

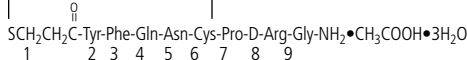
CSL Behring
Stimate®
 (desmopressin acetate)
 Nasal Spray, 1.5 mg/mL

Rx only

DESCRIPTION

Stimate® (desmopressin acetate) Nasal Spray is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. **Stimate® Nasal Spray** contains 1.5 mg/mL desmopressin acetate in a pH-adjusted aqueous solution with chlorobutanol and sodium chloride as inactive ingredients. **Stimate® Nasal Spray's** compression pump delivers 0.1 mL (150 mcg) of solution per spray. It is chemically defined as follows:

Mol. Wt. 1183.34 Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$



1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.

Stimate® Nasal Spray is provided as an aqueous solution for intranasal use.

Each mL contains:

Desmopressin acetate	1.5 mg
Chlorobutanol	5.0 mg
Sodium Chloride	9.0 mg
Hydrochloric acid to adjust pH to approximately 4	

CLINICAL PHARMACOLOGY

Stimate® Nasal Spray contains as active substance, desmopressin acetate, which is a synthetic analogue of the natural hormone arginine vasopressin. One spray or 0.1 mL (150 mcg) of **Stimate® Nasal Spray** solution has an antidiuretic activity of about 600 IU.

Desmopressin acetate has been shown to be more potent than arginine vasopressin in increasing plasma levels of Factor VIII activity in patients with hemophilia and von Willebrand's disease Type I. Dose-response studies were performed in healthy persons using doses of 150 to 450 mcg, administered as one to three sprays. The response to **Stimate® Nasal Spray** is dose-related, with maximal plasma levels of 150 to 250 percent of initial concentrations achieved for both Factor VIII and von Willebrand factor. The increase is rapid and evident within 30 minutes, reaching a maximum at about 1.5 hours.¹

The percentage increase of Factor VIII and von Willebrand factor levels in patients with mild hemophilia A and von Willebrand's disease was not notably different from that observed in normal healthy individuals when treated with 300 mcg of **Stimate® Nasal Spray**.^{1,4} In patients with von Willebrand's disease, levels of Factor VIII coagulant activity and von Willebrand factor antigen remained greater than 30 U/dL for 8 hours after a 300 mcg dose of **Stimate® Nasal Spray**.² After 300 mcg of **Stimate® Nasal Spray**, the percentage increase of Factor VIII and von Willebrand factor levels in patients with mild hemophilia A and von Willebrand's disease was less than observed after 0.3 mcg/kg of intravenous desmopressin acetate.^{2,4}

Plasminogen activator activity increases rapidly after intravenous desmopressin acetate infusion, but there has been no clinically significant fibrinolysis in patients treated with desmopressin acetate.

The effect of repeated intravenous desmopressin acetate administration when doses were given every 12 to 24 hours has generally shown a diminution of the Factor VIII activity increase noted after a single dose. It is possible to reproduce the initial response in some patients after an interval of one week, but other patients may require as long as 6 weeks.^{2,4,6}

The half-life of **Stimate® Nasal Spray** was between 3.3 and 3.5 hours, over the range of intranasal doses, 150 to 450 mcg.¹ Plasma concentrations of **Stimate® Nasal Spray** were maximal approximately 40 to 45 minutes after dosing.¹

The bioavailability of **Stimate® Nasal Spray** when administered by the intranasal route as a 1.5 mg/mL solution is between 3.3 and 4.1 percent.¹

The change in structure of arginine vasopressin to desmopressin acetate has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic doses are usually below threshold levels for effects on vascular or visceral smooth muscle.

INDICATIONS AND USAGE

Before the initial therapeutic administration of **Stimate® Nasal Spray**, the physician should establish that the patient shows an appropriate change in the coagulation profile following a test dose of intranasal administration of **Stimate® Nasal Spray**.^{2,4}

Desmopressin acetate is also available as a solution for injection (DDAVP® Injection) when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness.

Hemophilia A

Stimate® Nasal Spray is indicated for patients with hemophilia A with Factor VIII coagulant activity levels greater than 5%.

Desmopressin acetate will also stop bleeding in patients with hemophilia A with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.^{2,3}

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, **Stimate® Nasal Spray** provided effective hemostasis 100% of the time in 2 of the 5 patients. For those patients not responding in 100% of bleeding occasions, 45% (14 of 31) of bleeding episodes were effectively controlled with **Stimate® Nasal Spray**.

Desmopressin acetate is not indicated for the treatment of hemophilia A with Factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have Factor VIII antibodies.

von Willebrand's Disease (Type I)

Stimate® Nasal Spray is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with Factor VIII levels greater than 5%.

Desmopressin acetate will also stop bleeding in mild to moderate von Willebrand's disease patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas, mucosal bleeding or menorrhagia.^{2,3}

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, **Stimate® (desmopressin acetate) Nasal Spray** provided effective hemostasis 100% of the time in 75% of the patients (n=16). For those patients not responding in 100% of bleeding occasions, 78% (64 of 82) of bleeding episodes were effectively controlled with **Stimate® Nasal Spray**. Patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and Factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked after initial administration of **Stimate® Nasal Spray** to ensure that adequate levels have been achieved.

Stimate® Nasal Spray is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of Factor VIII antigen. See **WARNINGS**.

CONTRAINDICATIONS

Stimate® Nasal Spray is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of **Stimate® Nasal Spray**.

WARNINGS

For intranasal use only.

Patients who do not have need of antidiuretic hormone for its antidiuretic effect, in particular those who are young or elderly, should be cautioned to ingest only enough fluid to satisfy thirst, in order to decrease the potential occurrence of water intoxication and hyponatremia.

Fluid intake should be adjusted downward, particularly in very young and elderly patients, in order to decrease the potential occurrence of water intoxication and hyponatremia.¹

Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

Stimate® Nasal Spray should not be used to treat patients with Type IIB von Willebrand's disease since platelet aggregation may be induced.

PRECAUTIONS

General

Desmopressin acetate has infrequently produced changes in blood pressure causing either a slight elevation in blood pressure or a transient fall in blood pressure and a compensatory increase in heart rate. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

Stimate® Nasal Spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.

There have been rare reports of thrombotic events (thrombosis, acute cerebrovascular thrombosis, acute myocardial infarction) following desmopressin acetate injection in patients predisposed to thrombus formation. No causality has been determined; however, the drug should be used with caution in these patients.

Severe allergic reactions have been reported rarely.^{2,8-10} Fatal anaphylaxis has been reported in one patient who received intravenous DDAVP® (desmopressin acetate). It is not known whether antibodies to desmopressin acetate are produced after repeated administration.

Since **Stimate® Nasal Spray** is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case **Stimate® Nasal Spray** should be discontinued until the nasal problems resolve. For such situations, DDAVP® Injection should be considered.

Information for Patients: Patients should be informed that the bottle accurately delivers 25 doses of 150 mcg each. Any solution remaining after 25 doses should be discarded since the amount delivered thereafter may be substantially less than 150 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Patients should also be advised that if bleeding is not controlled, the physician should be contacted.^{2,3}

Hemophilia A: Laboratory tests for assessing patient status include levels of Factor VIII coagulant, Factor VIII antigen and Factor VIII ristocetin cofactor (von Willebrand factor) as well as activated partial thromboplastin time. Factor VIII coagulant activity should be determined before giving **Stimate® Nasal Spray** for hemostasis. If Factor VIII coagulant activity is present at less than 5% of normal, **Stimate® Nasal Spray** should not be relied on.

von Willebrand's Disease: Laboratory tests for assessing patient status include levels of Factor VIII coagulant activity, Factor VIII ristocetin cofactor activity, and Factor VIII von Willebrand factor antigen. The skin bleeding time may be helpful in following these patients.

Drug Interactions: Although the pressor activity of desmopressin acetate is very low, its use with other pressor agents should be done only with careful patient monitoring. DDAVP® Injection has been used with epsilon aminocaproic acid without adverse effects.

Carcinogenicity, Mutagenicity, Impairment of Fertility: There have been no long-term studies in animals to assess the carcinogenic, mutagenic or impairment of fertility potential of **Stimate® Nasal Spray**.

Pregnancy Category B: Reproduction studies performed in rats and rabbits by the subcutaneous route at doses up to 10 mcg/kg/day have revealed no evidence of harm to the fetus due to desmopressin acetate. This dose is equivalent to 10 times (for Factor VIII stimulation) or 38 times (for diabetes insipidus) the systemic human dose based on a mg/M² surface area.

There are no adequate and well-controlled studies in pregnant women. Several publications of desmopressin acetate's use in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low birth weight babies. However, no causal connection between these events and desmopressin acetate has been established. A 15-year, Swedish epidemiologic study of the use of desmopressin acetate in pregnant women with diabetes insipidus found the rate of birth defects to be no greater than that in the general population. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no uterotropic action and the physician will have to weigh the therapeutic advantages against the possible risks in each case.

Nursing Mothers: There have been no controlled studies in nursing mothers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable DDAVP® in breast milk following an intranasal dose of 10 mcg. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Stimate® Nasal Spray** is administered to a nursing woman.

Pediatric Use: Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. **Stimate® Nasal Spray** should not be used in infants younger than 11 months in the treatment of hemophilia A or von Willebrand's disease;

safety and effectiveness in children between 11 months and 12 years of age has been demonstrated.^{2,4}

Geriatric Use: Clinical studies of Stimate® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. However, other post-marketing experience has reported the occurrence of hyponatremia with the use of desmopressin acetate and fluid overload.

Therefore, in elderly patients fluid intake should be adjusted downward in an effort to decrease the potential occurrence of water intoxication and hyponatremia. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures, which could lead to coma.

Patients who do not have need of antidiuretic hormone for its antidiuretic effect should be cautioned to ingest only enough fluid to satisfy thirst, in an effort to decrease the potential occurrence of water intoxication and hyponatremia.

As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Infrequently, DDAVP® Injection has produced transient headache, nausea, mild abdominal cramps and vulval pain. These symptoms disappeared with reduction in dosage. Occasional facial flushing has been reported with the administration of DDAVP® Injection. Infrequently, high doses of intranasal DDAVP® have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

In addition to those listed above, the following have also been reported in clinical trials with **Stimate® (desmopressin acetate) Nasal Spray**: Somnolence, dizziness, itchy or light-sensitive eyes, insomnia, chills, warm feeling, pain, chest pain, palpitations, tachycardia, dyspepsia, edema, vomiting, agitation and balanitis.^{1,4}

DDAVP® Injection (desmopressin acetate) has infrequently produced changes in blood pressure causing either a slight elevation or a transient fall and a compensatory increase in heart rate. Severe allergic reactions including anaphylaxis have been reported rarely with DDAVP® Injection.

See **WARNINGS** for the possibility of water intoxication, hyponatremia and coma.¹¹

OVERDOSAGE

See **ADVERSE REACTIONS** above. In cases of overdosage, the dosage should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition.

There is no known specific antidote for desmopressin acetate or **Stimate® Nasal Spray**.

An oral LD₅₀ has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Hemophilia A and von Willebrand's Disease (Type I)

Stimate® Nasal Spray is administered by nasal insufflation, one spray per nostril, to provide a total dose of 300 mcg. In patients weighing less than 50 kg, 150 mcg administered as a single spray provided the expected effect on Factor VIII coagulant activity, Factor VIII ristocetin cofactor activity and skin bleeding time.^{3,4} If **Stimate® Nasal Spray** is used preoperatively, it should be administered 2 hours prior to the scheduled procedure.^{12,13}

The necessity for repeat administration of **Stimate® Nasal Spray** or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than every 48 hours should be considered in treating each patient.

The nasal spray pump can only deliver doses of 0.1 mL (150 mcg) or multiples of 0.1 mL. If doses other than these are required, DDAVP® Injection may be used.

The spray pump must be primed prior to the first use. To prime pump, press down 4 times. The bottle should be discarded after 25 doses since the amount delivered thereafter per spray may be substantially less than 150 mcg of drug.

HOW SUPPLIED

A 2.5 mL bottle with spray pump capable of delivering 25 doses of 150 mcg. KEEP REFRIGERATED AT 2-8°C (36°-46°F). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).

REFERENCES

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2. RHÔNE-POULENC RORER STUDY RG-83884-142: Nasal Spray Desmopressin (DDAVP). A Simple Technique for Treatment of Mild Hemophilia A and von Willebrand's disease.
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6. Lethagen S, Harris AS, Sjörin E and Nilsson IM: Intranasal and intravenous administration of desmopressin: Effect on FVIII:WV, pharmacokinetics and reproducibility. *Thromb. Haemost.*, 58:1033-1036, 1987.
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13. Rose EH and Aledort LM: Nasal spray desmopressin (DDAVP) for mild hemophilia A and von Willebrand's disease. *Ann. Int. Med.*, 114:563-568, 1991.

Manufactured for:
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King of Prussia, PA 19406-0901
US License No. 1767

By:
Ferring AB
Limhamn, Sweden
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PATIENT INSTRUCTION GUIDE

Stimate® (desmopressin acetate) Nasal Spray, 1.5 mg/mL

A better way to deliver desmopressin acetate

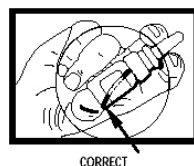
Delivering desmopressin acetate more efficiently

Your doctor has prescribed **Stimate® Nasal Spray** for the treatment of mild hemophilia A or mild to moderate von Willebrand's disease (Type 1). Follow the dosage schedule that is specified. The convenient nasal spray pump provides an efficient, reliable way to administer your medication. It is important, however, to adhere completely to the following instructions so that you will always receive a consistent dose of your medication.

CAUTION: The nasal spray pump accurately delivers 25 doses of 150 micrograms per spray. Any solution remaining after 25 sprays should be discarded since the amount delivered thereafter per spray may be substantially less than 150 micrograms of drug. Do not transfer any remaining solution to another bottle. Please read the following instructions carefully before using the spray pump.

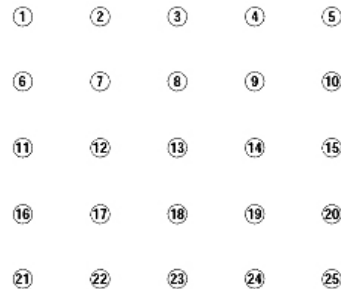
Using your Stimite® Nasal Spray Pump

1. Remove protective cap.
2. **When using for the first time, the spray pump must be primed by pressing down 4 times.**
3. Once primed, the spray pump delivers 150 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.



4. To administer a 150-microgram dose, place the spray nozzle in nostril and press the spray pump once. If a 300-microgram dose has been prescribed, spray once in each nostril. The spray pump cannot be used for doses less than 150 micrograms or doses other than multiples of 150 micrograms.
5. Replace the protective cap on bottle after use, and store in refrigerator. The pump will stay primed for up to one week under refrigeration. If the product has not been used for a period of one week, re-prime the pump by pressing once.
6. We have included a convenient check-off chart to assist you in keeping track of medication sprays used. This will help assure that you receive 25 "full sprays" of medication. Please note that the bottle has been filled with extra solution to accommodate the priming activity. When checking off sprays used, do not include the priming sprays.

Stimate® (desmopressin acetate) Nasal Spray, 1.5 mg/mL 25-Spray Check-off



1. Retain with medication or affix in convenient location, e-g., refrigerator.
2. Starting with spray #1, check off after each administration. If your doctor has prescribed a 2-spray dose (300-micrograms), two sprays must be checked off.
3. **Discard medication after 25 sprays.**

KEEP REFRIGERATED AT 2-8°C (36°-46°F).

When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 22°C (72°F).

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