PRODUCT MONOGRAPH

[Pr] NU-DESMOPRESSIN Spray, 10 µg/spray

(Desmopressin Acetate Nasal Solution)

ANTIDIURETIC

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intranasal	Spray 10 µg/metered dose	benzalkonium chloride 0.01% as a preservative, citric acid, sodium chloride, sodium phosphate dibasic and purified water

INDICATIONS AND CLINICAL USE

Diabetes Insipidus

NU-DESMOPRESSIN (desmopressin acetate) is indicated for the management of vasopressin sensitive central diabetes insipidus and for the control of temporary polyuria and polydipsia following head trauma, hypophysectomy or surgery in the pituitary region.

CONTRAINDICATIONS

- Hypersensitivity to desmopressin acetate or to any of the constituents.
- Type IIB or platelet-type (pseudo) von Willebrand's disease.
- Habitual or psychogenic polydipsia.
- Cardiac insufficiency or other conditions requiring treatment with diuretics.
- Moderate or severe renal insufficiency.
- Known hyponatremia.
- Primary Nocturnal Enuresis (PNE).

Worldwide post-marketing data indicate a higher incidence of hyponatremia in patients being treated with the desmopressin intranasal formulations compared to the oral formulations (Desmopressin Tablet). Since safer formulations are available, intranasal formulations are contraindicated for use in primary nocturnal enuresis.

WARNINGS AND PRECAUTIONS

Hyponatremia is the most important adverse event reported for desmopressin, resulting from water retention caused by the potent antidiuretic effect of desmopressin. Desmopressin may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated, hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

For intranasal use only. Desmopressin is not effective in controlling polyuria caused by renal disease, nephrogenic diabetes insipidus, psychogenic diabetes insipidus, hypokalemia or hypercalcemia.

Fluid intake or desmopressin dosage should be adjusted in order to reduce the possibility of water retention and hyponatremia especially in very young and elderly patients or when significant daily variables occur such as hot climate conditions, intense exercise or other situations where increased water intake can be expected (see Dosage and Administration). Particular attention should be paid to the risk of an extreme decrease in plasma osmolality and resulting seizures in young children. Should prodromal symptoms (headache, nausea and vomiting) which may herald impending hyponatraemia occur, treatment should be discontinued immediately and the patient should seek medical assessment.

Changes in the nasal mucosa resulting from rhinitis, scarring, edema or other disease may cause erratic, unreliable absorption in which case intranasal desmopressin should not be used. In the case of temporary rhinitis, consideration should be given to using an injectable form of desmopressin, until the nasal mucosa returns to normal.

General

Desmopressin at high dosage (40 μg or more) has very occasionally produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible tachycardia and changes in blood pressure.

In the control of diabetes insipidus, the lowest effective dose should be used and the effective dosage, as determined by urine volume and osmolality and, in some cases, plasma osmolality, should be assessed periodically.

Desmopressin should not be administered to dehydrated patients until water balance has been adequately restored.

Desmopressin should be used with caution in patients with conditions associated with fluid and electrolyte imbalance such as cystic fibrosis, heart failure and renal disorders because these patients are prone to hyponatremia. Desmopressin should also be used with caution in patients at risk for increased intracranial pressure.

Children and geriatric patients should be closely observed for possible water retention due to over-ingestion of fluids. When fluid intake is not excessive, there is little danger of water intoxication and hyponatremia with the usual intranasal doses of desmopressin used to control diabetes insipidus. Fluid intake should be carefully adjusted to prevent overhydration.

There are reports of changes in response over time, usually when the drug has been administered for periods longer than 6 months. Some patients may show decreased responsiveness, others a shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to local inactivation of the peptide.

There is some evidence from post-marketing data for the occurrence of severe hyponatremia in association with the nasal spray formulation of desmopressin, when it is used in the treatment of cranial diabetes insipidus.

Special Populations

Pregnant Women

Reproductive studies performed in rats and rabbits have revealed no evidence of harm to the fetus by desmopressin. The use of desmopressin in pregnant women with no harm to the fetus has been reported. However, no controlled studies in pregnant women have been carried out.

One investigator has reported three cases of malformations in children born to mothers suffering from diabetes insipidus and receiving desmopressin during pregnancy. However, several other published reports comprising more than 120 cases showed that women treated with desmopressin during pregnancy have given birth to normal children. Furthermore, a review of a very large data set identifying 29 children who were exposed to desmopressin during the entire pregnancy showed no increase in the malformation rate in the children born. Unlike preparations containing the natural hormone, desmopressin in antidiuretic doses has no uterotonic action, but the physician should weigh possible therapeutic advantages against potential risks in each case.

Nursing Women

There have been no controlled studies in nursing mothers. A single study on a post-partum woman demonstrated a marked change in maternal plasma desmopressin level following an intranasal dose of 10 μg, but little desmopressin was detectable in breast milk.

Pediatrics

Desmopressin has been used in children with diabetes insipidus. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease of plasma osmolality with resulting convulsions. Dosage in infants younger than 3 months has not been established. Dose should start at 5 μg or less. Use of desmopressin in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication.

Geriatrics

Older patients may be more sensitive to the antidiuretic effect of the usual adult dose of desmopressin. Patients over the age of 65 should be closely observed for possible water retention due to overingestion of fluids. Fluid intake should be carefully adjusted to prevent over-hydration.

Monitoring and Laboratory Tests

Diagnosis of Central Diabetes Insipidus

Central diabetes insipidus may be demonstrated by the inability to produce urine of osmolality above 175 mOsm/kg with dehydration severe enough to cause a loss of greater than 2% of body weight.

Patients are selected for therapy by establishing a diagnosis by means of a water deprivation test, the hypertonic saline infusion test, and/or response to 5 units arginine vasopressin given s.c. after dehydration. Continued response to desmopressin can be monitored by urine volume and osmolality. In cases of severe dehydration, plasma osmolality determination may be required.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Infrequently, high doses of desmopressin have produced transient headache and nausea. Nasal congestion, rhinitis, flushing, and mild abdominal cramps have been reported. These symptoms disappeared with reduction in dosage. Side effects reported from controlled clinical trials involving 638 subjects included headache (2%), rhinitis (1%), nasal discomfort (1%), epistaxis (1%) and abdominal pain (1%). Other effects, reported at a frequency of less than 1%, included dizziness, chills, wheezing, rash, edema of face and hands, nausea, constipation, anorexia, increased appetite, conjunctivitis and after taste in the mouth. These symptoms disappeared with reduction of dosage or withdrawal of drug. Adverse effects rarely necessitated discontinuance of the drug.

Treatment without concomitant reduction of fluid intake may lead to water retention/hyponatremia with accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain, and in serious cases, convulsions.

Very rare cases of emotional disturbances in children have been reported. Isolated cases of allergic skin reactions and more serious general allergic reactions have been reported.

Post-Market Adverse Drug Reactions

Hyponatremia has been reported at an approximate rate of 5 cases per 10 million doses from worldwide post marketing experience in patients treated with desmopressin intranasal formulations. The reported rate for desmopressin oral formulations worldwide is considerably less at about 1 case per 10 million doses. Patients are recommended to take the oral formulations (e.g., Desmopressin Tablet) which are available for children with PNE. Desmopressin is a potent antidiuretic, which may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated, hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

DRUG INTERACTIONS

Overview

Clofibrate, chlorpropamide and carbamazepine may potentiate the antidiuretic activity of desmopressin leading to an increased risk of water retention/hyponatremia, while demeclocycline, lithium and norepinephrine may decrease its activity. Indomethacin increases the urine concentrating effect of desmopressin without influencing the duration. The effect is probably without any clinical significance. Although the pressor activity of desmopressin is very low compared with the antidiuretic activity, use of large doses of desmopressin with other pressor agents should be done only with careful patient monitoring. The selective serotonin reuptake inhibitors (SSRIs, venlafaxine and citalopram), and the neuroleptic risperidone have been associated with water intoxication and hyponatremia in rare cases.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus

Central diabetes insipidus may be demonstrated by the inability to produce urine of osmolality above 175 mOsm/kg with dehydration severe enough to cause a loss of greater than 2% of body weight (see Laboratory Tests).

Dosing Considerations

Dosage must be individualized but clinical experience has shown that the average daily dose for adults is 10 μg to 40 μg NU-DESMOPRESSIN and for children 3 months to 12 years of age, 5 μg to 30 μg. This may be given as a single dose or divided into two or three doses. About one third of patients can be treated with a single daily dose. Geriatric patients may be more sensitive to the antidiuretic effect of the usual adult dose of NU-DESMOPRESSIN.

Dosage in children with central diabetes insipidus up to 3 months of age has not been established.

NU-DESMOPRESSIN Spray is not indicated for use in children with Primary Nocturnal Enuresis (PNE).

Dosage

Children (3 months to 12 years)

The usual dose range is 5 μg to 30 μg daily either as a single dose or divided into two doses. About 1/3 of patients can be controlled by a single daily dose of NU-DESMOPRESSIN administered intransally.

NU-DESMOPRESSIN Spray pump can only deliver 0.1 ml (10 μg) or multiples of 0.1 ml. In some patients, better control of polyuria is attained with smaller doses given at 6 to 8 hour intervals.

NU-DESMOPRESSIN Spray should be used in children who only require a single dose of 10 μg or more. The spray pump must be primed prior to use. To prime pump, press down four times. The bottle will now deliver 10 μg of drug.

Adult

Average daily dose is 10 μg to 40 μg. Most adults require 20 μg daily, administered in two divided doses (in the morning and the evening). Initially, therapy should be directed to control nocturia with a single evening dose. Response to therapy can be measured by the volume and frequency of urination and duration of uninterrupted sleep. The dosage of desmopressin should be adjusted according to the diurnal pattern of response, with the morning and evening doses being adjusted separately. Patients being switched from parenteral to intranasal administration generally require 10 times their maintenance intravenous dose intranasally.

In order to minimize the risk of hyponatremia, the following should be considered a part of individualized dosage titration;

- Desmopressin should be given with caution and the dosage adjusted as necessary during acute illness, febrile episodes, hot days and other conditions with increased water intake.

To institute therapy with NU-DESMOPRESSIN, patients should be withdrawn from previous medication and allowed to establish a baseline polyuria to permit determination of the magnitude and duration of the response to medication. In less severe cases, prior water loading may be desirable to establish a vigorous flow of urine. When the urine osmolality reaches a plateau at low level (in most cases, less than 100 mOsm/kg), the first dose of desmopressin (10 μg) is administered intranasally. A urine sample is obtained after two hours and hourly thereafter following desmopressin administration. Urine volume and osmolality are measured. When the patient has reached the previous baseline urine osmolality and urine flow, the drug effect has ceased and the next dose of desmopressin is administered. The cycle is then repeated until the patient has reached a stable condition.

In the event of signs of water retention/hyponatremia, treatment should be interrupted and the dose should be adjusted.

OVERDOSAGE

Overdose symptoms include headaches, abdominal cramps, nausea, and facial flushing. There is no known antidote. However, the following general recommendations can be provided. Asymptomatic hyponatremia is treated by discontinuing the desmopressin treatment and fluid restriction. Infusion of isotonic or hypertonic sodium chloride may be added in cases with symptoms. When the water retention is severe (convulsions and unconsciousness) treatment with furosemide should be added.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Desmopressin is a synthetic structural analogue of the antidiuretic hormone, arginine vasopressin, which alters the permeability of the renal tubule to increase resorption of water. The increase in the permeability of both the distal tubules and collecting ducts appears to be mediated by a stimulation of the adenylcyclase activity in the renal tubules.

Approximately 10 to 20% of the dose of desmopressin solution administered intranasally is absorbed through the nasal mucosa. Antidiuretic effects occur within 1 hour, peak in 1 to 5 hours, persist for 8 to 20 hours and then abruptly end over a period of 60 to 90 minutes. Duration of action varies greatly among individuals and is dependent upon the rate of absorption from the nasal mucosa, persistence in plasma, and effect on renal tubules.

Pharmacodynamics

Maximum urine concentration was studied in 10 healthy adults (24 to 37 years of age) after administration of 20, 40 and 80 µg desmopressin intranasally with one week between each administration. Maximum effect on urine osmolality occurred between 3 and 5 hours (Figure 1), and the 20 µg dose was as effective as the higher doses. There were no side effects and mean body weight increase during the 24 hours after desmopressin administration did not exceed 0.5 kg after any dose.

The use of desmopressin in patients with an established diagnosis of central diabetes insipidus will result in a reduction in urinary output with concomitant increase in urine osmolality and decrease in plasma osmolality. This will allow the resumption of a more normal lifestyle with a decrease in urinary frequency.

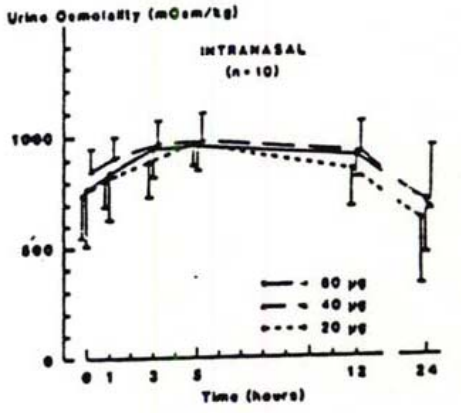


Figure 1

Urine osmolality after various doses of DDAVP given intranasaly (mean ± SD).

Desmopressin does not directly affect urinary sodium or potassium excretion, or serum sodium, potassium, or creatinine concentrations. Desmopressin does not stimulate uterine contractions, adrenocorticotropic hormone release or increase plasma cortisol concentrations. In children, intranasal administration of desmopressin has no effect on growth hormone, prolactin, or luteinizing hormone concentration. Intranasal doses of 20 μg of desmopressin have no effect on blood pressure or pulse rate, but mean arterial pressure may increase as much as 15 mm Hg with doses of 40 μg or more.

Pharmacokinetics

Absorption:

Following intranasal administration of desmopressin, approximately 10-20% of a dose is absorbed through the nasal mucosa. Patients with nasal congestion may require an increased dosage. Following intranasal administration of usual doses of in patients with neurohypophyseal diabetes insipidus, antidiuretic effects occur within 1 hour, peak in 1-5 hours, persist for 8-20 hours, and then abruptly end over a period of 60-90 minutes. Duration of action varies among individuals with a specific dose. The relatively prolonged duration of action of desmopressin may result from slower enzymatic inactivation of desmopressin than vasopressin or from sequestration of desmopressin in a membrane compartment.

Distribution:

The distribution of desmopressin has not been fully characterized. It is not known if desmopressin crosses the placenta. Some of the drug may be distributed into breast milk.

Excretion:

In contrast to the elimination of desmopressin after intravenous injection, which is bi-exponential with a rapid first phase and slower second phase half-life of 7.8 minutes and 75.5-103 minutes, respectively, the disappearance of desmopressin from plasma after intranasal administration follows an exponential time course with half-lives ranging between 0.4 to 4 hours after intranasal application.

The metabolic fate of desmopressin is unknown. Unlike vasopressin, desmopressin apparently is not degraded by aminopeptidases or other peptidases that cleave oxytocin and endogenous vasopressin in the plasma during late pregnancy.

STORAGE AND STABILITY

NU-DESMOPRESSIN Spray: Store at room temperature 15-30°C (59-86°F). Protect from light. Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NU-DESMOPRESSIN Spray (desmopressin acetate nasal solution) 10 µg/spray is available as a pre-compression metered dose spray pump. Each depression delivers 10 µg of desmopressin acetate.

Each mL of NU-DESMOPRESSIN Spray (desmopressin acetate nasal solution) contains 0.1 mg of desmopressin acetate in a buffered, isotonic, aqueous solution. Available in bottles of 2.5 mL (25 sprays) and 5.0 mL (50 sprays).

In addition to the active ingredient, desmopressin acetate, it also contains the non-medicinal ingredients: benzalkonium chloride 0.01% as a preservative, citric acid, sodium chloride, sodium phosphate dibasic and purified water.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

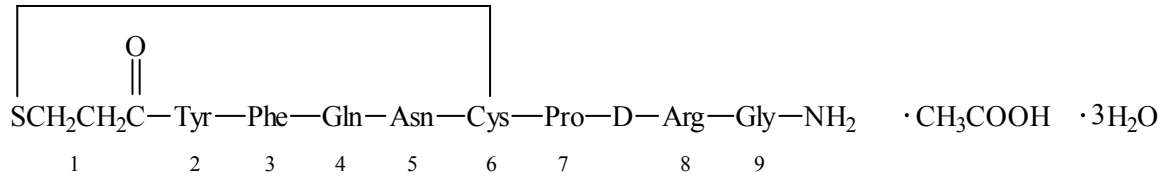
Common Name: Desmopressin Acetate

Chemical Name(s):

1) Vasopressin, 1-(3-mercaptopropanoic acid)-8-D-arginine-, monoacetate (salt), trihydrate

2) 1-(3-Mercaptopropionic acid)-8-D-arginine-vasopressin monoacetate (salt) trihydrate

Structural Formula:



Molecular Formula: $C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$

Molecular Weight: 1183.34

Description: Desmopressin acetate is a white, fluffy powder. It is soluble in water, ethanol (96%) and glacial acetic acid to a level of 34 mg/mL of solvent. An aqueous solution of 1 mg/mL at 24°C has a pH of 4.8.

Melting Point: Not applicable (compound may decompose upon heating).

Specific Rotation: $[\alpha]^{20}$, C=0.2

1% acetic acid: -77º ± 5º

CLINICAL TRIALS

DIABETES INSIPIDUS

Central diabetes insipidus (CDI), characterized by polyuria and compensatory polydipsia, results from a lack of natural antidiuretic hormone (AVP). Desmopressin administered to CDI patients compensates for the lack of AVP by altering kidney tubule permeability resulting in resorption of water.

Seven patients with previously untreated hereditary, hypothalamic diabetes insipidus self-administered desmopressin intranasally (Table 1). Mean urine volume during desmopressin therapy was 1.77 litres/24 hours, compared to a mean 7.11 litres/24 hours prior to treatment. All patients maintained normal values of Hb concentration, hematocrit, WBC, differential count, and serum concentrations of sodium, potassium, calcium and creatinine. Creatinine clearances were within normal limits, as were the morning levels of plasma cortisol. All showed a normal response to ACTH. Protein-bound iodine and I-tests were normal as were determinations of 17-keto and 17-hydroxy steroids. X-ray examination of femurs and humeri, with respect to fluorosis, revealed no abnormalities. There were no reported or observed side effects.

Table 1: Daily Urine Volumes Before, During, and Immediately After Withdrawal of Therapy with Desmopressin Intranasally, According to Measurements Performed by the Patients at Home (Mean of Determinations on 3 Days)

Pat. No.	Sex	Age (Yr)	Before Treatment (1/24h)	Desmopressin Dose (µg)	During Treatment (1/24h)	Treatment Withdrawn (1/24h)
1	M	38	15.2	20 × 2	2.2	21.2
2	M	42	7.4	10 × 2	2.1	11.0
3	M	44	6.6	20 × 2	2.0	16.2
4	F	40	6.6	5 × 2	1.9	10.5
5	M	56	5.0	10 × 2	1.9	8.1
6	F	22	3.5	5 × 2	1.7	5.6
7	F	72	2.5	No treatment	No treatment	No treatment
8	F	6	3.0	3 × 2	0.6	4.5

TOXICOLOGY

ACUTE TOXICITY

The acute toxicity of desmopressin is very low (Table 2). Mice tolerate i.v. doses of 2 mg/kg. At i.v. doses of 30 µg/kg in rats and 50 µg/kg in rabbits, only transient changes in clinical behaviour were observed. Intravenous doses up to 24 µg/kg in dogs did not produce any cardiovascular changes.

Table 2: Acute Toxicity of Desmopressin				
Species	**Number**	**LD_{50} Dose**	**Route**	**Reference**
Mice	10 (both sexes)	2 mg/kg	i.v.	17
Rats	12 (both sexes)	30 µg/kg	i.v.	3
Rabbits	6 (both sexes)	50 µg/kg	i.v.	4
Dogs	5 males	24 µg/kg	i.v.	5

SUBACUTE TOXICITY

Results from 14-day studies show that the drug given intravenously to rats at 18 µg/kg/day and to rabbits at 6 µg/kg/day caused no biologically significant changes in hematological and clinical chemistry parameters.

Rats which received 5 mg/kg/day subcutaneously for 3 weeks did not show any significant changes in weight, blood count, or organ changes.

CHRONIC TOXICITY

Subcutaneous Administration

Rat Studies: In a controlled 8-week experiment 20 rats received 2 µg/kg/day subcutaneous desmopressin. No increase in blood glucose or morphological or histological pancreatic changes occurred.

Rats (20 per group) which received desmopressin doses of 5, 50 or 500 ng/kg/day for 6 months did not show any significant changes in weight, blood values, or levels of transaminases. The weight of heart, lungs, and kidneys decreased in female animals in the lower dose groups but not in the higher ones. In the male animals, a decrease in non-esterifiable fatty acids was noted.

Dog Subcutaneous Studies: Dogs (3 per group) which received subcutaneous doses of 10 and 100 ng/kg/day desmopressin for 6 months did not show any significant changes in comparison with control groups in blood sugar or transaminases and did not show histological or morphological organ changes.

Reproduction Studies: In teratogenicity testing in Wistar rats, no teratologic or embryotoxic effects were observed in 369 fetuses from 40 females dosed with up to 50 ng/kg/day desmopressin acetate subcutaneously on Day 1 through Day 20 of gestation.

In a study of 78 Dutch belted rabbits which received subcutaneous desmopressin up to 10 µg/kg/day on Day 6 through Day 18 of pregnancy, no teratogenic or embryotoxic effects were observed in 296 fetuses. Weaning was unaffected.

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PART III: CONSUMER INFORMATION

Pr NU-DESMOPRESSIN Spray, 10 µg/spray

(Desmopressin Acetate Nasal Solution)

This leaflet is part III of a three-part "Product Monograph" published when NU-DESMOPRESSIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about NU-DESMOPRESSIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
NU-DESMOPRESSIN Spray is used to prevent or control the frequent urination, extreme thirst, and loss of water associated with *Diabetes Insipidus (water diabetes),* following head trauma and surgery in the pituitary gland.

Diabetes Insipidus (DI) is a medical condition in which your kidneys are unable to retain water. This results in the production of large volumes of urine which in turn makes you feel dry and very thirsty.

It is important to point out that DI is **not** related to the type of diabetes most people have heard of, Diabetes Mellitus (sugar diabetes).

In DI, there is no problem with the sugar in the blood or urine.

What it does:
NU-DESMOPRESSIN Spray contains desmopressin, an antidiuretic hormone. NU-DESMOPRESSIN Spray reduces the amount of urine that the body makes, thereby reducing symptoms of DI such as thirst and passing a lot of urine.

When it should not be used:
Do not take NU-DESMOPRESSIN Spray if any of the following conditions applies to you or your child:
- Allergic reaction to desmopressin acetate or any of the other ingredients in NU-DESMOPRESSIN Spray
- Bleeding problems such as Type II B or platelet-type (pseudo) von Willebrand's disease
- Excess fluid consumption
- Heart failure or other conditions requiring treatment with diuretics (water pills)
- Kidney problems or failure
- Hyponatremia (low blood sodium levels)
- Primary nocturnal enuresis (bedwetting)

What the medicinal ingredient is:
Desmopressin acetate.

What the nonmedicinal ingredients are:

The nonmedicinal ingredients are:

benzalkonium chloride 0.01% as a preservative, citric acid, sodium chloride, sodium phosphate dibasic and purified water

What dosage forms it comes in:

NU-DESMOPRESSIN Spray (desmopressin acetate nasal solution) 10 µg/spray is available as a pre-compression metered dose spray pump. Each depression delivers 10 µg of desmopressin acetate. Available in bottles of 2.5 mL (25 sprays) and 5.0 mL (50 sprays).

WARNINGS AND PRECAUTIONS

BEFORE you use NU-DESMOPRESSIN Spray talk to your doctor or pharmacist if you are:
- Breast-feeding
- Pregnant or think you might be pregnant

And/or if you have:
- hyponatremia (low blood sodium level)
- heart problems
- liver disease
- kidney problems
- bleeding problems
- fever
- cystic fibrosis
- any allergies to desmopressin acetate or any of the ingredients listed in "What the nonmedicinal ingredients are"

Before you commence treatment with this medicine, you should receive appropriate advice concerning fluid intake from your doctor. Excessive fluid intake may lead to a build up of water in the body resulting in water intoxication and hyponatremia. Talk to your doctor if you develop conditions associated with fluid and electrolyte imbalance, such as infections, gastroenteritis, diarrhea and vomiting because these patients are prone to hyponatremia.

NU-DESMOPRESSIN Spray should not be given to dehydrated patients until water balance is adequately

restored. Talk to your doctor before stopping or interrupting treatment with NU-DESMOPRESSIN Spray.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with NU-DESMOPRESSIN Spray include:

- Tricyclic antidepressants (amitriptyline, nortriptyline)
- Serotonin reuptake inhibitors (for example, fluoxetine or Prozac®, paroxetine or Paxil®, sertraline or Zoloft®, fluvoxamine or Luvox®, citalopram or Celexa®,venlafaxine or Effexor® XR, and risperidone or Risperdal®)
- Nonsteroidal anti-inflammatory drugs (NSAIDs such as etodolac or Ultradol®, ibuprofen or Advil® or Motrin®, naproxen or Naprosyn® ; celecoxib or Celebrex®)
- Chlorpromazine
- Carbamazepine
- Diuretics (water pills)
- Loperamide or Imodium®
- Clofibrate
- Chlorpropamide
- Demeclocyclin
- Lithium
- Norepinephrine

If you are taking any of these drugs, please talk to your doctor or pharmacist before taking NU-DESMOPRESSIN Spray.

PROPER USE OF THIS MEDICATION

How to Take NU-DESMOPRESSIN Spray:

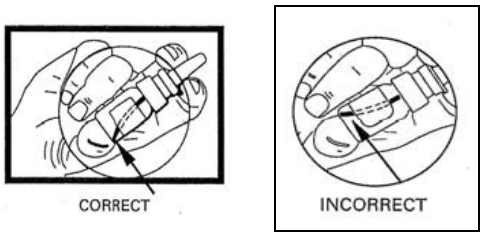
NU-DESMOPRESSIN Spray does NOT work like other nasal sprays. **It is NOT supposed to be sniffed like cold or allergy sprays.** If it is sniffed up the nose, it will not work. The spray ONLY works when it is absorbed inside the nose.

Getting ready to use NU-DESMOPRESSIN Spray:

Gently blow the nose. If the nose is blocked because of a cold or allergies, NU-DESMOPRESSIN may not work as well.

Using Your NU-DESMOPRESSIN Spray:

1. Do NOT shake the bottle.
2. Remove protective cap.
3. **The spray pump must be primed prior to the first use.**
   To prime pump, press down 4 times.
4. Once primed, the spray pump delivers 10 micrograms of medication each time it is pressed. To ensure dosing accuracy, tilt bottle so that dip tube inside the bottle draws from the deepest portion of the medication.



   To administer one 10-microgram dose, place the spray nozzle in nostril and press the spray pump once. If a higher dose has been prescribed, spray half the dose in each nostril. The spray pump cannot be used for doses less than 10 micrograms or doses other than multiples of 10 micrograms.
5. Replace the protective cap on bottle after use. The pump will stay primed for up to one week. If the product has not been used for a period of one week, re-prime the pump by pressing once.

Using NU-DESMOPRESSIN Spray for your child:

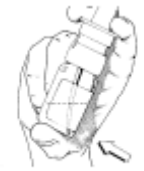
NU-DESMOPRESSIN Spray should only be used in children who require a dose of 10 µg NU-DESMOPRESSIN Spray taken 1, 2 or 3 times daily.

Ask your child to gently blow his/her nose. If the nose is blocked because of a cold or allergies, NU-DESMOPRESSIN Spray may not work as well.

1. Do NOT shake the bottle.
2. Remove protective cap.
3. The spray pump must be primed prior to the first use. To prime pump, press down 4 times.

4. Once primed, the spray pump delivers 10 micrograms of medication each time it is pressed. To ensure dosing accuracy, tilt bottle so that dip tube inside the bottle draws from the deepest portion of the medication.

5. Always keep the bottle upright so the tube stays in the liquid and no air gets inside the tube. If an air bubble forms, the right amount of spray will not come out.



6. Tilt the child's head back a little bit and insert the nozzle into one nostril. Ask the child to take a deep breath in and hold his/her breath only while you spray NU-DESMOPRESSIN Spray into the nostril. For each spray, press down firmly on the white collar using your index and middle fingers. Support the base of the bottle with your thumb.

7. Remove the nozzle from the child's nostril.

8. Have your child place one finger on the outside of the nostril you just sprayed.

9. Slowly count to 10 out loud. As you count, the child should hold the nostril closed so the spray will not drip out.

10. When you reach 10, the child can release the finger and breathe normally.

11. Replace the protective cap on bottle after use. The pump will stay primed for up to one week. If the product has not been used for a period of one week, re-prime the pump by pressing once.

Usual Dose

Take the medication only as directed by your doctor.

The doctor will prescribe the dose most suitable for you or your child. The most commonly used doses are:

Children (3 months to 12 years)

5–30 μg daily given as a single dose or divided into two or three doses.

Adults:

10-40 μg daily given as a single evening dose or divided into two or three doses.

Overdose:

If you or your child take too much of the medication, you should immediately contact your doctor and/or the emergency room of the nearest hospital and the local poison center. Symptoms of overdose may include headache, nausea, vomiting, abdominal cramps, facial flushing and weight gain due to water retention and, in severe cases, convulsions.

Missed dose:

If you miss a dose of NU-DESMOPRESSIN Spray, take the missed dose as soon as possible. Then go back to your regular dosing schedule. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects may be experienced. With NU-DESMOPRESSIN Spray, these may include:

Common Side Effects
Headache, nausea, mild abdominal pain, cramps or discomfort, stuffy nose, nasal irritation, facial flushing and nose bleed.

Uncommon Side Effects
Dizziness, feeling cold, wheezing, rash, swelling in the face and hands, constipation, anorexia (obsession with thinness generally sought through self-starvation), increased appetite (excessive desire for

food), conjunctivitis (pink eye or red eye) and an aftertaste in the mouth.

Rare Side Effects
Emotional problems in children and allergic skin reactions.

These have occurred usually when the medication is being adjusted. Once you are taking the right amount of medicine for your condition, these side effects will usually go away. Tell your doctor about any side effects you experience.

Excessive fluid intake may lead to a build up of water which dilutes the salt in the body in severe cases. This can become a serious problem and may lead to convulsions. Early symptoms may include an unusually bad or prolonged headache, confusion, unexplained weight gain, nausea and vomiting. If you experience one or more of these symptoms, stop taking this medicine. Tell your doctor immediately or go to the nearest emergency hospital.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	hyponatremia (low blood sodium level)		*	*
Very Rare	allergic reaction		*	*

This is not a complete list of side effects. For any unexpected effects while taking NU-DESMOPRESSIN Spray, contact your doctor or pharmacist.

HOW TO STORE IT

NU-DESMOPRESSIN Spray should be stored at room temperature, 15-30º C (59-86º F).

Protect from light. Do not freeze.

IMPORTANT: Always keep the bottle upright and store in an upright position.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health product to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free to 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you should require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Nu-Pharm Inc. at:

1-800-267-1438

This leaflet was prepared by Nu-Pharm Inc.
Richmond Hill, Ontario L4B 1E4.

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