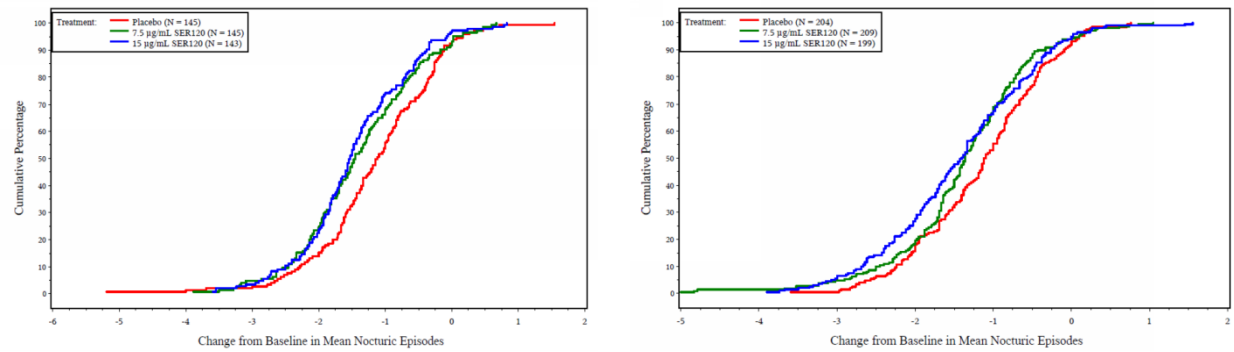
	OVERALL POPULATION			**NOCTURNAL POLYURIA SUBGROUP**		
	Noctiva 0.75 mcg N=262	**Noctiva 1.5 mcg N=260**	**Placebo N=260**	**Noctiva 0.75 mcg N=209**	**Noctiva 1.5 mcg N=199**	**Placebo N=204**
Baseline	32	34	32	31	34	32
Change from Baseline	-12	-14	-12	-13	-15	-11
Treatment Effect 95% Confidence Interval p-value	-1 (-3, 1) 0.45[1]	-3 (-5, -0.4) 0.02		-2 (-4, 1) 0.16[2]	-4 (-6, -1) <0.01[2]	

[1] Nominal p-value (not controlled for type 1 error) because the prespecified hierarchical testing procedure stopped when the 0.75 mcg dose failed on both co-primary efficacy endpoints
[2] Nominal p-values (not controlled for type 1 error)

Cumulative Distribution Functions: Figure 1 shows cumulative distribution function plots for the change from baseline in mean nocturic episodes per night for the nocturnal polyuria subgroup in both DB3 and DB4. These plots show the cumulative percentage of patients having up to a particular change from baseline in mean nocturic episodes per day. For example, in DB3 about

50% of patients in both the 0.75 mcg and 1.5 mcg arms had a mean reduction of at least 1.5 nocturic episodes per night compared to about 35% of patients treated with placebo. The plot for DB3 shows consistent separation between both the 0.75 mcg and 1.5 mcg doses and placebo, with considerable overlap of the two Noctiva doses. The plot for DB4 shows consistent separation between the 1.5 mcg dose and placebo. The 0.75 mcg dose separates from placebo and considerably overlaps with the 1.5 mcg dose on the right-half of the plot.

Figure 1. Cumulative Distribution Function for Change from Screening to the Treatment Period in the Mean Nocturic Episodes Per Night for DB3 (Left) and DB4 (Right). Intent-to-Treat Population, Nocturnal Polyuria Subpopulation.



8. Safety

Desmopressin formulations have been marketed in the United States for decades and have a well-known safety profile. This section summarizes the key safety findings for Noctiva. To be comprehensive, results are shown for the overall population. Findings in the subgroup of patients with nocturnal polyuria were not materially different. See the clinical safety review for details.

The number of patients exposed to Noctiva was adequate, with long-term exposures exceeding the minimum exposures recommended in the International Conference on Harmonization E1A guideline for drugs intended to treat chronic, non-life-threatening conditions. For the maximum recommended 1.5 mcg dose, 304 patients were exposed for at least six months and 218 patients were exposed for at least one year.

Deaths: There were five reported deaths in the clinical trials, three in the placebo-controlled trials and two in the uncontrolled extension trials. All five deaths occurred in Noctiva-treated patients. Three of these deaths are unlikely to be drug-related – one patient had hemorrhage in his left ventricle and ischemic changes on autopsy, another had findings consistent with a dissecting aortic aneurysm and intra-abdominal bleeding, and the third had cecal perforation, peritonitis, pneumonia, and multi-organ failure. A role of the drug could not be definitively excluded for the two remaining patients who were found dead, although both patients were elderly (79 and 80 years of age) and had multiple risk factors for heart disease. Note that the numerical imbalance of deaths in the placebo-controlled trials (3 vs. 0) is not inconsistent with the randomization scheme (about 2:1).

Serious Adverse Events: In the pooled database of controlled Phase 3 trials, the incidence of serious adverse events was similar for Noctiva (1.6-1.8% across doses) and placebo (1.7%). There was two reported serious adverse events of hyponatremia, one with Noctiva and the other with placebo. The Noctiva-treated patient had a serum sodium of 122 mmol/L six days after starting the 1.5 mcg dose. She may have had nausea, vomiting and diarrhea prior to the event, suggesting possible gastroenteritis. She should have been discontinued from the trial based on the discontinuation criteria but was continued on treatment without receiving therapy for the hyponatremia and had follow-up serum sodium measurements of 131-133 mmol/L over the next three clinic visits. She subsequently had a bout of weakness, nausea, and vomiting attributed to gastroenteritis and was found to have a serum sodium of 117 mmol/L in the sixth week of the treatment period, prompting treatment with intravenous fluids and discontinuation from the trial. Hyponatremia is discussed in greater detail below. The remaining serious adverse events do not raise any safety concerns.

Dropouts Due to Adverse Events: In the pooled DB3 and DB4 database, the incidence of adverse events leading to discontinuation was 4.2% with the Noctiva 0.75 mcg dose, 4.9% with the 1.5 mcg dose, and 4.0% with placebo. Hyponatremia or blood sodium decreased were the most common adverse events leading to discontinuation, affecting fewer than 1% of Noctiva-treated patients, but at a numerically greater incidence than placebo. Hyponatremia is discussed in more detail below.

Common Adverse Events: In the pooled DB3 and DB4 database, the incidence of adverse events was 49% in the Noctiva 0.75 mcg group, 47% with the 1.5 mcg dose, and 45% with placebo. The most common adverse events occurring in about 2-6% of Noctiva-treated patients and at a numerically higher incidence than with placebo appear to be related to the nasal route of administration (e.g., nasopharyngitis, nasal discomfort, sneezing, and nasal congestion). Other notable adverse events were urinary tract infection (3.5% with 0.75 mcg, 1.6% with 1.5 mcg, and 1.3% with placebo) and blood sodium decreased (1.1% with 0.75 mcg, 2.5% with 1.5 mcg, and 0% with placebo).

Hyponatremia: Hyponatremia is the most important risk associated with desmopressin products. DB3 and DB4 limited enrollment to adults at least 50 years of age and had no restrictions on fluid intake. These design features are expected to increase the risk of hyponatremia in the trials and were included to improve generalizability of the trial results to real-world use, where older patients are likely to be treated and uniform compliance with fluid restriction is unlikely. All patients in these trials were required to have normal serum sodium concentrations at baseline. Serum sodium was measured every two weeks during the 12-week treatment period. Patients were to be withdrawn if they had a serum sodium of 126-129 mmol/L with associated clinical symptoms or a serum sodium of ≤125 mmol/L regardless of symptoms.

Table 8 summarizes the incidence of hyponatremia in the pooled DB3 and DB4 database for the overall population and by age group (results are similar among the subgroup of patients with nocturnal polyuria). Noctiva clearly increases the risk of hyponatremia. Most of the hyponatremia was mild (130-135 mmol/L range). Severe hyponatremia (≤125 mmol/L) was infrequent (1.1% with the 1.5 mcg dose vs. 0.2% with placebo), and not detected with the 0.75

mcg dose. Overall, the incidence of hyponatremia was numerically higher with the 1.5 mcg dose, and among those ≥65 years of age. There was no consistent pattern based on sex (data not shown, but included in Dr. Kaufman's safety review).

Table 8. Hyponatremia in the Pooled DB3/DB4 Database (Adapted from Tables 25 and 32 in the Clinical Safety Review)

Serum Sodium Range (mmol/L)	0.75 mcg Dose n (%)	1.5 mcg Dose n (%)	Placebo n (%)
All Patients	**N=454**	**N=448**	**N=454**
130-134	38 (8.4%)	50 (11.2%)	20 (4.4%)
126-129	9 (2.0%)	9 (2.0%)	0
≤125	0	5 (1.1%)	1 (0.2%)
Age <65 years	**N=205**	**N=202**	**N=205**
130-134	10 (4.9%)	18 (8.9%)	9 (4.4%)
126-129	2 (1.0%)	0	0
≤125	0	0	0
Age ≥65 years	**N=249**	**N=246**	**N=249**
130-134	28 (11.2%)	32 (13.0%)	11 (4.4%)
126-129	7 (2.8%)	9 (3.7%)	0
≤125	0	5 (2.0%)	1 (0.4%)

All five patients with serum sodium ≤125 mmol/L were discontinued. All were receiving the 1.5 mcg dose, all were over 65 years of age (range 67-75), and four were men. Only the patient described above with the serious adverse event was symptomatic. Onset ranged from Day 6 through Week 12. Four of the patients were receiving systemic or inhaled glucocorticoids, three of whom were also receiving nonsteroidal anti-inflammatory drugs and one of whom was receiving a thiazide diuretic.

In the pooled DB3/DB4 database, there were 18 patients who had a nadir serum sodium of 126-129 mmol/L (one of whom had the hyponatremia 14 days after a single dose of Noctiva, which is unlikely to be drug-related). Nine of these patients were taking 0.75 mcg and nine were taking 1.5 mcg. All but two were at least 65 years of age, and 11 were men. Only one patient was symptomatic. Onset ranged from Week 2 through Week 12.

Across DB3 and DB4, about one-half of the 23 patients with serum sodium below 130 mmol/L had the nadir between weeks 2-6.

In the 126-week, open-label A2 extension trial, nine (2%) patients had a serum sodium concentration between 126-129 mmol/L, seven of whom were at least 65 years of age. Three patients (0.8%) had a serum sodium concentration ≤125 mmol/L, all of whom were at least 75 years of age. All of these patients received the 1.0 mcg dose daily.

9. Advisory Committee Meeting

We convened an advisory committee meeting to obtain independent advice on the Applicant's proposed indication, the clinical meaningfulness of the observed treatment effects, and whether the benefits of the drug outweigh the risks and support approval. Key recommendations are summarized below:

- Most committee members did not express concerns with the enrollment of patients at least 50 years of age and the lack of fluid restriction. Committee members noted that the incidence of nocturia increases with age, and safety risks are expected to be lower in younger patients. However, many committee members expressed concerns with the numerous exclusion criteria that limited generalizability of the results to all patients with nocturia. There was general consensus that the broad indication is not supported by the clinical trial population, with recommendations that the drug be indicated only in the subpopulation of patients with nocturia due to nocturnal polyuria.

- The committee overwhelmingly concluded (17 yes; 1 no; 1 no-voting) that there is sufficient evidence that at least one of the Noctiva doses is effective. Most agreed that the 1.5 mcg dose produced a clinically meaningful, but modest, effect. Most members stated that there was insufficient evidence to conclude that the 0.75 mcg dose is effective. Some members supported also approving the 0.75 mcg dose, in light of its apparent lower risk of hyponatremia.

- A majority of the committee voted that the benefits of Noctiva outweigh its risks and support approval (14 yes; 4 no; 1 no-voting), but only for an indication of nocturia due to nocturnal polyuria. Those who voted against approval stated that the benefits were modest in relation to the risks, that the trials did not limit enrollment to patients with nocturnal polyuria, and that the product may be inappropriately used (e.g., in the very elderly and with inadequate monitoring for hyponatremia). However, the committee members generally stated that the safety of Noctiva had been adequately characterized. Some members raised concerns that the frequency of real-world monitoring of serum sodium will be less than in the trials, with some recommending specific risk minimization approaches such as a Boxed Warning or a Risk Evaluation and Mitigation Strategy.

10. Pediatrics

This Application triggers the Pediatric Research Equity Act (PREA) because of the new indication. The Pediatric Review Committee agreed with a full waiver based on safety concerns (the indication for primary nocturnal enuresis was removed for approved intranasal desmopressin formulations based on reports of severe hyponatremia and seizures in children). In addition, pediatric studies would be impossible or impractical because nocturia due to nocturnal polyuria is rare in the pediatric population.

11. Other Relevant Regulatory Issues

Tradename: The DMEPA primary reviewer raised safety concerns with the proposed tradename, Noctiva, because of potential confusion with Nocdurna, which is under development for the same indication. DMEPA management, however, concluded that 'Noctiva,' is acceptable because of sufficient differences between 'Noctiva' and 'Nocdurna,' including differences in routes of administration (nasal spray vs. orally disintegrating tablet) and orthographic differences. See the DMEPA reviews for further details.

Inspections: The Office of Scientific Investigations (OSI) inspected two clinical sites that together enrolled over 100 patients across the two pivotal Phase 3 trials. One site was issued a Form FDA 483 and was classified as Voluntary Action Indicated (VAI). OSI determined that the isolated protocol deviations would not be expected to have a significant impact on efficacy or safety considerations and that the data from this site are acceptable for regulatory decision-making. The other site had no identified protocol deviations. See the OSI memorandum for further details.

12. Labeling

Key issues pertaining to labeling include the following:

- Noctiva will be indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void. See Section 13 for the rationale for narrowing the Applicant's proposed indication. The labeling will state that prior to starting treatment, health care providers should evaluate patients for possible causes for the nocturia, including excessive fluid intake prior to bedtime, and optimize the treatment of contributing conditions. The labeling will also state that nocturnal polyuria should be confirmed with a 24-hour urine collection, if one has not been obtained previously. There will be a Limitation of Use because the pivotal trials excluded patients younger than 50 years of age.

- Noctiva will be approved with a Boxed Warning and Medication Guide, because of the risk of hyponatremia. See Section 13 for the rationale. Labeling will inform health care providers that Noctiva can cause hyponatremia, which can be life-threatening, that Noctiva is contraindicated in patients at increased risk of severe hyponatremia (e.g., polydipsia, concomitant use with glucocorticoids or loop diuretics, renal impairment with an estimated glomerular filtration rate below 50 mL/min/1.73 m^2, and during illnesses that can cause fluid or electrolyte imbalances), that serum sodium should be normal before starting treatment, and monitored within seven days and approximately one month after initiating therapy or increasing the dose, and periodically thereafter, and that more frequent monitoring is recommended in patients at increased risk of hyponatremia (e.g., those ≥65 years of age, and those on concomitant medications that can predispose to hyponatremia). Labeling will also state that fluid intake in the evening and night-time hours should be moderated to decrease the risk of hyponatremia.

- The recommended dosage is 1.5 mcg for patients younger than 65 years of age who are not at increased risk for hyponatremia. For patients ≥65 years of age or younger patients at increased risk for hyponatremia, the recommended starting dose is 0.75 mcg, which can be increased if needed after at least seven days to 1.5 mcg provided the serum sodium has remained normal. The labeling explicitly states that the efficacy data are not as strong for the 0.75 mcg dose. Rationale for also approving the 0.75 mcg dose is provided in Section 13.

- Labeling will contraindicate Noctiva in patients with underlying conditions that could be exacerbated by volume retention, such as symptomatic heart failure and uncontrolled hypertension.

- The Adverse Reactions section will show data only for the patients with nocturnal polyuria. These data were not meaningfully different from those of the overall population, and will ensure consistency with the narrowed indication. This section will also show the incidence of hyponatremia in the trials, including the higher incidence among patients ≥65 years of age, and will provide details on the five patients who had severe hyponatremia.

- The Clinical Studies section will also only show data for the patients with nocturnal polyuria, consistent with the narrowed indication. No p-values will be reported because this was a post-hoc subgroup analysis. We will include descriptive figures for both DB3 and DB4 showing the percentage of patients by treatment arm who achieved various reductions from baseline in the mean number of nocturia episodes per night. We will limit the presentation of key secondary endpoints to the INTU Overall Impact Score (so that health care providers can see that the impacts of nocturia on some aspects of daily living is numerically small) and to the change from baseline in the percentage of nights with no nocturia and at most one nocturia episode (these endpoints help provide evidence of clinical meaningfulness, as explained in Section 13). We will not label the secondary endpoints of time from bedtime to first nocturic void and change from baseline in nocturic volume because these two endpoints are of unclear clinical relevance. For example, the Applicant has not provided data from its trials showing that the mean increase of up to about 40 minutes in the time from going to bed to first nocturic void translates into improvements in how patients feel or function.

The Carton and Container labeling has been reviewed by DMEPA, the Medication Guide and Instructions for Use have been reviewed by the Division of Medical Policy Programs, and the prescribing information has been reviewed by all scientific disciplines. We have also addressed comments from the Office of Prescription Drug Promotion that ensure labeling is not promotional. All outstanding labeling issues have been resolved. See the reviews for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

I concur with the recommendations from all review disciplines and from the Cross-Discipline Team Leader, that this application can be approved.

In both pivotal trials, the 1.5 mcg dose was statistically superior to placebo on both co-primary efficacy endpoints and on all key secondary endpoints controlled for type 1 error. The change from baseline in the mean number of nocturic episodes per night relative to placebo was 0.3-0.4, which is numerically small and of unclear clinical significance. However, the findings on the 50% responder co-primary endpoint together with the findings on two key secondary endpoints (the percentage of nights with no nocturia and the percentage of nights with at most one nocturic episode) provide convincing evidence of a clinically meaningful benefit. Compared to placebo, about 20% more patients on the 1.5 mcg dose at least halved their nightly nocturic voids, about 5% more nights on the 1.5 mcg dose were nocturia-free, and about 10-15% more nights on the 1.5 mcg dose had at most one nocturic episode. The percentage of nights with no nocturic voids and the percentage of nights with at most one nocturic void provide direct evidence of clinical benefit because having no nocturia reflects complete resolution, for those nights, of the symptom being treated, and having at most one nocturic episode per night reflects, for those nights, a reduction in nocturia below the threshold for which Noctiva would be indicated.

Although the Applicant achieved statistically significant results for the 1.5 mcg dose in the overall population, these findings do not support a general indication for the treatment of nocturia, regardless of cause. The trials had numerous exclusion criteria that limit generalizability of the efficacy and safety results to all causes of nocturia. In addition, most (~80%) of the randomized population had nocturnal polyuria. Although the nocturnal polyuria subgroup analysis was post-hoc, the 1.5 mcg dose was statistically superior to placebo in the overall randomized population and results for the nocturnal polyuria subgroup were essentially identical to the results from the overall randomized population. Based on these considerations, the indication will be narrowed from patients with nocturia who awaken at least twice per night to void to those who have nocturia due to nocturnal polyuria and who awaken at least twice per night to void. Because nocturia is a symptom of underlying condition(s), labeling will remind health care providers to evaluate patients for possible causes of the nocturia, including excessive fluid intake, and to optimize the treatment of underlying conditions before starting Noctiva. Labeling will also state that a 24-hour urine should be collected (if one has not been obtained previously) to diagnose nocturnal polyuria, as this is the only reliable method to confirm overproduction of urine at night.

What about the 0.75 mcg dose? This dose was not tested statistically in DB3 based on the prespecified, hierarchical testing procedure, because the 1.0 mcg dose (which is not proposed for marketing) failed on one of its co-primary efficacy endpoints. In DB4, the 0.75 mcg dose was superior to placebo on the mean change from baseline in nocturic episodes per night, but not on the 50% responder co-primary endpoint. Had the Applicant studied only the 0.75 mcg dose, these findings would not be sufficient for approval. Also, if safety concerns with the 0.75 mcg

and 1.5 mcg doses were similar, there would be no reason to consider approval of the 0.75 mcg dose. However, the following considerations support approval of the 0.75 mcg dose as an option for some patients:

- Both doses can cause hyponatremia, but the incidence of hyponatremia was higher with the 1.5 mcg dose. Severe hyponatremia (sodium ≤125 mmol/L) in DB3 and DB4 was only observed with the 1.5 mcg dose and among patients over 65 years of age.
- As shown in the cumulative distribution function plots for the mean change in nocturic episodes per night (Figure 1 in the Efficacy section), there was consistent separation between both the 0.75 mcg and 1.5 mcg doses and placebo in DB3, with considerable overlap of the two Noctiva doses. In DB4, the 0.75 mcg dose separated from placebo and considerably overlapped with the 1.5 mcg dose on the right-half of the plot. These data support that some patients have a response to the 0.75 mcg dose that is similar to that seen for some patients receiving the 1.5 mcg dose.
- Based on the pharmacokinetic data, there is large inter-individual variability in systemic exposure to desmopressin. For the 0.75 mcg dose, the coefficient of variation was 96% for Cmax and 146% for AUC. These data support that some patients will have higher exposures to the 0.75 mcg dose than others.

Based on these considerations, it is reasonable to approve the 1.5 mcg dose for patients who are not otherwise at increased risk for hyponatremia and to approve the 0.75 mcg dose as the starting dose for patients who are at increased risk of hyponatremia (e.g., those over 65 years of age). Some of these patients who are started on the 0.75 mcg dose may achieve sufficient benefit and can remain at that dose without exposure to a higher dose that carries a greater risk of hyponatremia. Those who do not achieve an adequate response to the 0.75 mcg dose and who have normal serum sodium on this dose can be uptitrated to the 1.5 mcg dose. The Applicant proposed uptitration after 2-4 weeks, if needed, but labeling will state that uptitration can occur sooner (after at least one week, provided serum sodium has remained normal), given that desmopressin has a short half-life and patients can readily gauge whether their symptoms are sufficiently improved.

With regard to risks, the most important safety concern is hyponatremia, which is a well-known side effect of desmopressin therapies. Currently approved desmopressin products mitigate this risk with Warnings and Precautions. However, those products are approved for different indications and have more narrow uses, such as diabetes insipidus, hemostasis during surgery for patients with Hemophilia A or von Willebrand's disease, and primary nocturnal enuresis in children. In contrast, Noctiva will be used in a diverse, older patient population that likely has multiple co-morbidities and concomitant medications that can predispose to hyponatremia. We have concluded that a Boxed Warning for hyponatremia is necessary to ensure that the modest benefits of the drug outweigh the risks. A Boxed Warning is appropriate because severe hyponatremia can be life-threatening and is very serious in proportion to the potential benefit of the drug, and because hyponatremia can be mitigated with interventions (e.g., periodic monitoring of serum sodium). In addition, the drug will be approved with a Medication Guide because there are actions patients can undertake to reduce their risk of severe hyponatremia, such as recognizing the symptoms of hyponatremia, avoiding excessive fluid intake, and checking

with their health care provider before starting new medications that may increase the risk of hyponatremia.

The key measures for minimizing the risk of hyponatremia are described in the Labeling section above and include contraindications in patients with conditions that predispose to severe hyponatremia, serum sodium assessments, moderation of fluid intake close to bedtime, and the lower starting dose for patients at risk of hyponatremia (e.g., those over 65 years of age). Labeling will state that serum sodium should be normal prior to initiating or resuming therapy, or increasing the dose, and that serum sodium should be monitored periodically, with more frequent monitoring in patients at increased risk of hyponatremia. Labeling will specifically recommend monitoring serum sodium within one week and approximately one month after starting treatment or increasing the dose. This timing is based on the patient in the pivotal trials treated with the 1.5 mcg dose who developed symptomatic hyponatremia within one week of starting treatment, and because about one-half of the 23 patients with serum sodium <130 mmol/L in the DB3/DB4 database had the nadir serum sodium within 2-6 weeks after starting treatment. These are reasonable measures to mitigate the risk of hyponatremia and ensure the benefits of Noctiva outweigh the risks. I concur with the Division of Risk Management that a Risk Evaluation and Mitigation Strategy is not needed at this time to ensure the benefits outweigh the risks.

Based on the above considerations, I conclude that the benefits of Noctiva outweigh its risks when used according to labeling and that the application can be approved.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

As noted in the Clinical Pharmacology section, two separate sprays of 0.75 mcg could potentially result in greater desmopressin exposures than those achieved with one spray of 1.5 mcg, increasing the risk for hyponatremia. This scenario could potentially occur when patients are uptitrated from 0.75 mcg to 1.5 mcg, and there is remaining drug in their 0.75 mcg bottle(s). Therefore, we are requiring a postmarketing trial to compare the bioavailability of two sprays of 0.75 mcg and one spray of 1.5 mcg. Until those results are available, labeling will explicitly state that two sprays of 0.75 mcg are not interchangeable with one spray of 1.5 mcg.

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/s/

HYLTON V JOFFE
03/03/2017