

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201656Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	201656
<b>Submission #</b>	1 (Sequence 0000)
<b>OSE RCM #</b>	2016-394
<b>PDUFA Goal Date</b>	March 3, 2017
<b>Reviewer Name(s)</b>	Somya Dunn, MD
<b>Acting DRISK Team Leader</b>	Leah Hart, Pharm.D.
<b>Acting Deputy Division Director DRISK</b>	Jamie Wilkins Parker, Pharm.D.
<b>Review Completion Date</b>	February 22, 2017
<b>Established Name</b>	Desmopressin Acetate
<b>(Proposed) Trade Name</b>	Noctiva
<b>Applicant</b>	Serenity Pharmaceuticals LLC
<b>Therapeutic Class</b>	Vasopressin analogue
<b>Formulation(s)</b>	Nasal Spray
<b>Dosing Regimen</b>	0.75 mcg or 1.5 mcg per spray
<b>Proposed Indication(s)</b>	Nocturia

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## **EXECUTIVE SUMMARY**

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Noctiva (desmopressin acetate) is necessary to ensure the benefits outweigh the risks. Serenity Pharmaceuticals, LLC., submitted a New Drug Application (NDA 201656) to the Division of Bone, Reproductive and Urologic Products (DBRUP) with the proposed indication to treat nocturia in adults who wake up two or more times per night to void. The Applicant submitted a REMS consisting of a communication plan and Medication Guide to mitigate the risk of hyponatremia.

DRISK and the DBRUP agree that a REMS is not needed to ensure the benefits of Noctiva outweigh its risk. The risk of hyponatremia is a well-known risk of medications containing desmopressin. The risk of hyponatremia will be communicated through labeling, including a Medication Guide. Language in the Prescribing Information (PI) and Medication Guide will include a boxed warning for hyponatremia. In addition, instructions on monitoring serum sodium levels, medical situations where Noctiva should be either temporarily or permanently discontinued and patient education on signs and symptoms of hyponatremia will be included in the label.

## **1 Introduction**

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for Noctiva (desmopressin acetate) is necessary to ensure the benefits outweigh the risks. Serenity Pharmaceuticals, LLC., submitted a New Drug Application (NDA) 201656 to the Division of Bone, Reproductive and Urologic Products (DBRUP) with the proposed indication to treat nocturia in adults who wake up two or more times per night to void. The Applicant submitted a REMS consisting of a communication plan and Medication Guide to mitigate the risk of hyponatremia.

## **2 Background**

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### **2.1 PRODUCT INFORMATION**

Noctiva is a nasal spray formulation of desmopressin, a synthetic peptide analogue of vasopressin (human anti-diuretic hormone). The mechanism of action is the same as vasopressin; it works by stimulating reabsorption of water in the kidney, leading to more concentrated urine and less water excretion.

Noctiva was submitted as a 505 (b)(2) application. Several desmopressin formulations, including a nasal spray, are currently marketed and FDA-approved for the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgery. The PI for these products does not contain a Medication Guide (MG) or a boxed warning, but does have a Warning and Precaution for hyponatremia. There are no FDA-approved drugs indicated for the treatment of nocturia. The proposed indication is for the

treatment of nocturia in adults who wake up two or more times per night to void, thus this medication would be used in the outpatient setting. The Applicant proposed two different strength dose devices with 0.75 mcg or 1.5 mcg spray of desmopressin in each with a recommended starting dose of 0.75 mcg each night [REDACTED] (b) (4). The Applicant proposes that as needed, the dose may be increased to 1.5 mcg each night. Noctiva is a low-dose version of desmopressin that contains an excipient not used in other desmopressin formulations, cyclopentadecanolide (CPD) [REDACTED] (b) (4) [REDACTED]

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 201656 relevant to this review:

- July 17, 2015: The Applicant submitted a pre-NDA meeting briefing package for Noctiva. A draft high level eCTD Table of Contents for the proposed NDA was included in the meeting package which indicated that a Risk Management Plan would be submitted to the NDA.
- February 4, 2016: The Agency received NDA 201656 for the treatment of nocturia in adults who wake up two or more times per night to void with a proposed communication plan REMS.
- October 19, 2016: Advisory Committee Meeting was held (Bone, Reproductive and Urologic Drugs Advisory Committee—BRUDAC). The committee voted to approve Noctiva 14 to 4.
- October 28, 2016: The Agency sent a request for subgroup efficacy and safety analyses on patients in two of their four placebo-controlled studies (DB3 and DB4) studies who had nocturnal polyuria at baseline as this is the population that the Applicant is seeking indication for.
- November 4, 2016: The Applicant submitted the requested data and analyses.
- November 16, 2016: The Agency sent the Applicant a letter notifying them that the data submitted on November 4, 2016 would be a Major Amendment and result in a three month extension of the review clock.

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

Nocturia is defined by the International Continence Society as a patient needing to awaken at night one or more times to void.<sup>1</sup> Nocturia can be a symptom of one or more underlying conditions or disease processes and there are a variety of conditions associated with it including overactive bladder, obstructive sleep apnea, diabetes mellitus, benign prostatic hypertrophy (BPH), and edematous states

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<sup>1</sup> Van Kerroebroeck, P., et. al., The Standardization of Terminology in Nocturia: Report from the Standardization sub-committee of the International Continence Society. *NeuroUrol and Urodynamics*. 2002; 00: 179-183.

such as congestive heart failure. The condition is considered the result of one of three pathophysiologic processes: polyuria (increase in 24-hour urine), nocturnal polyuria (an increase in nighttime urine production with greater than one-third of 24 hour urine volume produced at night) or bladder storage problems (for example, Benign Prostatic Hyperplasia (BPH)).<sup>2</sup> The prevalence of nocturia increases with age and a recent systematic review suggests that the annual incidence of nocturia is 12% among adults older than 60 years of age.<sup>3</sup>

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

In the United States there are no approved medications for the treatment of nocturia. Generally, management of this condition focuses on treating the underlying pathophysiology or disease process. Subcutaneous, intravenous, tablet and higher dose nasal spray formulations of desmopressin are approved by the FDA for the treatment of central diabetes insipidus, primary nocturnal enuresis in children, and to maintain hemostasis in patients with von Willebrand's Disease and Hemophilia A during surgical procedures. None of the FDA-approved desmopressin products are indicated for the treatment of nocturia. Hyponatremia is listed as a warning in all approved labeling for desmopressin regardless of the route of administration or indication. In over 80 countries, oral and sublingual formulations of desmopressin (trade names of Minirin<sup>®</sup> and Minirin Melt<sup>®</sup>, respectively) are approved for the symptomatic treatment of adults with nocturia associated specifically with nocturnal polyuria.

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<sup>2</sup> Cornu JN, Abrams P, Chapple CR, Dmochowski RR, et. al. A Contemporary Assessment of Nocturia: Definition, Epidemiology, Pathophysiology, and Management – a Systematic Review and Meta-analysis. *European Urology* 62 (2012): 877-890.

<sup>3</sup> Pesonen JS, Cartwright R, Mangera A, et. Al. Incidence and Remission of Nocturia: A systematic Review and Meta-analysis. *Eur Urol.* 2016 Aug; 70 (2): 372-81.

Product Trade Name (Generic)  Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
FDA Approved Treatments				
DDAVP (desmopressin acetate) tablets 9/6/1995	Antidiuretic replacement for diabetes insipidus; primary nocturnal enuresis	Central Diabetes Insipidus: dosing is patient specific and diurnal pattern.  Adults: 0.05 mg BID initial, titrate per adequate diuresis  Primary Nocturnal Enuresis:  6 years and older: 0.2 mg at bedtime, titrate up to 0.6 mg at bedtime	Hyponatremia, caution use in patients with psychogenic polydipsia, cystic fibrosis, heart failure, electrolyte imbalance, and renal disorders.	None
DDAVP Nasal Spray (desmopressin acetate) 2/21/1978	Antidiuretic replacement therapy for central cranial diabetes insipidus; Management of temporary polyuria and polydipsia	Adults: 0.1 to 0.4 ml daily, as single dose or divided two-three doses daily  Children 3 months-12 years: 0.05 ml-0.3 ml daily, as single dose or divided into two doses	For intranasal use only, use only when oral administration not feasible.  Hyponatremia is common side effect; fluid intake should be adjusted downward and used with caution with habitual polydipsia.	Patient Instruction Guide on how to use medication
Stimate Nasal	Hemophilia A ;	One spray per nostril,	Hyponatremia;	Patient Instruction

Spray (desmopressin acetate spray, metered)  3/7/1994	Von Willebrand's Disease (Type I)	total dose of 300 mcg.  Patients less than 50 kg: 150 mcg in single spray	shouldn't be used in patient with Type IIB von Willebrand's disease since platelet aggregation may be induced.	Guide on how to use metered spray
Desmopressin Acetate injection, solution  3/30/1984	Hemophilia A;  Von Willebrand's Disease (Type I)  Diabetes Insipidus	Diabetes Insipidus  Adults: 0.5 ml to 1 ml daily, IV or SC in two divided doses  Hemophilia A and Von Willebrand's Disease (Type I):  IV: 0.3 mcg/kg/weight over 15-30 minutes	Shouldn't be used in patient with Type IIB von Willebrand's disease since platelet aggregation may be induced.  Fluid restriction should be recommended to reduce chances of hyponatremia.	None

#### 4 Benefit Assessment

In this submission the Applicant is seeking approval of Noctiva for the treatment of adult nocturia. To support this approval, the safety and efficacy data from two Phase 3, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical studies were submitted (DB3 and DB4). Study titled DB3 used three doses of Noctiva versus placebo (0.75 mcg, 1.0 mcg and 1.5mcg) and study titled DB4 used two doses of Noctiva versus placebo (0.75 mcg and 1.5mcg). The clinical program evaluated approximately 1900 patients and the long-term safety studies evaluated 769 patients with exposures up to 126 weeks in duration.

Both trials had the same co-primary efficacy endpoints:

- Mean number of nocturic episodes per night during the efficacy assessment period (change from baseline in the mean number of nocturic episodes per night)
- Percentage of patients with  $\geq 50\%$  reduction of the mean number of voids per night during the treatment period compared to baseline

Efficacy data from the two studies demonstrated that Noctiva 1.5 mcg achieved statistically significant improvement in the two pre-specified co-primary efficacy endpoints compared with placebo (1.5 mcg dose  $p < 0.0001$  for DB3 and  $p < 0.001$  for DB4). The 1.5mcg dose resulted in a mean reduction of 0.3-0.4 nocturia episodes per night compared to placebo. The 1.5 mcg dose also met all secondary endpoints. The 0.75 mcg dose produced a mean reduction of 0.2 nocturia episodes per night compared to placebo and the percentage of subjects with a  $\geq 50\%$  reduction in nocturia episode frequency was 7-8% greater compared to placebo. The clinical reviewer noted that although statistical significance was not achieved for either endpoint, the data suggest that the 0.75 mcg dose reduces nocturia episode frequency more than does placebo.<sup>4</sup>

Given the broad, general indication for nocturia regardless of the underlying etiology and the extensive exclusion criteria in the phase 3 trials, DBRUP is considering that Noctiva should not be approved to treat nocturia irrespective of etiology as they are concerned about the risk of hyponatremia (discussed in Section 5) and assert that properly treating underlying serious conditions is very important. The BRUDAC panelists expressed similar concerns. Therefore, DBRUP is considering an indication for Noctiva 1.5 mcg for the treatment of adults with nocturia due to “nocturnal polyuria” (see Section 3.1, this is one of three causes of nocturia defined as an increase in nighttime urine production with greater than one-third of 24 hour urine volume produced at night). However, they requested data on the subgroup of patients that had nocturnal polyuria. This data was sent in as a Major Amendment to the application and is under review.

## 5 Risk Assessment & Safe-Use Conditions

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### 5.1 HYPONATREMIA

The risk of hyponatremia is the most significant known risk associated with desmopressin. If hyponatremia is severe and not treated appropriately or in a timely manner, it can result in seizures, coma and/or death. The overall incidence of severe hyponatremia from desmopressin therapy is unknown. On December 7, 2007, the FDA issued an alert to inform healthcare professionals of the risk of severe hyponatremia associated with desmopressin use. This was largely due to postmarketing reports of hyponatremic seizures occurring mostly in pediatric patients that taking intranasal desmopressin for primary nocturnal enuresis; this at the time was an indication for the intranasal formulation. The FDA

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<sup>4</sup> Easley, O/Kaufman, M. Clinical Review for Noctiva (desmopressin), NDA 201656, February 17, 2017

subsequently removed this indication from the currently marketed intranasal desmopressin formulations.<sup>5</sup>

Overall, in the clinical development program, 31 (2.2%) subjects in the Noctiva treatment group reported an adverse event (AE) of either decreased serum sodium or hyponatremia compared to one (0.1%) subject in the placebo group. Two of the events (one in the Noctiva treatment group and one in the placebo group) met the criteria for a serious adverse event (discussed below) and 11 (10 in the Noctiva treatment group and one in the placebo group) led to discontinuation from the study.

The main safety database focused on by the clinical reviewer consisted of controlled trials DB3 and DB4 and the open label extension of DB3 (trial A2) since these studies utilized the proposed doses. In these studies, at the 1.5 mcg dose, the incidence of hyponatremia (as defined in study protocols  $\leq 125$  mmol/L) was 1.1% compared to 0.2% in the placebo group. In addition, nadir serum sodium values falling between 126 to 129 mmol/L for the 1.5 mcg, 0.75 mcg, and placebo treatment groups had incidences of 2.0%, 2.0%, and 0%, respectively. The incidence of hyponatremia was slightly higher in patients over the age of 65. There was one serious adverse event (SAE) due to hyponatremia in the placebo group and one in the 1.5 mcg group, neither led to seizure or coma. The patient in the 1.5 mcg group was from study DB4; she was sent to the ER where she was treated with normal saline IV, but was not admitted to the hospital. There were no deaths that were determined due to hyponatremia in the clinical program.

### 5.1.1 SAFE-USE CONDITIONS

The review team has recommended that serum sodium should be monitored during Noctiva treatment and specifics are detailed in the labeling, which is still under discussion with the Applicant. However at this time, the Dosage and Administration section of the label states that (b) (4)

[REDACTED]

Furthermore, providers should instruct patients to temporarily discontinue Noctiva if they require systemic or inhaled pulmonary corticosteroid therapy as this was found to be associated with increase in hyponatremia during the clinical program. In the DB3 and DB4 studies, of the five Noctiva subjects with nadir serum sodium values  $\leq 125$  mmol/L, all were 65 years of age or older and four of the five were being treated with corticosteroids: three with an inhaled corticosteroid and one with oral prednisone.

<sup>5</sup><http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm125561.htm>

Hyponatremia was found to be dose-proportional and greater in older subjects (discussed below Section 5). If approved, DBRUP is considering labeling that in patients older than 65 years of age Noctiva should be initiated at 0.75 mcg, and escalating to the 1.5 mcg dose in those patients who do not respond to the lower dose provided their serum sodium has remained in the normal range. Their rationale for recommending approval of 0.75 mcg for use in the elderly despite it not meeting the pre-specified efficacy endpoints are predominantly due to concerns of hyponatremia in this group of patients, differences found in nocturia episodes that may be meaningful to some patients in spite of lack of statistical significance and a post-hoc analysis of the nocturnal polyuria sub-population for Noctiva 0.75 mcg which met both primary efficacy endpoints.

Patient Counseling in the label advises providers to caution patients that they may potentially develop symptomatic hyponatremia (b) (4) and experience one or more of the following signs or symptoms: headache, nausea/vomiting, (b) (4) restlessness, fatigue, (b) (4) muscle (b) (4) cramps, and abnormal mental status (b) (4). Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. However, patients with hyponatremia may be asymptomatic. There will also be a Medication Guide with similar warnings regarding the signs and symptoms of hyponatremia for patients.

## 6 Expected Postmarket Use

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Noctiva will be prescribed primarily in an outpatient setting to be self-administered. As previously mentioned, Noctiva data is currently under review to determine the final indication. Noctiva will be an option for patients that do not have an obvious underlying cause or are resistant to other therapies. Urologists and internists are the most likely prescribers and they are familiar with treating the underlying conditions associated with nocturia and are likely to be aware of the risk of hyponatremia when using desmopressin-containing products. Although labeling negotiations are still in progress, there are several contraindicated comorbidities and conditions for Noctiva such as history of hyponatremia, renal impairment and known or suspected syndrome of inappropriate antidiuretic hormone secretion (SIADH). There will also be a boxed warning (see below Section 7), and several recommendations for monitoring serum sodium. These details in the label will be used to communicate to providers the importance of using Noctiva in the indicated population. Furthermore, desmopressin has been available for years with the well-known risk of hyponatremia. Though formulations of desmopressin are approved in other countries for nocturia, these formulations are different than Noctiva and data from these products cannot be compared or used to predict what will happen with Noctiva.

## 7 Risk Management Activities Proposed by the Applicant

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The Applicant proposed a REMS to mitigate the risk of hyponatremia. The goal of the proposed REMS for Noctiva is to minimize the risk of patients developing hyponatremia. The proposed REMS elements are a Medication Guide and communication plan.

The proposed Medication Guide addresses the risk of hyponatremia and describes the symptoms that patients should be alerted to that may indicate that they are experiencing hyponatremia. The Medication Guide also warns that severely low salt levels may result in more serious side effects such as seizure, coma, or breathing difficulties.

The proposed communication plan consists of a Dear Health Care Professional Letter which is proposed as a one-time mass mailing targeted to potential Noctiva prescribers to communicate the risk and ways to mitigate the risk. The Applicant also proposed a timetable for submission of assessments so that the effectiveness of the REMS program could be evaluated by FDA.

## 8 Discussion of Need for a REMS

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The Clinical Reviewer recommends approval of Noctiva on the basis of the efficacy information currently available for the treatment of adults with nocturia due to nocturnal polyuria (defined as greater than one-third of 24-hour urine volume produced at night) who awaken two or more times per night to void. Nocturia is relatively common among the elderly and becomes increasingly prevalent with age, with profound influences on health and quality of life (QoL). Sleep fragmentation and disruption may result in daytime sleepiness, tiredness, mood changes, and cognitive dysfunction with poor concentration and performance.<sup>6</sup> More than 60% of men and women reported that nocturia had a negative effect on their QoL.<sup>7</sup> There is currently no FDA approved for the treatment of nocturia.

Desmopressin is a synthetic form of vasopressin, a well-studied hormone secreted in the body. There are four desmopressin products currently approved and each has hyponatremia or a history of hyponatremia as a contraindication and hyponatremia addressed in the Warning section of the label (not PLLR format). These products do not contain a boxed warning in their label, a MG or a REMS.

The side effect of hyponatremia is well-known and the intended prescribing population is likely aware of this risk. If approved, DBRUP is considering labeling that in patients older than 65 years of age Noctiva should be initiated at 0.75 mcg, and escalating to the 1.5 mcg dose in those patients who do not respond to the lower dose provided their serum sodium has remained in the normal range. The 0.75 mcg is was found to be reasonably safe in the elderly population and the review division considers that it may provide a clinically meaningful benefit especially in light of no other treatment options

Though the label has not yet been finalized, the risk of hyponatremia will be communicated through the product labeling, including a boxed warning and MG.

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<sup>6</sup> Hetta J. The impact of sleep deprivation caused by nocturia. *BJU Int.* 1999;84:27–8.

<sup>7</sup> Schatzl G, Temml C, Schmidbauer J, Dolezal B, Haidinger G, Madersbacher S. Cross-sectional study of nocturia in both sexes: Analysis of a voluntary health screening project. *Urology.* 2000;56:71–5.

The boxed warning for hyponatremia will emphasize the seriousness of this risk. Hyponatremia is also covered in Contraindications as contraindicated in patients with a history of hyponatremia, and it will be a Warning and Precaution (W and P), [REDACTED] (b) (4)

Though hyponatremia is a risk that needs to be considered in the risk/benefit evaluation, hyponatremia is a known risk of desmopressin-containing products and will be communicated via labeling. Therefore, DBRUP and DRISK have determined that a REMS is not necessary to ensure that the benefits outweigh the risk for Noctiva.

## 9 Conclusion & Recommendations

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Based on the available data, if approved, risk mitigation measures beyond professional labelling are not necessary to ensure the benefits outweigh the risk of hyponatremia for Noctiva for the proposed indication of nocturia or the potential indication of nocturnal polyuria. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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/s/  
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LEAH M HART-BANKS  
02/22/2017

JAMIE C WILKINS PARKER  
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**NDA 201656 NOCTIVA (SER120)  
0.75 mcg and 1.5 mcg**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

(b) (4)

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