

PRODUCT MONOGRAPH

OCTOSTIM[®]

Desmopressin Acetate

Injection (15 µg/mL)

Nasal Spray (1.5 mg/mL)

(Each metered dose delivers 150 µg/spray)

USP

Antihemorrhagic

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OCTOSTIM[®]

Desmopressin Acetate Injection
Desmopressin Acetate Nasal Spray

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	15 µg/mL	Hydrochloric acid, purified water, sodium chloride
Intranasal	1.5 mg/mL (each metered dose delivers 150 µg/spray)	Benzalkonium chloride solution, citric acid monohydrate, disodium phosphate dihydrate, purified water, sodium chloride

INDICATIONS AND CLINICAL USE

Octostim[®] injection and nasal spray is indicated for:

- The prevention of bleeding in patients with mild hemophilia A and mild von Willebrand's disease Type I.

Octostim[®] injection is indicated for:

- The prevention or treatment of bleeding in patients with uremia.

Hemophilia A

OCTOSTIM[®] is indicated for patients with hemophilia A with Factor VIII levels greater than 5%.

OCTOSTIM[®] will often maintain hemostasis in patients with hemophilia A during surgical procedures and postoperatively, when injected 30 minutes prior to or administered by nasal spray 2 hours prior to the scheduled procedure.

OCTOSTIM[®] will also stop bleeding in hemophilia A patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding. In certain clinical situations, it may be justified to try OCTOSTIM[®] in patients with Factor VIII levels between 2-5%, however, these patients should be carefully monitored.

Von Willebrand's Disease (Type I)

OCTOSTIM[®] injection is indicated for patients with mild to moderate classic von Willebrand's Disease (Type I) with Factor VIII levels greater than 5%. OCTOSTIM[®] will often maintain hemostasis in surgical procedures and postoperatively when administered 30 minutes prior to, or administered by nasal spray 2 hours prior to the scheduled procedure.

OCTOSTIM[®] will usually stop bleeding in mild to moderate von Willebrand's patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

Those von Willebrand's disease patients who are least likely to respond are those with severe homozygous von Willebrand's disease with Factor VIII antigen and von Willebrand's Factor (ristocetin cofactor) activities less than 1%. Other patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and Factor VIII coagulant activity, Factor VIII antigen and von Willebrand's Factor activities should be checked during administration of OCTOSTIM[®] to ensure that adequate levels are being achieved.

OCTOSTIM[®] is not indicated for the treatment of severe classic Type I von Willebrand's disease and Type II B and when there is evidence of an abnormal molecular form of Factor VIII antigen (See CONTRAINDICATIONS.)

Other Hemostatic Disorders

OCTOSTIM[®] injection is indicated for the treatment of prolonged bleeding time in patients with uremia. It will assist in the maintenance of hemostasis in such patients during surgical procedures and post operatively when administered prior to the procedure.

Therapeutic efficacy (i.e. normalization of bleeding time) should be established in individual patients at the time of diagnosis of the bleeding disorder, or at least 72 hours prior to an elective treatment, by administration of a test dose of OCTOSTIM[®] (see Laboratory Tests in WARNINGS AND PRECAUTIONS section).

CONTRAINDICATIONS

OCTOSTIM[®] is contraindicated in patients with known hypersensitivity to desmopressin acetate, the nasal spray is also contraindicated patients with known hypersensitivity to the preservative.

Because of the risk of platelet aggregation and thrombocytopenia, OCTOSTIM[®] should not be used patients with type II B or platelet-type (pseudo) von Willebrand's disease.

OCTOSTIM[®] should not be used in patients with cardiac insufficiency, or other conditions requiring treatment with diuretic agents.

OCTOSTIM[®] nasal spray should not be used in cases of habitual and psychogenic polydipsia, presence or a history of hyponatremia or Syndrome of Inappropriate ADH secretion (SIADH).

WARNINGS AND PRECAUTIONS

OCTOSTIM[®] (desmopressin acetate) treatment without concomitant restriction of water intake may lead to water retention/hyponatremia with or without accompanying signs and symptoms (reduced serum sodium, weight gain, and, in severe cases, convulsions). Other signs include persistent headache and nausea/vomiting. If these symptoms are present, serum sodium must be checked. The fluid intake should be restricted to the least possible and the body weight should be checked regularly. Should there be a gradual increase of the body weight, a decrease of serum sodium to below 130 mmol/l or plasma osmolality to below 270 mOsm/kg body weight, the fluid intake must be reduced drastically and the administration of OCTOSTIM[®] interrupted.

Precautions to prevent fluid overload must be taken in:

- the very young and elderly patients
- conditions characterized by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure

Children, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia.

Treatment with desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterized by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis), and the fluid and electrolyte balance should be carefully monitored, especially in situations with excessive bleeding.

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.

OCTOSTIM[®] must be used with caution in patients prone to vascular headaches, and patients with coronary insufficiency and hypertensive cardiovascular diseases because of possible changes in blood pressure and tachycardia.

Rapid infusion rates may result in severe hypotension; therefore, the speed of intravenous infusion of OCTOSTIM[®] should not be shorter than 20-30 minutes. A maximum dose of 0.3 µg/kg should not be exceeded.

Lack of therapeutic effect has been noted in patients who have been febrile or otherwise “stressed” for several days. Whenever possible, therapeutic efficacy (i.e., Factor VIII response in hemophilia and bleeding time correction in other disorders) should be established in individual patients prior to use and followed throughout the course of treatment. The coincident use of anti-

fibrinolytic agents to counteract desmopressin-induced plasminogen activator release has been recommended, however, benefit has not been clearly established.

The benefits of desmopressin versus other hemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active postoperative bleeding and variceal bleeding in patients with cirrhosis.

Desmopressin should not be used routinely in the bleeding trauma patient (grade 2C). Desmopressin (0.3 µg/kg) can be administered in patients treated with platelet-inhibiting drugs or with von Willebrand disease (Grade 2C).

The addition of desmopressin does not improve and may worsen the efficacy of terlipressin in controlling acute variceal bleeding in cirrhotic patients.

Desmopressin use is not recommended in patients with cirrhosis undergoing elective surgery or at the time of variceal bleeding (B2). Desmopressin administration in patients with cirrhosis undergoing dental extraction may be considered (B2).

OCTOSTIM[®] should not be used to treat patients with Type IIB von Willebrand's disease since platelet aggregation may be induced (see CONTRAINDICATIONS).

OCTOSTIM[®] should not be used in patients with Hemophilia B because it has no effect on Factor IX levels.

OCTOSTIM[®] has no therapeutic effect in Glazmann's thrombaesthesia.

OCTOSTIM[®] does not reduce prolonged bleeding time in thrombocytopenia.

OCTOSTIM[®] spray should not be used when the intranasal route may be compromised. These situations include changes in the nasal mucosa such as scarring, edema, nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. These conditions may lead to unreliable absorption. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. For such situations, OCTOSTIM[®] injection should be used.

Tachyphylaxis may develop with repeated use.

There have been rare reports of thrombotic events (thrombosis, cerebral thrombosis, cerebrovascular accident and disorder (stroke), acute myocardial infarction, angina pectoris and chest pain,) following desmopressin acetate injection in patients predisposed to thrombus formation. No causality has been determined; however, the drug should be used with caution in elderly patients and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease.

Persistently increased endogenous Factor VIII levels are a risk factor for venous thromboembolism (VTE). The evidence for elevated vWF levels as a risk factor for VTE is less strong, but some studies have demonstrated an association.

Severe allergic reactions have been reported rarely. Fatal anaphylaxis has been reported in one patient who received intravenous OCTOSTIM[®]. It is not known whether antibodies to desmopressin acetate are produced after repeated administration.

OCTOSTIM[®] has an antidiuretic effect. Patients receiving this drug should be cautioned to reduce their ingestion of fluids for at least 6 hours after receiving the drug. Patients receiving intravenous fluids must be placed on fluid input/output monitoring.

Safety and effectiveness of OCTOSTIM[®] Spray in children under 11 months has not been demonstrated.

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 OCTOSTIM[®] spray is administered to a nursing woman.

Due to the presence of benzalkonium chloride OCTOSTIM Nasal spray may cause bronchospasm, skin irritation.

General

Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50 ml/min).

Severe bladder dysfunction and outlet obstruction should be ruled out before starting treatment.

OCTOSTIM[®] (desmopressin acetate) produces changes in blood pressure; either an elevation or a decrease and a compensatory tachycardia. Subcutaneous and intranasal administration usually results in a slight change that is transient. Greater changes may occur with intravenous infusion, especially if administered rapidly (see WARNINGS). It should, therefore, be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

Before the initial therapeutic administration of OCTOSTIM[®] Spray, the physician should establish that the patient shows an appropriate change in the coagulation profile following a test dose of intranasal administration of OCTOSTIM[®] Spray.

OCTOSTIM[®] should not be administered to dehydrated patients until water balance has been adequately restored.

OCTOSTIM[®] should be used with caution in patients with cystic fibrosis because these patients are prone to hyponatremia. Children and geriatric patients should be closely observed for possible water retention due to over ingestion of fluids.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. Published reports stress that, as opposed to preparations containing the natural hormone, desmopressin acetate in antidiuretic doses has no uterotonic action, but the physician will have to weigh the possible therapeutic advantage against potential danger in each case.

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due desmopressin acetate. Subcutaneous doses up to 4 times the human dose for Factor VIII stimulation on a mg/m² basis (or 12.5 times the human dose on a mg/kg basis) and doses up to 4 times the human dose for diabetes insipidus on a mg/m² basis (or 12.5 times the human dose on a mg/kg basis) were studied. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported.

Published data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Nursing Women:

There have been not controlled studies in nursing mothers. A single study on a post-partum woman demonstrated a marked change in plasma desmopressin acetate level following an intranasal dose of 10 µg, but little drug was detectable in breast milk. (See WARNINGS AND PRECAUTIONS).

Results from analyses of milk from nursing mothers receiving a high dose of desmopressin (300 µg intranasally), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

Pediatrics

No controlled trials have been conducted in children with renal insufficiency.

Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. No controlled trials have been conducted in infants under 3 months of age with von Willebrand's disease or Hemophilia A. The physician should weigh possible therapeutic advantages against potential risks in each case. OCTOSTIM Spray should not be used in infants younger than 11 months in the treatment of hemophilia A or von Willebrand's disease.

Monitoring and Laboratory Tests

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 OCTOSTIM[®] for hemostasis. If Factor VIII coagulant activity is present at less than 5% of normal, OCTOSTIM[®] should not be relied upon alone.

von Willebrand's Disease

Laboratory tests for assessing patient status include levels of Factor VIII coagulant, Factor VIII antigen and Factor VIII ristocetin cofactor (von Willebrand factor). The skin bleeding time may be helpful in following these patients and should always be assessed pre-operatively.

Uremia

A test dose of OCTOSTIM[®] should be administered at the time of diagnosis of the bleeding disorder, or at least 72 hours prior to an elective treatment. The skin bleeding times should be measured before and 1 hour after OCTOSTIM[®] administration.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reaction with desmopressin is hyponatraemia/water retention, which is associated with headache, nausea, vomiting, water intoxication, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps/spasms, dizziness, decreased consciousness, confusion, generalized or local oedemas (peripheral, face), and in severe cases brain oedema, hyponatraemic encephalopathy, convulsions and coma. Hyponatraemia is reversible in two thirds of the adult cases reported during post-marketing. In the rest of the cases, 7% are reported as not recovered at the time when the events were reported and 21% had an unknown outcome. Treatment should be individualised and rapid overcorrection should be avoided to reduce the risk of further complications.

Post-marketing hypersensitivity reactions including local allergic reactions such as dyspnoea, erythema, generalized or local oedemas (peripheral, face), pruritus, rash, rash macular, rash maculopapular, rash erythematous, skin plaque and urticaria, have been reported in association with DDAVP injection. More serious hypersensitivity reactions including anaphylactic shock and reaction, and anaphylactoid shock and reaction have also been reported in association with DDAVP injection. Allergic reactions usually occur rapidly after drug administration and may occur during first time usage or after repeated exposure of DDAVP injection.

Rare post marketing cases of deep vein thrombosis, cerebrovascular accident/disorder (stroke), cerebral thrombosis, hypertension, pulmonary embolism, myocardial infarction, angina pectoris and chest pain have been reported in patients treated with desmopressin.

Persistently increased endogenous FVIII levels are a risk factor for venous thromboembolism (VTE). The evidence for elevated vWF levels as a risk factor for VTE is less strong, but some studies have demonstrated an association.

OCTOSTIM[®] has produced transient headache, nausea, facial flushing, tachycardia, hypotension, oliguria, abdominal cramps and vulvar pain. Nasal congestion and rhinitis have also been reported with the nasal spray formulation. The frequency varies with the dosage and the route of administration.

See WARNINGS AND PRECAUTIONS for the possibility of water intoxication and hyponatremia. Very occasionally, intravenous injection of OCTOSTIM[®] has produced local erythema, swelling or burning pain along the course of the vein.

Side effects following intravenous administration to 297 patients included transient facial flushing (approximately 18%), fatigue (3%), headache (2%), and oliguria (1%). Other effects reported at a frequency of less than 1% included nausea, dizziness, syncope and abdominal cramping.

Side effects following subcutaneous administration to 190 subjects included transient facial flushing (7%). Other effects reported at a frequency of less than 1% included hypotension, transient headache, abdominal tension, nausea, tachycardia and discomfort at the injection site.

Side effects following intranasal administration to 78 patients included facial flushing and warmth (24%), dizziness or headache (13%), palpitations (9%), nausea (6%), fatigue (6%), red eyes (4%), decreased diuresis (3%), nasal congestion, rhinitis, tachycardia. Other effects reported at a frequency of less than 1% include abdominal cramps, allergic reactions both to desmopressin and to the preservative, somnolence.

Severe hypotension was observed in some patients who received OCTOSTIM[®] intravenously during cardiac surgical procedures and this may have resulted from rapid infusion rates. A dosage of 0.3 µg/kg should not be exceeded, and the infusion rate of 20 to 30 minutes should not be exceeded.

Additional Post-Marketing Adverse Reaction Reports

The following post-marketing events have been reported:

Respiratory, thoracic and mediastinal disorders – dyspnea

Gastrointestinal disorders – nausea, vomiting

Nervous system disorders – headache, dizziness

General disorders and administration site conditions - injection/infusion site reactions including swelling, pain, extravasation, erythema, bruising and nodules, generalized or local oedemas (peripheral, face), chills

DRUG INTERACTIONS

Overview

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 (desmopressin acetate) injection has been used with epsilon aminocaproic acid without adverse events.

Precautions to avoid hyponatraemia, including careful attention to fluid restriction and more frequent monitoring of serum sodium, must be taken in case of concomitant treatment with substances which affect water and/or sodium homeostasis, are known to release antidiuretic hormone and suspected to induce SIADH, e.g., opioids, tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine, antidiabetics of the sulfonylurea group particularly chlorpropamide, urea, fludrocortisone and NSAIDs, as these may cause an additive antidiuretic effect and increase the risk of water retention/hyponatraemia.

Desmopressin should be used cautiously in patients who are receiving lithium, large doses of epinephrine, demeclocycline, heparin or alcohol, because the antidiuretic response to desmopressin may be decreased.

Concurrent administration of clofibrate with desmopressin reportedly potentiates and prolongs the antidiuretic effect of desmopressin.

Indomethacin may augment the magnitude but not the duration of the response to desmopressin.

DOSAGE AND ADMINISTRATION

Administration

OCTOSTIM[®] injection is administered by subcutaneous injection or as an intravenous infusion over 20 to 30 minutes to provide a dose of 0.3 µg/kg. The maximum intravenous dose is 20 µg. If OCTOSTIM[®] injection is used pre-operatively, it should be administered 30 minutes prior to the scheduled procedure. The peak effect is obtained one hour after administration. Response is immediate for bleeding time reduction.

Dilution for Infusion

Dilute in sterile physiological saline and infuse slowly over 20 to 30 minutes. In adults and children weighing more than 10kg, 50 mL of diluent is used; in children weighing 10 kg or less, 10 mL of diluent is used.

OCTOSTIM[®] spray is administered by nasal inhalation, one spray per nostril, to provide a total dose of 300 µg. In patients weighing less than 50 kg, 150 µg is administered as a single spray to provide the expected effect on Factor VIII coagulant activity, Factor VIII ristocetin cofactor activity and skin bleeding time. If OCTOSTIM[®] spray is used pre-operatively, it should be administered 2 hours prior to the scheduled procedure.

The necessity for repeat administration of OCTOSTIM[®] 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.

OVERDOSAGE

OCTOSTIM[®] (desmopressin acetate) at excessive doses may cause headaches, abdominal cramps, nausea and facial flushing. In such cases the dosage should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. Rapid intravenous infusion may cause hypotension. A maximum intravenous dose of 0.3 µg/kg should not be exceeded. The infusion rate of 20 to 30 minutes should not be exceeded.

There is no known specific antidote for OCTOSTIM[®]. Water intoxication responds rapidly to diuretic therapy (e.g., furosemide) and appropriate replacement fluid support, without interference with hemostatic effects.

Overdosage leads to a prolonged duration of action with an increased risk of fluid retention and hyponatremia.

Although the treatment of hyponatremia should be individualized, the following general recommendations can be given. Asymptomatic hyponatremia is treated with discontinuation of desmopressin treatment and fluid restriction. Infusion of isotonic or hypertonic sodium chloride may be added in cases with symptoms. When fluid retention is serious (convulsions and unconsciousness), treatment with furosemide should be added.

For up-to-date information on the management of a suspected drug overdose, contact the Regional Poison Control Center.
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ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

OCTOSTIM[®] (desmopressin acetate) is a synthetic structural analogue of the natural human hormone, arginine vasopressin with deamination of 1-cysteine and substitution of 8-L-arginine by 8-D-arginine.

OCTOSTIM[®] administration causes a transient increase in all components of the Factor VIII complex (Factor VIII coagulant activity, Factor VIII related antigen, and ristocetin cofactor) and in plasminogen activator. Either directly or indirectly, OCTOSTIM[®] causes these factors to be released very rapidly from their endothelial cell storage sites. In addition, OCTOSTIM[®] may have a direct effect on the vessel wall, with increased platelet spreading and adhesion at injury sites.

A second dose given before endothelial cell stores are replenished will not have as great an effect as the initial dose. Responses as great as the initial one usually are seen if 48 hours or more have elapsed between doses.

The pharmacokinetic and pharmacodynamic profiles after subcutaneous or intravenous administration to healthy volunteers are equivalent. The plasma half-life following subcutaneous, intravenous and intranasal administration ranges from 3.2 to 3.6 hours.

Pharmacodynamics

Desmopressin causes a dose-dependent increase in plasma Factor VIII (antihemophilic factor), plasminogen activator, and, to a smaller degree, Factor VIII-related antigen and ristocetin cofactor activities. The mechanism by which desmopressin lowers bleeding time remains speculative.

Structural modifications of vasopressin present in desmopressin result in reduced smooth muscle contracting and vasopressor properties compared with vasopressin and lyspressin. Initial studies of intranasal desmopressin at a subtherapeutic dose of 20 µg resulted in no effect on blood pressure or pulse rate, but mean arterial pressure increases as much as 15 mm Hg were observed with doses of 40 µg or more. In the therapeutic dose range, cardiovascular changes in normal, healthy volunteers were not considered to be clinically meaningful, but 27 of 32 volunteers had notable changes in systolic and/or diastolic blood pressure, and 8 had notable changes in pulse. Some volunteers experienced increases in diastolic blood pressure of greater than or equal to 20%; one volunteer experienced an increase in systolic blood pressure of 35% (40 mm Hg); and others experienced decreases in diastolic blood pressure, in some cases with compensatory tachycardia.

Desmopressin has been shown to interact with renal (V₂) vasopressin receptors which mediate its antidiuretic effect on renal tubes. The extrarenal effects of Desmopressin in normal persons, which include stimulation of the release of Factor VIII coagulant and von Willebrand factory (ristocetin cofactor) and a decrease in blood pressure, may be mediated by interaction with receptors in other tissues which are similar to the renal V₂ receptors.

Desmopressin has not been reported to stimulate uterine contractions.

Injection

Dose-response studies were performed in healthy persons, using doses of 0.1 to 0.4 µg/kg. OCTOSTIM[®] provokes an average increase in Factor VIII coagulant activity two to five times baseline levels.

Plasminogen activator activity increases about threefold, after OCTOSTIM[®] infusion, but is of such short duration of action that there has been no clinically significant fibrinolysis in patients treated with OCTOSTIM[®]. The Factor VIII related antigen and ristocetin cofactor activity were also increased to a smaller degree, but still were dose dependent. The above responses reach a maximum at a point ranging from one to two hours.

The effect of repeated OCTOSTIM[®] administration when doses were given every 12 to 24 hours has generally shown a gradual diminution of the Factor VIII activity increase, noted with a single dose. The initial dose is reproducible in any particular patient if there are 2 or 3 days between administration, when endothelial cell storage sites are replenished.

The percentage increase of Factor VIII levels in patient with mild haemophilia A and von Willebrand's disease was not significantly different from that observed in normal healthy individuals when treated with 0.3 µg/kg of OCTOSTIM[®] infused over 10 minutes.

Desmopressin has also reportedly increased Factor VIII activity and to a lesser extent, Factor VIII related antigen and ristocetin cofactor in patients with uremia; these changes were accompanied by a shortening of bleeding time. In addition, the drug induced release into the plasma of the larger multimers of Factor VIII/von Willebrand factor in these patients.

Nasal Spray

Dose-response studies were performed in healthy persons using doses of 150 to 450 µg administered as one to three sprays. The response is dose-related, with maximal plasma levels of 150 to 250 percent of initial concentration 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.

In patients with von Willebrand's disease, levels of Factor VIII coagulant activity and von Willebrand's factor antigen remained greater than 30 U/dL for 8 hours after a 300 µg dose of OCTOSTIM[®] spray.

After 300 µg of OCTOSTIM[®] 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 µg/kg of intravenous OCTOSTIM[®].

In a trial comparing intranasal and intravenous Desmopressin in patients with mild/moderate hemophilia A or von Willebrand's disease, an intranasal dose of 300 µg desmopressin resulted in a 54% and 75% respective increase in Factor VIII:C and von Willebrand antigen, compared to intravenous desmopressin. The mean maximum percent decrease in bleeding time following intranasal desmopressin was 1.5 times that observed following intravenous desmopressin.

Intranasal desmopressin was tested for prevention and therapy of bleeding complications in mild Factor VIII deficiency when these individuals were undergoing various procedures (surgery, dental extraction etc.), Factor VIII:C levels increased above baseline after intranasal administration of desmopressin. The change in levels was evident after 15 minutes, and peaked at 2 hours after dosing.

Desmopressin 300 µg intranasally generally leads to at least a twofold increase in plasma of factor VIII coagulant activity (VIII:C). Also the content of von Willebrand factor-antigen (vWF:Ag) increases, but to a lesser extent. At the same time there is a release of plasminogen activator (PA).

A prolonged bleeding time is shortened to the same extent after doses of either 300 µg desmopressin intranasally, or intravenous doses of 0.3 µg/kg body weight.

Pharmacokinetics

Injection

Following IV infusion of desmopressin, the increase in plasma Factor VIII activity occurs within 15-30 minutes and peaks between 90 minutes and 3 hours after administration; the increase in Factor VIII activity is dose dependent, with a 300-400% maximum increase reportedly occurring after IV infusion of 0.4 µg/kg dose. Plasma Factor VIII-related antigen activity has also been reported to peak within 3 hours after IV infusion of the drug. The subcutaneous route of OCTOSTIM[®] administered has been compared with the intravenous route in healthy volunteers and found to produce a bioequivalent response in terms of pharmacokinetic profile.

Desmopressin acetate was administered to 10 healthy volunteers in a randomized cross-over study at a dose of 0.4 µg/kg by intravenous infusion and subcutaneous injection. The pharmacokinetic data are summarized in Table 1.

Table 1: Pharmacokinetics of OCTOSTIM after subcutaneous and intravenous administration to 10 healthy volunteers. Mean √ S.D.

Dose and route of administration	AUC (pg/h/mL⁻¹)	C_{max} (pg/mL)	T_{max} (min)	Half-life (min⁻¹)
0.4µg/Kg i.v.	3109 ± 1056			3.62 ± 0.42
0.4µg/Kg s.c. (4 µg/mL ampoule)	3492 ± 659	568 ± 203	87 ± 66	3.50 ± 0.39
0.4µg/Kg s.c. (40 µg/mL ampoule)	3164 ± 393	544 ± 46	60 ± 7	3.17 ± 0.33

Subcutaneous administration of OCTOSTIM[®] showed the same plasma half-life, from 3.2 to 3.6 hours, as intravenous OCTOSTIM[®]. The plasma profile indicates that the elimination of OCTOSTIM[®] from plasma follow first order kinetics. There is no significant difference in AUC between subcutaneous and intravenous OCTOSTIM[®]. A similar study in 14 hemophiliac patients

also showed that the subcutaneous route of administration is bioequivalent to the intravenous route.

Nasal Spray

The bioavailability relative to intravenous administration is about 3-5%. Maximum plasma concentration following a dose of 300 µg is reached after approximately 1 hour and amounts to 400 pg/mL on average. The half-life of OCTOSTIM[®] spray was between 3.3 and 3.5 hours, over the range of intranasal doses, 150 to 450 µg. Plasma concentrations of OCTOSTIM[®] spray were maximal, approximately 40 to 45 minutes after dosing.

STORAGE AND STABILITY

OCTOSTIM[®] injection should be stored at refrigerator temperature 2-8° C. Do not freeze.

OCTOSTIM[®] spray should be stored in upright position at 15-25°C. Do not freeze.

SPECIAL HANDLING INSTRUCTIONS

Diluted solutions

Continuous intravenous infusion

For intravenous infusion of OCTOSTIM[®] in adults and children weighing 10 kg or more, a dose of 0.3 µg/kg should be drawn up into a syringe, and added to an IV bag containing 50 mL of sterile physiological saline.

For children weighing less than 10 kg, a dose of 0.3 µg/kg should be added to 10 mL of sterile physiological saline.

It is recommended that the storage of the diluted solutions at room temperature does not exceed 24 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

Each mL of OCTOSTIM[®] injection contains desmopressin acetate 15 µg, with sodium chloride and hydrochloric acid to adjust the pH to 3.5, in water for injection.

Each mL of OCTOSTIM[®] spray contains desmopressin acetate 1.5 mg, benzalkonium chloride, (preservative) citric acid monohydrate, disodium phosphate dihydrate purified water, and sodium chloride.

Availability

OCTOSTIM[®] injection is available in a 1 mL ampoule containing 15 µg desmopressin. Ampoules are clear glass with a red identification ring and a blue dot indicating the cut area.

Instructions for Opening Ampoules

1. Hold ampoule with blue dot pointing upwards. Shake or tap ampoule to empty the tip.
2. With blue dot pointing upwards, snap off tip by forcing it downwards.

OCTOSTIM[®] spray is available in 2.5 mL glass bottles furnished with a pre-compression pump with applicator and protection cap. The spray pump is designed to give 100 µl (0.1 mL or 150 µg desmopressin acetate) per activation. The nasal pump can only deliver doses of 150 µg or multiple doses of 150 µg. If doses other than these are required, OCTOSTIM[®] injection may be used.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

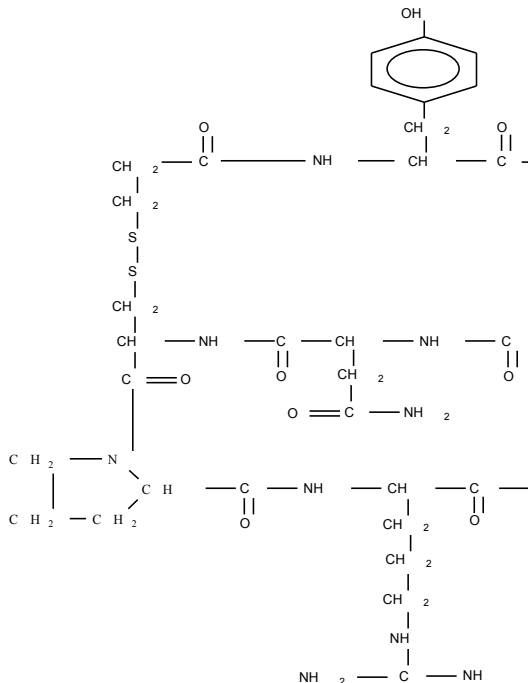
Proper name: Desmopressin Acetate

Chemical name: 1-Desamino-8-arginine-vasopressin acetate trihydrate
1-(3-mercaptopropionic acid)-8-D-arginine-vasopressin
monoacetate (salt) trihydrate

Molecular formula and molecular mass:

Molecular Formula:	Acetate:	$C_{48}H_{74}N_{14}O_{17}S_2$
	Free Base:	$C_{46}H_{64}N_{14}O_{12}S_2$
Molecular Weight:	Acetate:	1183.2
	Free Base:	1069.2

Structural formula:



Physicochemical properties:

Desmopressin acetate is a white lyophilized powder which is soluble in water, methanol, ethanol, and acetic acid, and sparingly soluble in chloroform and ethyl acetate. An aqueous solution of 1 mg/mL at 24EC has a pH of 4.8.

CLINICAL TRIALSPivotal Comparative Bioavailability Study

A randomized, single dose, two-way crossover comparative bioavailability study was conducted with 35 evaluable healthy male subjects. The maximal concentration and systemic exposure of desmopressin were measured and compared following an intranasal dose of desmopressin (300 µg; 150 µg in each nostril) as a spray formulation, which was either stored at room temperature or under refrigerated conditions. The results of the comparison between the two formulations are provided below.

Desmopressin (300 µg dose; 150 µg per nostril) From measured data				
Parameter	Test*	Geometric Mean Arithmetic Mean (CV%) Reference[†]	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (pg.h/ml)	1364.5 1509.4 (41.2)	1485.9 1628.9 (42.0)	92	83 – 102
AUC _{Inf} (pg.h/mL)	15.05.5 1673.6 (41.3)	1651.0 1815.4 (42.5)	91	82 – 101
C _{max} (pg/mL)	299.2 336.0 (48.4)	312.2 347.1 (45.2)	96	85 – 108
T _{max} ² (h)	0.75 (42.8)	0.88 (54.8)		
T _½ ²	3.54 (14.1)	3.58 (17.8)		

- * Octostim Spray (stored at room temperature)
[†] Octostim Spray (stored under refrigerated conditions)
² Expressed as the arithmetic mean (%CV) only.

TOXICOLOGY

Acute toxicity

The acute toxicity of desmopressin acetate is low (Table 2). Mice tolerate IV doses of 2 mg/kg. At IV doses of 30 µg/kg in rats and 40 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 OCTOSTIM

Species	Number	LD50 Dose	Route
Mice	10 both sexes	<2 mg/kg	IV
Rats	12 both sexes	>30 µg/kg	IV
Dogs	5 males	>24 µg/kg	IV

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, causes no biologically significant changes in hemotological and clinical chemistry parameters. Post-mortem examinations did not reveal any abnormalities.

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

Rat Subcutaneous Studies

In a controlled 8 week experiment, 20 rats received 2 µg/kg/day SC desmopressin acetate. No increase in blood glucose nor morphological or histological pancreatic changes occurred.

Rats (20 per group) which received desmopressin acetate 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 male animals, a decrease in non-esterifiable fatty acids was noted.

Dog Subcutaneous Studies

Dogs (3 per group) which received SC doses of 10 and 100 ng/kg/day desmopressin acetate 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.

Reproductive 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 acetate 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.

There have been no long-term studies in animals to assess the impairment of fertility potential of OCTOSTIM[®].

Carcinogenicity and Mutagenicity

There have been no long-term studies in animals to assess the carcinogenic or mutagenic potential of OCTOSTIM[®].

REFERENCES

1. Bichet DG, Razi M, Lonergan M, Arthus M-F, et al. Hemodynamic and coagulation responses to I-desamino[8-D-Arginine] vasopressin in patients with congenital nephrogenic diabetes insipidus. *N. Engl J Med* 1988;318:881-7.
2. Burroughs AK, Matthews K, Qadire M, Thomas N, Kernoff P, Tuddenham E, McIntryry N. Desmopressin and bleeding time in patients with cirrhosis. *Brit Med J* 1985; 291:1377-81.
3. Burrow GN, Wassenaar W, Robertson GL, and Sehl H. DDA VP treatment of diabetes insipidus during pregnancy and the post-partum period. *Acta Endocrinologica* 1981;97:23.
4. Christolini A, Dragoni F, Ferrari A, La Verde G, et al. Intranasal DDA VP: biological and clinical evaluation in mild factor VIII deficiency. *Haemostasis* 1991;21:273-7.
5. Dilthey G, Dietrich W, Spannagl M, Richter JA. Influence of desmopressin acetate on homologous blood requirements in cardiac surgical patients pretreated with aspirin. *J Cardiothorac. Vasco Anesth.* 1993;7(4):425-430.
6. Frankville DD, Harper GB, Lake CL, Johns RA. Hemodynamic consequences of desmopressin administration after cardiopulmonary bypass. *Anesthesiology* 1991;74:988-96.
7. Ghirardini A, Chistolini A, Tirindelli MC, Di Paolantonio T, Iacopine G, Mariani P, Chirletti P, Agrestini F, Mariani G. Clinical evaluation of subcutaneously administered DDA VP. *Thrombosis Research* 1988;49:363-72.
8. Gotti E, Mecca G, Valentine C, Cortinovic E, Bertani T, Remuzzi G. Renal biopsy inpatient with acute renal failure and prolonged bleeding time: A preliminary report. *Amer. J of Kid Dis* 1985;6(6):397-9.
9. Kentro TB, Lottenberg R, Kitchens CS. Clinical efficacy of desmopressin acetate for hemostatic control in patients with primary platelet disorders undergoing surgery. *Am J of Hem* 1987;24:215-9.
10. KernoffPBA, Lee CA, Karayiannis P and Thomas He. High risk of non-A non-B hepatitis after a first exposure to volunteer of commercial clotting factor concentrates: effects of prophylactic immune serum globulin. *British Journal of Haematology* 1985;60:469-79.
11. Kobrinsky N, Improved haemophilia A carrier detection by OCTOSTIM stimulation of Factor VIII. *J Ped* 1984;104:717-24.
12. Kobrinsky N. Shortening of bleeding time by I-desamino-8-arginine vasopressin in various bleeding disorders. *Lancet* 1984;1145-8.

13. Kohler M, Hellstem P, Teiter B, von Blohn G, Wenzel E. The subcutaneous administration of the vasopressin analogue I-desamino-8-d-arginine vasopressin in patients with von Willebrand's disease and hemophilia. *Klin Wochenschr* 1984;62:543-8.
14. Kohlor A, Harris A. Pharmacokinetics and hematological effects of desmopressin. *Eur J Clin Pharmacol* 1988;2:978-9.
15. Lethagen S, Egervall K., Bemtorp E and Bengtsson. The administration of desmopressin by nasal spray: a dose-determination study in patients with mild haemophilia A or von Willebrand's disease. *Haemophilia* 1995;1:97-102.
16. Lethagen S, Harris AS, Nilsson IM, Intranasal desmopressin (DDA VP) by spray in mild hemophilia A and von Willebrand's disease Type 1. *Blut* 1990;60:187-191.
17. Lethagen S, Rugan P, Bergqvist D. Blood loss and safety with desmopressin or placebo during aorta-iliac graft surgery. *Eur. J. Vase. Surg.* 1991;5(2):173-8.
18. Lusher JM, Miller E, Wiseman CH, Draughn M, et al. Use of highly concentrated intranasal spray formulation of desmopressin in persons with congenital bleeding disorders. In: Lusher JM, Kessler CM, eds. *Hemophilia and von Willebrand's disease in the 1990's*. Elsevier Science Publishers B.V. 1991; 317-24.
19. Lusher JM. Myocardial infarction and stroke - is the risk increased by desmopressin? In: Mariani G, Mannucci PM, Cattaneo M, eds. *Desmopressin in Bleeding Disorders*. New York, Plenum Press, 1993;347-53.
20. Lusher JM. Response to I-deamino-8-D-arginine vasopressin in von Willebrand disease. *Haemostasis* 1994;24:276-84.
21. Manucci PM, Pareti FI, Ruggeri AM and Capitano A. I-deamino-8-D-arginine vasopressin. A new pharmacological approach to the management of haemophilia and von Willebrand's disease. *The Lancet* 1977;(April23),869-72.
22. Mannucci PM, Vicente V, Vianello L, Cattaneo M, Alberca I, Coccato MP, Faioni E, Mari D. Controlled trial of desmopressin in liver cirrhosis and other conditions associated with a prolonged bleeding time. *Blood* 1986;67:(4)1148-53.
23. Mannucci PM, Vicente V, Alberca I, Sacchi E, Longo G, Harris AS, Lindquist. Intravenous and subcutaneous administration of desmopressin (DDA VP) to hemophiliacs: Pharmacokinetics and factor VIII responses. *Thrombosis and Haemostasis* 1987;58(4): 1037-9.
24. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmennan TS. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 1983;308;8-12.

25. Nilsson IM, Lethagen S. Current status of DDA VP formulations and their use. In Lusher JM, Kessler CM, eds. Hemophilia and von Willebrand's disease in the 1990's. Elsevier Science Publishers B.V. 1991;443-53.
26. Nilsson IM, Lethagen S. Intranasal application of DDA VP - biological function, pharmacokinetics and reproducibility. In: Mariani G, Mannucci PM, Cattaneo M, eds. Desmopressin in Bleeding Disorders. New York:Plenum Press, 1993;309-16.
27. Reich DL, Hammerschlag BC, Rand JH, Weiss-Bloom L, Perucho H, Galla J, Thys DM. Desmopressin acetate is a mild vasodilator that does not reduce blood loss in uncomplicated surgical procedures. J. Cardiothorac. Vase. Anesth. 1991;5(2):142-5.
28. Rose EH, Aledort LM. Nasal spray desmopressin (DDA VP) for mild hemophilia A and von Willebrand's disease. Ann Int Med 1991;114:563-8.
29. Salmenpera M, Kuitunen A, Hynynen M, Heinonen J. Hemodynamic responses to desmopressin acetate after CABG: A double-blind trial. J. Cardiothorac. Vase. Anesth. 1991;5(2):146-9.
30. Schulmar S, Johnsson H, Egberg N, Bomback. DDA VP-induced correction of prolonged bleeding time in patients with congenital platelet function defects. Thrombosis Research 1987;45:165-74.
31. Soslau G, Schwartz AB, Putatunda B, Conroy JD, Parker J, Abel RF, Brodsky I. Desmopressin-induced improvement in bleeding times in chronic renal failure patients correlates with platelet serotonin uptake and A TP release. Am J Med Sci 1990; 300(6):372-9.
32. Temeck BK, Bachenheimer LC, Katz NM, Coughlin SS, Wallace RB. Desmopressin acetate in cardiac surgery. South. Med. J. 1994;87(6):611-5.
33. Vigano GL, Mannucci PM, Lattuada A, Harris A, Remuzzi G. Subcutaneous desmopressin (DDA VP) shortens the bleeding time in uremia. Am J Haematol 1988;31 :32-5.
34. Watson AJ, Keogh JAB. I-deamino-8-D-arginine vasopressin as a therapy for the bleeding diathesis of renal failure. Am J Nephrol 1984;4:49-51.

PART III: CONSUMER INFORMATION

OCTOSTIM® Desmopressin Acetate

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

ABOUT THIS MEDICATION

What the medication is used for:

Octostim® Injection and Octostim® Spray are used to treat bleeding disorders called hemophilia A and von Willebrand's disease.

Octostim® Injection and Octostim® Spray are used by people who have mild to moderate hemophilia A or von Willebrand's disease to help increase clotting factors when they have medical, dental or minor surgical procedures done.

Octostim® Injection is also used by people who have uremia (urea in the blood) to help control bleeding during surgical procedures and after their operations.

How does it work?

Octostim® Injection and Octostim® Spray contain a hormone called desmopressin. In mild to moderate hemophilia A, desmopressin helps to stop and control bleeding by increasing the amount of clotting Factor 8 from the cells which line the blood vessels.

In von Willebrand's disease, desmopressin helps your body make more von Willebrand factor to reduce blood loss during women's menstrual periods, and to help control bleeding episodes. Because the effects of this medicine can vary, your doctor will prescribe it on a trial basis to see how much it increases the amount of clotting factors in your blood and to monitor side effects.

What is hemophilia?

Hemophilia is a rare genetic bleeding disorder that almost always occurs in males. A person with hemophilia inherits problems with certain blood-clotting factors, making them unable to work properly. Blood-clotting factors are needed to help stop bleeding after a cut or injury and to prevent spontaneous bleeding. The hemophilia gene can contain many different errors, leading to different degrees of abnormality in the amount of clotting factors produced. Diseases in this category include:

- hemophilia A
- hemophilia B
- von Willebrand's disease

Hemophilia A is the most common type of hemophilia. It is caused by a deficiency of active clotting Factor 8. About 80% of all people with hemophilia have type A, and most of these cases are severe. Approximately 1 out of every 5,000 male babies is born with hemophilia A.

Hemophilia B (Christmas disease) is caused by a lack of active clotting Factor 9. It is less common, occurring in 1 out of every 30,000 male babies, **and does not respond to Octostim.**

When a person with hemophilia is injured, he does not bleed harder or faster than a person without hemophilia; he bleeds longer. Small cuts or surface bruises are usually not a problem, but more traumatic injuries may result in serious problems and potential disability after bleeding episodes.

There are different levels of hemophilia: mild, moderate and severe. These three levels of hemophilia can overlap. The severity of the disease is defined by how much clotting factor is produced and in what situations bleeding most often occurs.

Mild hemophilia: Clotting Factor 8 or clotting Factor 9 level is 5% of normal or greater. Mild hemophilia might not be discovered until there is excessive bleeding after major injury or surgery. The first episode may not occur until adulthood.

Moderate hemophilia: Clotting Factor 8 or clotting Factor 9 level is 1% to 5% of normal. People with moderate hemophilia tend to have bleeding episodes after injuries (a fall, sprain or strain). They may also experience occasional bleeding episodes without obvious cause. These are called spontaneous bleeding episodes.

Severe hemophilia: Clotting Factor 8 or clotting Factor 9 is less than 1% of normal. People with severe hemophilia have bleeding following minor injury and may have frequent spontaneous bleeding episodes, often into joints and muscles.

The percentage of clotting factors stays about the same throughout a person's life. All family members who have hemophilia will usually have similar forms.

What causes hemophilia?

Hemophilia A and hemophilia B are caused by an inherited defect in a chromosome. The defect affects how much clotting factor a person will produce and how the factor will function. Hemophilia is mild when the clotting factor functions are close to normal and the amount of clotting factor is only somewhat reduced. The less normal the function and the amount of clotting factor, the more severe the hemophilia.

What are the symptoms?

Symptoms of hemophilia are usually first noticed during infancy or childhood. However, some people who have milder forms of hemophilia may not develop symptoms until later in life.

The following are signs of hemophilia that may be noticed shortly after birth:

- Bleeding into the muscle, resulting in a deep bruise after receiving a routine vitamin K shot
- Prolonged bleeding after a boy is circumcised
- In rare cases, prolonged bleeding after the umbilical cord is cut at birth.

Other symptoms of hemophilia include:

- Bleeding into a joint or muscle that causes pain and swelling
- Abnormal bleeding after an injury or surgery
- Easy bruising
- Blood in the urine
- Bleeding after dental work

How is hemophilia diagnosed?

Blood tests will determine whether you have hemophilia. Genetic tests are available if you want to know whether you are a carrier of hemophilia (only females can be carriers).

What is the treatment for hemophilia?

Hemophilia treatment varies depending on the severity of your condition.

Mild hemophilia A: Treatment involves slow injection of a hormone, desmopressin (Octostim® Injection) by your doctor into one of the veins to stimulate a release of more of your own clotting factor to stop the bleeding. Occasionally, desmopressin is given as a nasal medication (Octostim® Spray).

Moderate to severe hemophilia A or hemophilia B: Your bleeding may stop only after an infusion of clotting factor derived from human blood or from genetically engineered products called recombinant clotting factors.

What is von Willebrand's disease?

Von Willebrand's disease is a bleeding disorder caused by a defect or deficiency of a blood clotting protein, called von Willebrand factor. Von Willebrand factor is a protein critical to the initial stages of blood clotting. This glue-like protein, produced by the cells that line the blood vessels' walls, interacts with blood cells called platelets to form a plug which prevents the blood from flowing at the site of injury. People with von Willebrand's disease are unable to make this plug because they do not have enough von Willebrand factor or their factor is missing or does not work well.

The von Willebrand factor usually carries another blood-clotting protein called Factor 8. If you have von Willebrand's disease, the two proteins may not attach properly to each other and your blood will not clot as well as it should.

There are three types of von Willebrand's disease:

Type 1: A shortage of von Willebrand factor (mild). This type of von Willebrand's disease can result in mild to moderate bleeding episodes, depending on how much von Willebrand factor is missing. About 70% to 80% of all cases of von Willebrand's disease are type I. Some people with type I disease do not need treatment and may not be aware that they have a blood disorder.

Type 2: A flawed von Willebrand factor (usually mild). Although the body produces normal amounts of the von Willebrand factor, it doesn't work properly. Type 2 is further classified (2a or 2b) depending on the type of flaw.

Type 3: A complete lack of von Willebrand factor (more severe). Type 3 von Willebrand's disease is very rare. When the body does not produce von Willebrand factor, the cells (platelets) needed to form a clot do not work properly and clotting Factor VIII levels are low, both of which can lead to severe bleeding. People with type 3 disease are in more danger of anemia and excessive bleeding after an accident or during surgery.

What causes von Willebrand's disease?

Von Willebrand's disease is usually passed down through families. It is the most common bleeding disorder present at birth (congenital), but most cases are mild. About 1% of people inherit this disease. If one parent has von Willebrand's disease, a child has a 50% chance of having the condition. Men and women are equally likely to have von Willebrand's disease.

What are the symptoms?

Most cases of von Willebrand's disease are mild. Some people with type I von Willebrand's disease have no more bleeding than members of the general population. Mild von Willebrand's disease may not be noticed until you have excessive bleeding after an injury, dental procedure, or surgery. Severe cases (Type 3) are often recognized early in childhood because of unusual and heavy bleeding.

Excessive bleeding is the main symptom of von Willebrand's disease. The severity of the condition varies from person to person, even within the same family. Over half of all women with von Willebrand's disease have very heavy menstrual bleeding. Other symptoms include frequent nosebleeds and heavy bleeding after injury or surgery.

Von Willebrand's disease causes symptoms similar to the bleeding disorder hemophilia, but usually less severe.

How is von Willebrand's disease diagnosed?

Von Willebrand's disease can be hard to diagnose. If you have symptoms that suggest a blood clotting disorder, your doctor will ask about your medical history, especially about episodes of excessive bleeding. Test that can help with the diagnosis include:

- Blood tests that measure bleeding time, von Willebrand factor activity test, or von Willebrand factor antigen
- Genetic testing that shows a defect in your von Willebrand factor.

How is von Willebrand's disease treated?

If you have von Willebrand's disease, you will need to prevent and treat bleeding episodes throughout your life. The course of von Willebrand's disease is difficult to predict because it may stay at the same level of activity or get better or worse as you get older.

When it should not be used:

Octostim® Spray should not be used in infants younger than 11 months.

There are people who should not take Octostim® Injection and Octostim® Spray. Tell your doctor or pharmacist if you have:

- Hemophilia B
- Hyponatremia (low blood sodium levels)
- Syndrome of Inappropriate ADH secretion (SIADH)
- Any heart, liver or kidney problems
- Bleeding problems such as Type II B or platelet-type (pseudo) von Willebrand's disease
- An allergy to desmopressin acetate or any of the other ingredients in Octostim (see What the nonmedicinal ingredients are)

Patients who are hypersensitive to this drug or any non-medicinal ingredient in the formulation (see the section **What the nonmedicinal ingredients are**) should not take Octostim Spray or Injection.

What the medicinal ingredient is:

Octostim® Injection and Octostim® Spray contains an active drug called desmopressin acetate.

What the nonmedicinal ingredients are:

The nonmedicinal ingredients of Octostim® Spray are: benzalkonium chloride solution, citric acid monohydrate, disodium phosphate dihydrate, purified water and sodium chloride,

The nonmedicinal ingredients of Octostim® Injection are: hydrochloric acid, purified water and sodium chloride

What dosage forms it comes in:

Octostim® Spray is filled in a 2.5 mL glass bottle with a pre-compression pump and protective cap. The spray pump is

designed to give 100 ug (0.1 mL or 150 µg desmopressin acetate) per actuation.

Octostim® Injection is contained in a clear glass ampoule with a red identification ring and a blue dot indicating the cut area.

WARNINGS AND PRECAUTIONS

Before you use Octostim® Injection and Octostim® 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 such as Type II B or platelet-type (pseudo) von Willebrand's disease
- 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.

Treatment with desmopressin should be stopped or carefully adjusted if any new illnesses arise that are associated with fluid and/or electrolyte imbalance (such as infections, fever, stomach flu). The fluid and electrolyte balance should be carefully monitored, especially in situations with excessive bleeding.

Due to the presence of benzalkonium chloride OCTOSTIM Nasal spray may cause bronchospasm.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Octostim® Injection and Octostim® Spray include:

- Tricyclic antidepressants (amitriptyline, nortriptyline)
- Chlorpromazine
- Carbamazepine
- Urea
- Fludrocortisone
- Clofibrate
- Chlorpropamide
- Lithium
- Norepinephrine
- Indomethacin
- Heparin
- Alcohol

- NSAIDs (i.e.; ibuprofen)
- Opioids
- SSRI's (e.g. paroxetine, citalopram, fluvoxamine)
- Sulfonylureas (e.g. glyburide, glipizide, tolbutamide)

If you are taking any of these drugs, please talk to your doctor or pharmacist before taking Octostim®

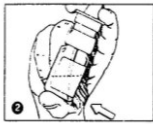
PROPER USE OF THIS MEDICATION

How to take Octostim® Spray

1. Gently blow your nose. If you can't clear your nasal passage, inform your doctor.
2. Remove the protective cap from the bottle.
3. The very first time the spray is used, prime the pump by pressing downwards on the white collar using your index and middle fingers while supporting the base of the bottle with your thumb (see Figure # 1). Press down at least 5 times until an even spray appears. The spray is now ready for use.



4. In a standing or sitting position, hold the bottle in a way which places the dip tube in the position indicated by the arrow (see Figure # 2). Tilt your head backward slightly and carefully insert the nasal applicator into one nostril (see Figure # 3).



5. For each spray your physician has instructed you to take, press firmly downwards once on the white collar using your index and middle fingers while supporting the base of the bottle with your thumb. Hold your breath as you administer the dose.
6. If more than 1 spray is prescribed by your physician, repeat steps 4 and 5 above for the other nostril.

Replace the protective cap on the bottle.

If the spray has not been used during the last 48 hours, it is necessary to prime it again. Press downwards on the white collar a couple of times until an even spray appears before placing the nasal applicator in the nostril.

IMPORTANT: The end of the tube inside the bottle must always be submerged in the liquid when administering the spray. Always keep the bottle upright and store in an upright position.

How many sprays should I take?

Take the medication only as directed by your doctor.

Usual Dose

Follow your doctor's direction on how much medicine you should take. The usual dose taken by nasal inhalation is one spray per nostril, to provide a total dose of 300 µg. In patients weighing less than 50 kg, 150 µg is administered as a single spray to provide the expected effect on Factor 8 coagulant activity, Factory 8 ristocetin cofactor activity and skin bleeding time.

If OCTOSTIM® spray is used before an operation; it is administered 2 hours prior to the scheduled procedure.

How to administer Octostim Injection

Octostim® injection is administered by subcutaneous injection or by slow intravenous infusion over 20 to 30 minutes to provide a dose of 0.3 µg/kg. Octostim® Injection should be diluted with sterile saline (diluent) before infusion.

Dilution for Infusion

Octostim® Injection should be diluted with sterile physiological saline and infused slowly over 20 to 30 minutes. In adults and children weighing more than 10 kg, 50 mL of diluent is used; in children weighing 10 kg or less, 10 mL of diluent is used.

Maximum Dose

The maximum intravenous dose is 20 µg. If Octostim® Injection is used pre-operatively; it is administered 30 minutes prior to the scheduled procedure. The peak effect is obtained one hour after administration. Response is immediate for bleeding time reduction.

Overdose

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

Call your doctor or poison control center, or go to an emergency room.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects may be experienced. The frequency varies with the dosage and the route of administration. These may include headache, nausea and mild abdominal cramps, low blood pressure, facial flushing, dizziness and fatigue. 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, abdominal pain, faintness, muscle cramps/spasms, tiredness, dizziness, swelling of hands/feet and in severe cases, coma. If you experience one or more of these symptoms, you should stop taking the 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				
Symptoms / 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)		T	T

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

HOW TO STORE IT

Octostim® Injection should be stored in the refrigerator at 2° – 8°C but do not freeze.

Octostim® Spray should be stored in upright position at 15-25°C. Do not freeze.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

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

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at : 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 1908C

Ottawa, ON K1A 0K9

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

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

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found by contacting the sponsor, Ferring Inc., at: 1-866-384-1314.

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