HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NOCTIVA™ safely and effectively. See full prescribing information for NOCTIVA.

NOCTIVA (desmopressin acetate) nasal spray, for intranasal use
Initial U.S. Approval: 1978

WARNING: HYPONATREMIA

See full prescribing information for complete boxed warning.

- **NOCTIVA can cause hyponatremia, which may be life-threatening if severe. (5.1, 6.1)**
- **NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids. (4, 5.1)**
- **Ensure serum sodium is normal before starting or resuming NOCTIVA. Measure serum sodium within seven days and approximately one month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia. (2.3, 5.1)**
- **If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued. (5.1)**

INDICATIONS AND USAGE

NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void. (1)

Limitation of Use: Not studied in patients younger than 50 years of age. (1)

DOSAGE AND ADMINISTRATION

- Prime with 5 actuations before initial use. Re-prime with 2 actuations if not used for more than 3 days. (2.1)
- For patients < 65 years of age who are not at increased risk for hyponatremia: Use one spray of 1.66 mcg in either nostril nightly approximately 30 minutes before going to bed. (2.2)
- For patients ≥ 65 years of age or younger patients at risk for hyponatremia: Use 0.83 mcg nightly, which can be increased to one spray of 1.66 mcg after at least 7 days, if needed, provided the serum sodium has remained normal. (2.2)

DOSAGE FORMS AND STRENGTHS

Preservative-free nasal spray delivering 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg desmopressin) or 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg desmopressin) in each spray (0.1 mL). (3)

CONTRAINDICATIONS

- Hyponatremia or a history of hyponatremia (4)
- Polydipsia (4)
- Primary nocturnal enuresis (4)
- Concomitant use with loop diuretics or systemic or inhaled glucocorticoids (4)
- Estimated glomerular filtration rate below 50 mL/min/1.73 m^2 (4)
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) (4)
- During illnesses that can cause fluid or electrolyte imbalance (4)
- New York Heart Association (NYHA) Class II-IV congestive heart failure (4)
- Uncontrolled hypertension (4)

WARNINGS AND PRECAUTIONS

- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure. (5.2)
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved. (5.3)

ADVERSE REACTIONS

Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension / blood pressure increased, back pain, epistaxis, bronchitis and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Monitor serum sodium more frequently when NOCTIVA is concomitantly used with drugs that may cause water retention and increase the risk for hyponatremia (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, nonsteroidal anti-inflammatories, lamotrigine and carbamazepine). (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use of NOCTIVA is not recommended. (8.1)
- Pediatric: Do not use NOCTIVA for primary nocturnal enuresis in children. (4, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: HYPONATREMIA

- **NOCTIVA can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest or death (5.1, 6.1).**
- **NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids (4, 5.1).**
- **Ensure serum sodium concentrations are normal before starting or resuming NOCTIVA. Measure serum sodium within seven days and approximately one month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia (2.3, 5.1).**
- **If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued (5.1).**

1 INDICATIONS AND USAGE

NOCTIVA is indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Nocturnal polyuria was defined in the NOCTIVA clinical trials as night-time urine production exceeding one-third of the 24-hour urine production.

Before starting NOCTIVA:

- Evaluate the patient for possible causes for the nocturia, including excessive fluid intake prior to bedtime, and optimize the treatment of underlying conditions that may be contributing to the nocturia.
- Confirm the diagnosis of nocturnal polyuria with a 24-hour urine collection, if one has not been obtained previously.

Limitation of Use:

NOCTIVA has not been studied in patients less than 50 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration and Priming Instructions

- Only administer NOCTIVA intranasally. Do not shake the bottle.
- Prime NOCTIVA before using for the first time by pumping 5 actuations into the air away from the face.
- Re-prime by pumping 2 actuations into the air if the product has not been used for more than 3 days.
- If a dose is missed, do not double the dose at next use.
- Two sprays of NOCTIVA 0.83 mcg are not interchangeable with one spray of NOCTIVA 1.66 mcg. Prescribe the NOCTIVA nasal spray 1.66 mcg/0.1 mL bottle for patients who are or will be taking the 1.66 mcg dose.

2.2 Recommended Dosage

- **For patients younger than 65 years of age who are not at increased risk for hyponatremia:**
  - The recommended dose is one spray of NOCTIVA 1.66 mcg in either the left or right nostril approximately 30 minutes before going to bed.

- **For patients ≥65 years of age, or younger patients at increased risk for hyponatremia:**
  - The recommended starting dose is one spray of NOCTIVA 0.83 mcg in either the left or right nostril approximately 30 minutes before going to bed.
  - After at least 7 days of treatment, the dose can be increased to 1.66 mcg, if needed, provided the serum sodium is within the normal range during treatment with the 0.83 mcg dose.
  - The 0.83 mcg dose did not meet all prespecified efficacy endpoints in clinical trials but may have a lower risk of hyponatremia *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

2.3 Monitoring of Serum Sodium Concentration

Check serum sodium concentrations:

- Prior to initiating or resuming NOCTIVA or increasing the dose. NOCTIVA is contraindicated in patients with hyponatremia or a history of hyponatremia *[see Contraindications (4)]*.
- Within 7 days and approximately one month after initiating therapy or increasing the dose.
- Periodically during NOCTIVA therapy, as clinically appropriate. More frequent serum sodium monitoring is recommended

for patients 65 years and older and for those at increased risk of hyponatremia.

If the patient develops hyponatremia, NOCTIVA may need to be temporarily or permanently discontinued, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia *[see Warning and Precautions (5.1)*].

3 DOSAGE FORMS AND STRENGTHS

- Preservative-free desmopressin acetate nasal spray.
- Each spray delivers 0.1 mL of NOCTIVA.
- Each spray of the 0.83 mcg/0.1 mL strength of desmopressin acetate contains 0.83 mcg of desmopressin acetate (equivalent to 0.75 mcg of desmopressin).
- Each spray of the 1.66 mcg/0.1 mL strength of desmopressin acetate contains 1.66 mcg of desmopressin acetate (equivalent to 1.5 mcg of desmopressin).

4 CONTRAINDICATIONS

NOCTIVA is contraindicated in patients with the following conditions due to an increased risk of severe hyponatremia:

- Hyponatremia or a history of hyponatremia *[see Warnings and Precautions (5.1)*]
- Polydipsia
- Primary nocturnal enuresis *[see Use in Specific Populations (8.4*)]
- Concomitant use with loop diuretics [*see Warnings and Precautions (5.1)*]
- Concomitant use with systemic or inhaled glucocorticoids [*see Warnings and Precautions (5.1), Drug Interactions (7.1)*]
- Renal impairment with an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 *[see Use in Special Populations (8.6)]*
- Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection

NOCTIVA is contraindicated in patients with the following conditions because fluid retention increases the risk of worsening the underlying condition:

- Congestive heart failure (New York Heart Association Class II to IV) *[see Warnings and Precautions (5.2)]*
- Uncontrolled hypertension

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Hyponatremia

NOCTIVA can cause hyponatremia [*see Boxed Warning and Adverse Reactions (6.1)*]. Severe hyponatremia can be life-threatening if it is not promptly diagnosed and treated, leading to seizures, coma, respiratory arrest or death.

NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as those with excessive fluid intake, those who have illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids *[see Boxed Warning, Contraindications (4), and Clinical Pharmacology (7.1)]*.

Before starting or resuming NOCTIVA, ensure that the serum sodium concentration is normal. Consider the 0.83 mcg dose as the starting dose for patients who may be at risk for hyponatremia [*see Dosage and Administration (2.3, 2.2) and Clinical Studies (14)*].

When NOCTIVA is administered, fluid intake in the evening and night-time hours should be moderated to decrease the risk of hyponatremia. Monitor the serum sodium concentration within seven days and approximately one month of initiating NOCTIVA or increasing the dose, and periodically thereafter. The frequency of serum sodium monitoring should be based on the patient's risk for hyponatremia. For example, more frequent monitoring is recommended for patients 65 years of age or older or those on concomitant medications that can increase the risk of hyponatremia, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine, and thiazide diuretics [*see Drug Interactions (7.2)*].

If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued, and treatment for the hyponatremia instituted, depending on the clinical circumstances, including the duration and severity of the hyponatremia [*see Dosage and Administration (2.3)*].

5.2 Fluid Retention

NOCTIVA can cause fluid retention, which can worsen underlying conditions that are susceptible to volume status. Therefore,

NOCTIVA is contraindicated in patients with New York Heart Association Class II to IV congestive heart failure or uncontrolled hypertension *[see Contradindications (4)]*. In addition, NOCTIVA is not recommended in patients at risk for increased intracranial pressure or those with a history of urinary retention, and should be used with caution (e.g., monitoring of volume status) in patients with New York Heart Association Class I congestive heart failure.

5.3 Concurrent Nasal Conditions

Discontinue NOCTIVA in patients with concurrent nasal conditions that may increase systemic absorption of NOCTIVA (e.g., atrophy of nasal mucosa, and acute or chronic rhinitis), because the increased absorption may increase the risk of hyponatremia. NOCTIVA can be resumed when these conditions resolve.

6 ADVERSE REACTIONS

The following adverse reaction is described elsewhere in the labeling:

- Hyponatremia *[see Boxed Warning and Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized, double-blind, placebo-controlled, multi-center trials conducted in adults 50 years of age and older evaluated the efficacy and safety of NOCTIVA nasal spray compared to placebo. At baseline, 1045 patients treated with NOCTIVA 0.83 mcg or 1.66 mcg, or placebo had nocturia due to nocturnal polyuria, wakening at least 2 times per night to urinate. Nocturnal polyuria was defined as night-time urine production exceeding one-third of the 24-hour urine production. The mean age of the patients studied with nocturia due to nocturnal polyuria was 67 years with 42% between 50 and 64 years of age, and 58% aged 65 years and older. Fifty-seven percent were men and 43% were women. Caucasians comprised 79%, Blacks 12%, Hispanics 6%, and Asians 2% of the trial population.

During these trials, serious adverse reactions were reported in 2%, 2%, and 3% of patients with nocturia due to nocturnal polyuria treated with NOCTIVA 0.83 mcg, NOCTIVA 1.66 mcg, and placebo, respectively. There was one case of hyponatremia in the 1.66 mcg group and one case in the placebo group classified as serious adverse reactions**.**

Adverse Reactions Leading to Discontinuation

Among patients with nocturia due to nocturnal polyuria, the discontinuation rate due to adverse reactions was 4.0% with NOCTIVA 0.83 mcg, 4.4% with NOCTIVA 1.66 mcg, and 2.3% with placebo. Table 1 displays the most common adverse reactions leading to discontinuation in patients with nocturia due to nocturnal polyuria.

Table 1: Most Common Adverse Reactions (≥2 incidences) Leading to Discontinuation in Patients with Nocturia due to Nocturnal Polyuria in Two Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	NOCTIVA 1.66 mcg (N=341)	NOCTIVA 0.83 mcg (N=354)	Placebo (N=349)
Hyponatremia/Blood Sodium Decreased	4 (1.2%)	3 (0.9%)	1 (0.3%)
Nasal Discomfort	2 (0.6%)	0	3 (0.9%)
Nasal Congestion	2 (0.6%)	0	0
Atrial Fibrillation	2 (0.6%)	0	0
Dizziness	0	2 (0.6%)	1 (0.3%)
Dyuria	1 (0.3%)	2 (0.6%)	0

Most Common Adverse Reactions

Table 2 summarizes the most common adverse reactions reported by patients with nocturia due to nocturnal polyuria. This table shows adverse reactions reported in at least 2% of patients treated with NOCTIVA and at a higher incidence with the 1.66 mcg dose than with placebo.

Table 2: Common Adverse Reactions (Reported by ≥2% of NOCTIVA-treated Patients and at a Higher Incidence with the 1.66 mcg Dose than with Placebo) in Two Double-blind, Placebo-Controlled Clinical Trials in Patients with Nocturia due to Nocturnal Polyuria

Adverse Reactions	NOCTIVA 1.66 mcg (N=341)	NOCTIVA 0.83 mcg (N=354)	Placebo (N=349)
Nasal Discomfort	20 (5.9%)	12 (3.4%)	17 (4.9%)
Nasopharyngitis	13 (3.8%)	8 (2.3%)	10 (2.9%)
Nasal Congestion	10 (2.9%)	5 (1.4%)	5 (1.4%)
Sneezing	9 (2.6%)	8 (2.3%)	5 (1.4%)
Hypertension/Blood Pressure Increased	9 (2.6%)	6 (1.7%)	4 (1.1%)
Back Pain	8 (2.3%)	4 (1.1%)	3 (0.9%)
Epistaxis	7 (2.1%)	7 (2.0%)	4 (1.1%)
Bronchitis	7 (2.1%)	3 (0.8%)	3 (0.9%)
Dizziness	6 (1.8%)	7 (2.0%)	5 (1.4%)

No overall changes were observed in the safety profile during the open-label, uncontrolled extension trial with up to 126 weeks of follow-up.

Hyponatremia

Table 3 shows the incidence of serum sodium concentrations below the normal range reported in the two placebo-controlled trials.

Table 3: Hyponatremia in Two, Double-blind, Placebo-controlled Clinical Trials in Patients with Nocturia due to Nocturnal Polyuria

Serum Sodium Concentrations (mmol/L)	NOCTIVA 1.66 mcg (N=341)	NOCTIVA 0.83 mcg (N=354)	Placebo (N=349)
130-134	42 (12.3%)	33 (9.3%)	18 (5.2%)
126-129	7 (2.1%)	8 (2.3%)	0
≤125	5 (1.5%)	0	1 (0.3%)

Of the five patients on NOCTIVA 1.66 mcg with serum sodium ≤ 125 mmol/L, all were 65 years of age or older. Four were men. The onset of the hyponatremia ranged from 6 days to 12 weeks after the start of dosing. Four of these patients were taking a concomitant systemic or inhaled glucocorticoid and three were taking an NSAID.

Sex
The incidence of hyponatremia with NOCTIVA was similar in men and women.

Age
Patients 65 years of age and older treated with NOCTIVA had a higher incidence of hyponatremia compared to those younger than 65 years of age (see Table 4).

Table 4: Hyponatremia, Based on Age, in Two, Double-blind, Placebo-controlled Clinical Trials in Patients with Nocturia due to Nocturnal Polyuria

Serum Sodium Concentrations (mmol/L)	NOCTIVA 1.66 mcg <65 years (N=146)	NOCTIVA 1.66 mcg ≥65 years (N=195)	NOCTIVA 0.83 mcg <65 years (N=148)	NOCTIVA 0.83 mcg ≥65 years (N=206)	Placebo <65 years (N=144)	Placebo ≥65 years (N=205)
130-134	14 (9.6%)	28 (14.4%)	8 (5.4%)	25 (12.1%)	7 (4.9%)	11 (5.4%)
126-129	0	7 (3.6%)	2 (1.4%)	6 (2.9%)	0	0
≤125	0	5 (2.6%)	0	0	0	1 (0.5%)

7 DRUG INTERACTIONS

No specific pharmacokinetic studies were conducted to evaluate potential drug-drug interactions between NOCTIVA and other medications.

7.1 Drugs That May Cause Severe Hyponatremia

Concomitant use of NOCTIVA and loop diuretics or systemic or inhaled glucocorticoids is contraindicated because of the risk of severe hyponatremia *[see Boxed Warning, Contraindications (4), and Warnings and Precautions (5.1)]*. NOCTIVA can be started or resumed three days or five half-lives after the glucocorticoid is discontinued, whichever is longer.

7.2 Drugs That May Cause Water Retention

Monitor serum sodium more frequently in patients taking NOCTIVA concomitantly with medications that may cause water retention and increase the risk for hyponatremia (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opioid analgesics, NSAIDs, lamotrigine and carbamazepine) *[see Warnings and Precautions (5.1)]*.

7.3 Drugs Administered Intranasally

The drug interaction potential between NOCTIVA and other intranasally administered drugs has not been studied. NOCTIVA is not recommended for use in patients who require treatment with other drugs via the nasal route.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary
There are no data with NOCTIVA use in pregnant women to inform any drug-associated risks. No adverse developmental outcomes were observed in animal reproduction studies with administration of desmopressin during organogenesis to pregnant rats and rabbits at doses approximately <1 and 31 times, respectively, the maximum recommended human dose based on nasal surface area (*see Data*).

NOCTIVA is not recommended for the treatment of nocturia in pregnant women. Nocturia is usually related to normal, physiologic changes during pregnancy that do not require treatment with NOCTIVA.

In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Desmopressin acetate did not cause fetal harm in teratology studies in rats and rabbits at doses from 0.05 to 10 mcg/kg/day, which is approximately <1 times (rat) and 31 times (rabbit) the maximum recommended human dose based on nasal surface area.

8.2 Lactation

Desmopressin is present in small amounts in human milk and is poorly absorbed orally by an infant. There is no information on the effects of desmopressin on the breastfed infant or on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for NOCTIVA and any potential adverse effects on the breastfed infant from NOCTIVA or from the underlying maternal condition.

8.4 Pediatric Use

NOCTIVA is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal formulations of demospressin. Studies of NOCTIVA have not been conducted in pediatric patients [*see Contraindications (4*)].

8.5 Geriatric Use

Patients 65 years and older treated with NOCTIVA had a higher incidence of hyponatremia compared to patients less than 65 years old treated with NOCTIVA [*see Dosage and Administration (2.2), Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

8.6 Renal Impairment

Desmopressin is mainly excreted in the urine. The area under the concentration-time curve (AUC) and terminal half-life of desmopressin in renally impaired patients with an eGFR below 50 mL/min/1.73 m^2 is 3- to 4-fold greater than in patients with an GFR above 50 mL/min/1.73 m^2. Therefore, NOCTIVA is contraindicated in patients who have renal impairment with an eGFR below 50 mL/min/1.73 m^2 [*see Contraindications (4) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

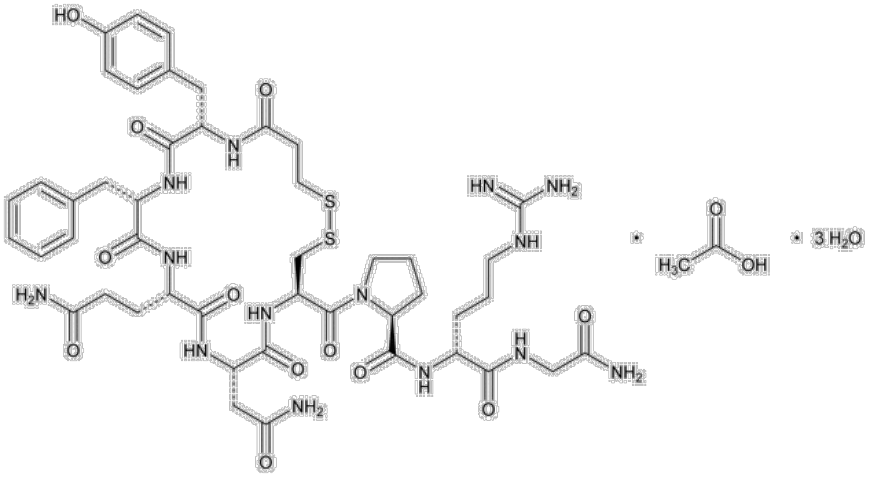
The effect of hepatic impairment on the pharmacokinetics of desmopressin has not been studied.

10 OVERDOSAGE

Signs of overdose may include effects from hyponatremia such as seizure, altered mental status, cardiac arrhythmias and worsening edema. Other signs of overdose may include oliguria and rapid weight gain due to fluid retention *[see Warnings and Precautions (5.1)*]. In case of overdosage, NOCTIVA should be discontinued immediately, serum sodium should be assessed and appropriate medical treatment initiated.

11 DESCRIPTION

Desmopressin acetate is a synthetic analogue of 8-arginine vasopressin, an endogenous pituitary hormone also known as antidiuretic hormone (ADH). Its chemical name is 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate, and its molecular weight is 1183.31. Its molecular formula is $C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$. Its chemical structure is:



Desmopressin acetate is a white powder that is freely soluble in water. It is also soluble in alcohol and glacial acetic acid. NOCTIVA (desmopressin acetate) nasal spray is formulated for intranasal use as a milky white emulsion without preservatives at pH 5.5.

NOCTIVA is available as an oil-in-water emulsion at two dose strengths, 0.83 mcg and 1.66 mcg of desmopressin acetate per spray, for nasal administration. Each spray is 0.1 mL. The dose strengths are expressed as desmopressin acetate and are equivalent to 0.75

mcg and 1.5 mcg of desmopressin free base per spray, respectively. Both formulations also contain the following inactive ingredients: cyclopentadecanolide; cottonseed oil; sorbitan monolaurate; polysorbate 20; citric acid, anhydrous; sodium citrate dihydrate; and water for injection.

After initial priming, each actuation of NOCTIVA 0.83 mcg/0.1 mL or 1.66 mcg/0.1 mL delivers a dose of 0.83 mcg or 1.66 mcg of desmopressin acetate, respectively.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Desmopressin is a synthetic analog of vasopressin. Desmopressin is a selective agonist at V2 receptors on renal cells in the collecting ducts, increasing water re-absorption in the kidneys, and reducing urine production.

12.3 Pharmacokinetics

Absorption

Following nasal spray administration of NOCTIVA, the median time to peak plasma concentrations (Tmax) was 0.25 hour for the 0.83 mcg dose and 0.75 hour for the 1.66 mcg dose. The mean (± S.D.) peak plasma concentration (Cmax) was 4.00 (± 3.85) pg/mL for the 0.83 mcg dose and 9.11 (± 6.90) pg/mL for the 1.66 mcg dose. Plasma NOCTIVA concentrations generally declined below 2 pg/mL (lower limit of quantitation) between four to six hours post-dose.

Elimination

Following an intranasal dose of 1.66 mcg of NOCTIVA, the median apparent terminal half-life ($T_{1/2}$) was 2.8 hours. The distribution of $T_{1/2}$ in patients with an eGFR above 50 mL/min/1.73 m^2 ranged from 1.4-3.8 hours.

Excretion

Desmopressin is mainly excreted in urine.

Specific Populations

Sex and Age

There were no significant differences in systemic exposure (AUC and Cmax) with respect to patient sex or age, among subjects 50 years and older.

Renal Impairment

The pharmacokinetics of NOCTIVA were evaluated in 8 renally impaired patients with an eGFR less than 50 mL/min/1.73 m^2, matched to 8 patients with an eGFR greater than 50 mL/min/1.73 m^2. The AUC and $T_{1/2}$ of desmopressin were approximately 3 to 4 fold higher for the group with eGFR below 50 mL/min/1.73 m^2. Therefore, NOCTIVA is contraindicated in patients who have renal impairment with an eGFR below 50 mL/min/1.73 m^2 [*see Contraindications (4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There have been no long-term studies in animals to assess the carcinogenic, mutagenic or impairment of fertility potential of NOCTIVA nasal spray.

14 CLINICAL STUDIES

The efficacy of NOCTIVA in patients with nocturia due to nocturnal polyuria was established in two 12-week randomized, double-blind, placebo-controlled, multi-center trials in adults at least 50 years of age. At baseline, patients were required to have a six-month history of at least two nocturic episodes per night, on average, and at least 13 documented nocturia episodes over 6 nights during screening. The majority of patients in these trials were Caucasian (79%). The mean age was 67 years (range 50-90 years), 57% were men and 43% were women.

In Trial 1, a total of 612 patients with nocturia due to nocturnal polyuria were randomized to receive either NOCTIVA 1.66 mcg (n=199), NOCTIVA 0.83 mcg (n=209) or placebo (n=204). In Trial 2, a total of 433 patients were randomized to receive NOCTIVA 1.66 mcg (n=143), 0.83 mcg (n=145) or placebo (n=145). In both trials, nocturnal polyuria was defined as a night-time urine production exceeding one-third of the 24-hour urine production confirmed with a 24-hour urine frequency/volume chart.

Each trial had two co-primary efficacy endpoints: (1) The change in mean number of nocturic episodes per night from baseline during the 12-week treatment period, and (2) The percentage of patients who achieved at least a 50% reduction from baseline in the mean number of nocturia episodes per night during the 12-week treatment period.

Secondary efficacy endpoints in both trials included the percentage of nights during the treatment period with no nocturia and the percentage of nights during the treatment period with at most one nocturia episode. Trial 1 included a patient-reported outcome instrument known as the INTU (Impact of Nighttime Urination) questionnaire as the first-ranked secondary efficacy endpoint that

assessed the impacts of nocturia on some aspects of patients' daily lives, with an overall impact score ranging from 0 to 100 points.

Many conditions can cause nocturia. The efficacy and safety of NOCTIVA have not been established for all causes of nocturia. NOCTIVA is indicated only for patients who have nocturia due to nocturnal polyuria. The results for the co-primary efficacy endpoints among patients with nocturia due to nocturnal polyuria are shown in Table 5.

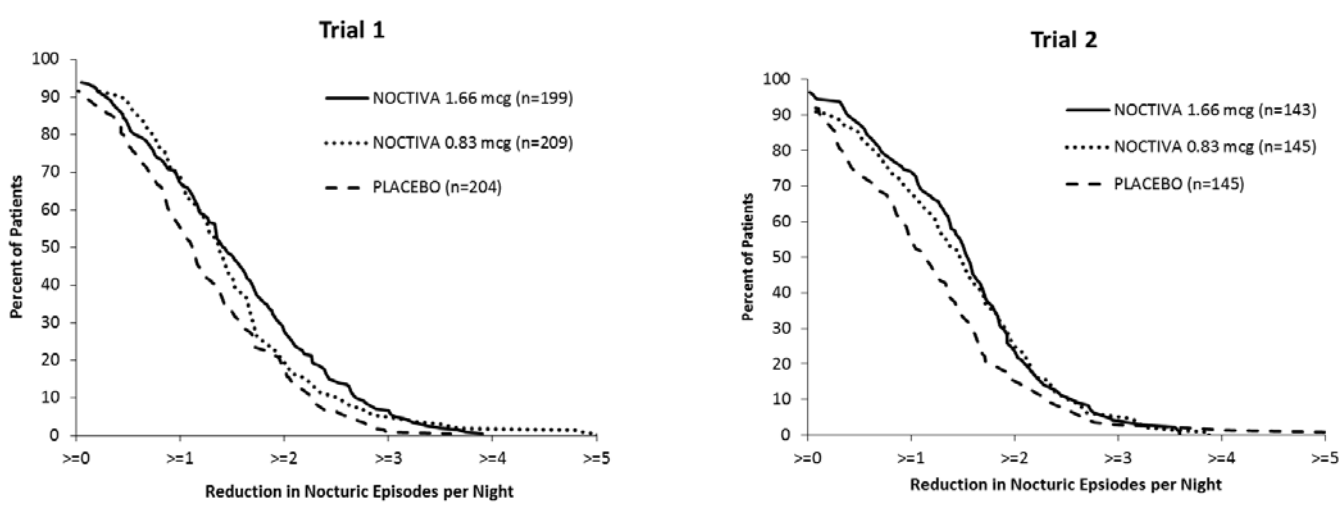
Table 5: Co-Primary Efficacy Endpoints in the Pivotal Trials (Intent-to-Treat Population* with Nocturia Due to Nocturnal Polyuria)

	Trial 1			**Trial 2**		
	NOCTIVA 1.66 mcg (N=199)	**NOCTIVA 0.83 mcg (N=209)**	**Placebo (N=204)**	**NOCTIVA 1.66 mcg (N=143)**	**NOCTIVA 0.83 mcg (N=145)**	**Placebo (N=145)**
Change in Mean Number of Nocturic Episodes Per Night from Baseline						
Baseline (mean)	3.4	3.4	3.2	3.3	3.4	3.4
Change from baseline †	-1.5	-1.5	-1.2	-1.5	-1.4	-1.1
Difference from placebo †	-0.3	-0.3	-	-0.4	-0.3	-
95% CI †	-0.5 to -0.1	-0.4 to 0.0	-	-0.6 to -0.2	-0.5 to -0.1	-
Percentage of Patients Achieving at Least a 50% Reduction in Nocturic Episodes per Night from Baseline						
	47%	35%	27%	49%	41%	29%
Difference from placebo ‡	21%	8%	-	20%	12%	-
95% CI ‡	12% to 30%	-0.4% to 17%		9% to 31%	1% to 23%	

*Intent-to-treat population: all randomized patients who received study drug and had at least three days of post-randomization efficacy data recorded in their diary.
CI: confidence interval
†: obtained from ANCOVA model; ‡ obtained from stratified Cochran-Mantel-Haenszel (CMH) analysis.

Figure 1 shows the percentage of patients in each treatment arm who achieved various reductions from baseline in the mean number of nightly nocturic episodes. In both trials, there was consistent separation between the NOCTIVA 1.66 mcg and placebo curves.

Figure 1: Percentage of Patients Achieving Various Reductions From Baseline in Mean Number of Nightly Nocturic Episodes (Intent-to-Treat Population* with Nocturia Due to Nocturnal Polyuria)



*Intent-to-treat population: all randomized patients who received study drug and had at least three days of post-randomization efficacy data recorded in their diary.

The results for selected secondary efficacy endpoints among patients with nocturia due to nocturnal polyuria are shown in Table 6.

Step 7. Replace the cap on the bottle **(See Figure L)**.

Figure L

Re-priming NOCTIVA

If you do not use NOCTIVA for more than 3 days, you will need to re-prime the bottle before you start using it again.
If you miss a dose, take the next dose at your regular time. Do not take 2 doses at the same time.

To re-prime your bottle of NOCTIVA, hold the bottle upright and away from your face. Completely press (pump) the nasal applicator 2 times. Your NOCTIVA is now ready to use.

Storage:

- **Before opening**, store NOCTIVA upright in a refrigerator between 36°F to 46°F (2°C to 8°C).
- **After opening**, store NOCTIVA upright at room temperature between 68ºF to 77ºF (20ºC to 25ºC). Throw away (discard) NOCTIVA 60 days after opening. Write the date the bottle is opened on the bottle label.

Keep NOCTIVA and all medicines out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by: Renaissance Lakewood, LLC for Serenity
Renaissance Lakewood, LLC
Lakewood, NJ, U.S.A.
Serenity Pharmaceuticals, LLC
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