

PRODUCT MONOGRAPH

PrOCTOSTIM[®]

Desmopressin Acetate Injection
(15 mcg/mL)
Intravenous or subcutaneous
USP

Antihemorrhagic

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PrOCTOSTIM®

Desmopressin Acetate Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous, subcutaneous	15 mcg/mL	Hydrochloric acid, purified water, sodium chloride

INDICATIONS AND CLINICAL USE

OCTOSTIM® (desmopressin acetate injection) is indicated for:

- The prevention of bleeding in patients with mild hemophilia A and mild von Willebrand's disease Type I.
- 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 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[®] 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 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[®] 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 or to any of the excipients.

Because of the risk of platelet aggregation and thrombocytopenia, OCTOSTIM[®] should not be used in 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[®] 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 hyponatremia.

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 mcg/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 mcg/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.

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.

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[®] is administered to a nursing woman.

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 administration usually results in a slight change that is transient. Greater changes may occur with intravenous infusion, especially if administered rapidly. It should, therefore, be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

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 no 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 mcg, 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 mcg 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. The physician should weigh possible therapeutic advantages against potential risks in each case. No controlled trials have been conducted in infants under 3 months of age with von Willebrand's disease or Hemophilia A thus OCTOSTIM should not be used in this patient population.

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 hyponatremia/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, hyponatremic encephalopathy, convulsions and coma. Hyponatremia 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 desmopressin injection. More serious hypersensitivity reactions including anaphylactic shock and reaction, and anaphylactoid shock and reaction have also been reported in association with desmopressin injection. Allergic reactions usually occur rapidly after drug administration and may occur during first time usage or after repeated exposure of desmopressin 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.

OCTOSTIM[®] has produced transient headache, nausea, facial flushing, tachycardia, hypotension, oliguria, abdominal cramps and vulvar pain. 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 mcg/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.

Desmopressin acetate injection has been used with epsilon aminocaproic acid without adverse events.

Precautions to avoid hyponatremia, 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/hyponatremia.

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[®] is administered by subcutaneous injection or as an intravenous infusion over 20 to 30 minutes to provide a dose of 0.3 mcg/kg. The maximum intravenous dose is 20 mcg. If OCTOSTIM[®] 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 10 kg, 50 mL of diluent is used; in children weighing 10 kg or less, 10 mL of diluent is used.

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 mcg/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.

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 and intravenous 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 mcg 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 mcg 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 (V_2) 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 factor (ristocetin cofactor) and a decrease in blood pressure, may be mediated by interaction with receptors in other tissues which are similar to the renal V_2 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 mcg/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 mcg/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.

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 mcg/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 mcg 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.

A prolonged bleeding time is shortened to the same extent after doses of either 300 mcg desmopressin intranasally, or intravenous doses of 0.3 mcg/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 mcg/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 mcg/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 \pm S.D.

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

STORAGE AND STABILITY

OCTOSTIM[®] should be stored at refrigerator temperature 2-8°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 mcg /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 mcg /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[®] contains desmopressin acetate 15 mcg, with sodium chloride and hydrochloric acid to adjust the pH to 3.5, in water for injection.

Availability

OCTOSTIM[®] is available in a 1 mL ampoule containing 15 mcg 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

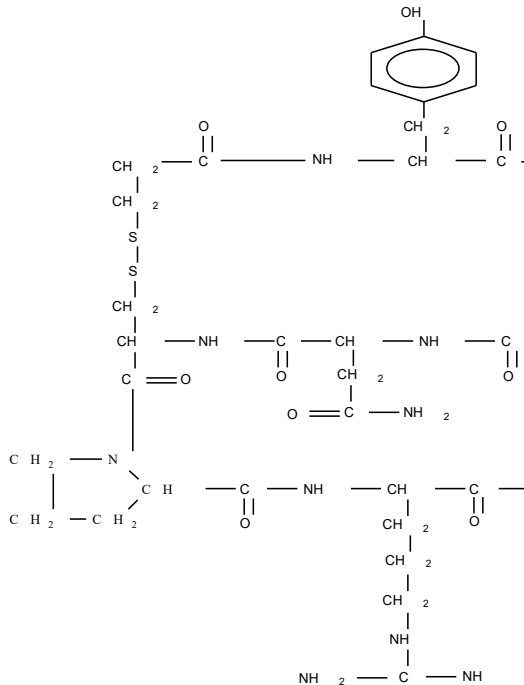
Proper name: Desmopressin Acetate

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 24°C has a pH of 4.8.

TOXICOLOGYAcute toxicity

The acute toxicity of desmopressin acetate is low (Table 2). Mice tolerate IV doses of 2 mg/kg. At IV doses of 30 mcg /kg in rates and 40 mcg /kg in rabbits, only transient changes in clinical behaviour were observed. Intravenous doses up to 24 mcg /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 mcg /kg	IV
Dogs	5 males	>24 mcg /kg	IV

Subacute Toxicity

Results from 14-day studies show that the drug given intravenously to rates at 18 mcg //kg/day and to rabbits at 6 mcg /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 ToxicityRat Subcutaneous Studies

In a controlled 8 week experiment, 20 rats received 2 mcg /kg/day subcutaneous 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 subcutaneous 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 mcg /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[®] (desmopressin acetate injection).

Carcinogenicity and Mutagenicity

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

PART III: CONSUMER INFORMATION

PrOCTOSTIM® Desmopressin Acetate Injection

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® is used to treat bleeding disorders called hemophilia A and von Willebrand's disease.

OCTOSTIM® is 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® 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® contains 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®) by your doctor into one of the veins to stimulate a release of more of your own clotting factor to stop the bleeding.

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 I: 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. Tests 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® should not be used in infants younger than three months in the treatment of hemophilia A or von Willebrand's disease.

There are people who should not take OCTOSTIM®. 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®.

What the medicinal ingredient is:

OCTOSTIM® contains an active drug called desmopressin acetate.

What the nonmedicinal ingredients are:

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

What dosage forms it comes in:

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®, 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.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with OCTOSTIM® 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 administer OCTOSTIM Injection

OCTOSTIM® is administered by subcutaneous injection or by slow intravenous infusion over 20 to 30 minutes to provide a dose of 0.3 mcg /kg.

OCTOSTIM® 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 mcg. If OCTOSTIM® 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 AND WHAT TO DO ABOUT THEM

Symptoms / effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Rare hyponatremia (low blood sodium level)		√	√

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

Keep out of reach and sight of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Call toll-free at : 1- 866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about OCTOSTIM:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html>); Ferring.ca, or by calling 1-866-384-1314

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