

NEW ZEALAND DATA SHEET

OCTOSTIM 15 microgram/mL solution for injection

Desmopressin acetate

1 PRODUCT NAME

OCTOSTIM solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml OCTOSTIM solution for injection contains desmopressin acetate 15 microgram equivalent to desmopressin 13.4 microgram.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

OCTOSTIM injection is indicated for:

- Shortening or normalisation of prolonged bleeding time prior to an invasive therapeutic or diagnostic operation, or for therapeutic control of bleeding in patients with prolonged bleeding time as a consequence of congenital or substance-induced thrombocyte dysfunction, uremia, cirrhosis of the liver or in patients with prolonged bleeding time of unknown etiology.
- For the therapeutic control of bleeding and bleeding prophylaxis in connection with minor surgical procedures in patients with mild haemophilia A and von Willebrand's disease who respond positively to a test dose. In exceptional cases, even moderate forms of the disease can be treated. OCTOSTIM must not be used in patients with von Willebrand's disease type IIB.

4.2 Dose and method of administration

Shortening, normalisation or therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation in patients with prolonged bleeding time

0.3mcg/kg body weight subcutaneously or diluted in physiological saline to 50-100ml and given as an intravenous infusion over 15-30 minutes. If a positive effect is obtained, the initial OCTOSTIM dose may be repeated 1-2 times with intervals of 6-12 hours. Further repetition of the dose may result in a reduced effect.

In patients with haemophilia A the desired increase of VIII:C is appraised by the same criterion as in the treatment with factor VIII-concentrate. If the OCTOSTIM infusion does not lead to the desired increase of the concentration of VIII:C in plasma, the treatment may be complemented with administration of factor VIII concentrate. Treatment of haemophilia patients should be conducted in consultation with each patient's coagulation laboratory.

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Determination of coagulation factors and bleeding time before OCTOSTIM treatment.

Plasma levels of VIII:C and vWF:Ag increase substantially after desmopressin administration. However, it has not been possible to establish any correlation between the plasma concentration of these factors and the bleeding time, either before or after desmopressin. The effect of desmopressin on the bleeding time should therefore, if possible, be tested in the individual patients. The bleeding time test should be as standardised as possible, e.g. with the use of Simplate II. Determination of bleeding time and plasma levels of the coagulation factors should be conducted in co-operation or consultation with the Coagulation Laboratories in the country.

Treatment control

The VIII:C concentration must be monitored regularly since in a few cases the effect has been seen to decrease with repeated doses.

In connection with administration of OCTOSTIM the patient's blood pressure must be monitored carefully.

Posology for special populations

Renal impairment

OCTOSTIM injection should be used with caution in patients with moderate and severe renal insufficiency (see section 5.2).

Hepatic impairment

No dose adjustment is needed for patients with hepatic impairment (see section 5.2).

Paediatric population

Shortening, normalisation or therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation

See adults

Method of administration

The injection is administered by subcutaneous injection or intravenous infusion. For instructions for use and handling of the medicinal product, see section 6.6.

4.3 Contraindications

OCTOSTIM solution for injection is contraindicated in cases of:

- hypersensitivity to the active substances or to any of the excipients listed in section
- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40mL/kg/24hours)
- a history of unstable angina pectoris and/or known cardiac insufficiency and other conditions requiring treatment with diuretics
- known hyponatraemia
- syndrome of inappropriate ADH secretion (SIADH)
- von Willebrand's disease type IIB

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4.4 Special warnings and precautions for use

Special Warnings

When OCTOSTIM injection is prescribed, it is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatremia with or without accompanying warning signs and symptoms see section 4.8.

In addition for renal concentration capacity testing:

When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 L to quench thirst from 1 hour before until 8 hours after administration. Renal concentration capacity testing in children below the age of 1 year should only be performed in hospital and under careful supervision.

In addition for haemostatic use:

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.

Measures to prevent fluid overload must be taken in patients requiring treatment with diuretic agents.

Special attention must be paid to the risk of fluid retention/hyponatraemia (see section 4.8). The fluid intake should be restricted to the least possible and the body weight should be checked regularly. If there is a gradual increase of the body weight, 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.

OCTOSTIM injection does not reduce prolonged bleeding time in thrombocytopenia.

Precautions

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for central diabetes insipidus.

Precautions must be taken in patients at risk for increased intracranial pressure.

Infants, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia. Treatment with OCTOSTIM injection should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.

Special attention should be given when desmopressin is co-administered with other drugs affecting water and/or sodium homeostasis (see section 4.5). In patients with chronic therapy with drug(s) affecting water and/or sodium homeostasis, OCTOSTIM injection should be administered after confirmation of normal baseline sodium.

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

OCTOSTIM injection should not be used in patients with hypersensitivity to desmopressin or to any of the excipients in the product (see section 4.8).

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Due to post-marketing reports with OCTOSTIM injections of deep vein thrombosis, cerebrovascular accident and disorder (stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using OCTOSTIM injection in elderly patients and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease.

4.5 Interaction with other medicines and other forms of interaction

Special attention should be given when desmopressin is co-administered with other drugs affecting water and/or sodium homeostasis, e.g. opioids, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine and some antidiabetics of the sulfonylurea group since concurrent use can lead to an increased risk of fluid retention/hyponatraemia (see section 4.4 **Error! Reference source not found.**).

It is unlikely that OCTOSTIM injection will interact with drugs affecting hepatic metabolism, since OCTOSTIM injection has been shown not to undergo significant liver metabolism in in vitro studies with human microsomes. However, formal in vivo interaction studies have not been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Published data on a limited number of exposed pregnancies in women with diabetes insipidus (n=53) as well as data on exposed pregnancies in women with bleeding complications (n=216) indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. To date, no other 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.

Animal reproduction studies have shown no clinically relevant effects on parents and offspring. In vitro analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentration corresponding to recommended dose.

Breastfeeding

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300micrograms intranasally), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis. Therefore, it is not considered necessary to stop breastfeeding.

Fertility

Studies with desmopressin in animals have shown no impairment of fertility in male and female rats.

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4.7 Effects on ability to drive and use machines

OCTOSTIM injection has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction with MINIRIN/OCTOSTIM injection during post-marketing is hyponatraemia. Hyponatraemia may cause headache, nausea, vomiting, water intoxication, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness, generalized or local oedemas (peripheral, face), and in severe cases brain oedema, hyponatraemic encephalopathy, convulsions, and coma (see section 4.4).

Rare cases of serious hypersensitivity reactions including anaphylactoid shock and reaction have been reported in association with MINIRIN/OCTOSTIM injection (see section 4.4).

Tabulated list of adverse reactions

The below table is based on the frequency of adverse drug reactions reported in clinical trials with MINIRIN injection conducted in adults for treatment of central diabetes insipidus and haematological indications (n=53) and OCTOSTIM injections (n=76), combined with the post marketing experience for MINIRIN/OCTOSTIM injections. Reactions only seen in post marketing or in other desmopressin formulations have been added in the 'Not known' frequency column. The table below shows the frequencies of adverse reactions reported. Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$) and Not known (cannot be estimated from the available data).

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Table 1. Frequency of adverse drug reactions reported (clinical trials, spontaneous reports including the literature)

MedDRA Organ Class	Common (≥ 1/100 to < 1/10)	Rare (1/1000)	Very rare (< 1/10,000)	Not known ⁴
Immune system disorders				Hypersensitivity reactions including anaphylactic reaction and other serious allergic conditions
Metabolism and nutrition disorders			Hyponatraemia	Water intoxication ¹ Weight increased ¹
Psychiatric disorders				Confusional state ¹
Nervous system disorders	Headache ²	Dizziness ²		Coma ¹ Loss of consciousness ^{1,3} Hyponatraemic encephalopathy ¹ Brain oedema ^{1,3} Convulsions ¹
Cardiac disorders	Tachycardia			Myocardial infarction ³ Angina pectoris ³ Chest pain ³
Vascular disorders	Flushing Hypotension			Deep vein thrombosis ³ Cerebrovascular accident and disorder (stroke) ³ Cerebral thrombosis ³ Hypertension ³
Respiratory, thoracic and mediastinal disorders				Dyspnoea Pulmonary embolism ³
Gastrointestinal disorders	Nausea ² Abdominal pain ¹			Vomiting ²
Skin and subcutaneous tissue disorders				Rash maculo-papular Rash erythematous Rash macular Urticaria Erythema Pruritus Rash
General disorders and administration site conditions	Fatigue			Generalized or local oedemas ² (peripheral, face) Injection/infusion site reactions including swelling, pain, extravasation, erythema, bruising and nodules Chills ³ Malaise ¹

1. Reported with hyponatraemia
2. Reported with or without hyponatraemia
3. Reported mainly for the hematological indications (high dose)
4. Adverse drug reactions from spontaneous reports (frequency not known). The adverse drug reactions have been derived from post-marketing experience with MINIRIN/OCTOSTIM via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Description of selected adverse reactions

During post-marketing the most frequently reported adverse reaction with MINIRIN/OCTOSTIM is hyponatraemia. Hyponatraemia may cause headache, nausea, vomiting, water intoxication, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusional state, decreased consciousness, generalized or local oedemas (peripheral, face), and in severe cases brain oedema, hyponatraemic encephalopathy, convulsions, and coma. Nausea, vomiting, headache and dizziness have been reported without registered hyponatraemia. The hyponatraemia is a result of the antidiuretic effect, arising from increased water reabsorption by the renal tubules and osmotic dilution of plasma. Special attention should be paid to the precautions addressed in section 4.4.

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Hyponatraemia is reversible. Treatment should be individualised and rapid overcorrection should be avoided to reduce the risk of further complications (see sections 4.2 and 4.4).

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

Rare post marketing cases of deep vein thrombosis, cerebrovascular accident/disorder (stroke), cerebral thrombosis, pulmonary embolism, myocardial infarction, angina pectoris and chest pain have been reported in patients treated with desmopressin. Due to confounding factors and/or missing information, a causal relationship with MINIRIN/OCTOSTIM injection has not been established/confirmed.

Paediatric population

Adverse reaction data from clinical trials in children is very limited.

Other special populations

Elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of developing hyponatraemia (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

Overdose of OCTOSTIM solution for injection leads to a prolonged duration of action with an increased risk of water retention and hyponatremia.

Treatment

Although the treatment of hyponatremia should be individualised, and can include discontinuation of OCTOSTIM treatment, fluid restriction and symptomatic treatment.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues

ATC code: H01B A02.

OCTOSTIM solution for injection contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and

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substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Desmopressin at high dosage, 0.3mcg/kg body weight intravenously, leads to a two- to four-fold 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 the plasminogen activator (t-PA).

Administration of desmopressin has also been shown to lead to a shortening or normalisation of the bleeding time in patients with prolonged bleeding time as in uremia, liver cirrhosis, congenital or drug-induced thrombocyte dysfunction and in patients with prolonged bleeding time of unknown etiology.

By administration of desmopressin instead of factor VIII concentrates, the risk of transmission of HIV-infection and hepatitis virus is avoided.

5.2 Pharmacokinetic properties

Absorption

The bioavailability following subcutaneous injection compared with intravenous administration is about 85%. Maximal plasma concentration after 0.3 micrograms/kg given as a subcutaneous injection is achieved after approximately 60 minutes and it amounts to 600 pg/ml in average.

Distribution

The distribution of desmopressin is best described by a two-compartment distribution model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg.

Biotransformation

The in-vivo metabolism of desmopressin has not been studied. In vitro human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolized in the liver by the cytochrome P450 system, and thus human liver metabolism in vivo by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolizing system.

Elimination

The total clearance of desmopressin has been calculated to 7.6 L/hr. In healthy subjects the fraction excreted unchanged was 52% (44-60%). Plasma half life varies between 3 and 4 hours. The duration of the haemostatic effect depends of the half-life for VIII:C which is about 8-12 hours.

Characteristics in specific groups of patients

Renal Impairment:

Precautions must be taken in patients with moderate and severe renal insufficiency.

Hepatic impairment:

No studies have been performed in this population. It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in in vitro studies with human microsomes.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No studies of the carcinogenic potential have been performed.

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

OCTOSTIM 15 microgram/ml solution for injection in 1 ml ampoules:
Sodium chloride, hydrochloric acid, water for injection.

6.2 Incompatibilities

This medicinal products must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

OCTOSTIM solution for injection should be stored at 2°C-8°C.

6.5 Nature and contents of container

Colourless, Type I glass ampoule. One vial of solution for injection contains 1ml (nominal volume).
Pack size: 10 x 1ml

6.6 Special precautions for disposal and other handling

For intravenous infusion the dose (0.3 microgram/kg body weight) should be diluted 50-100 ml 0.9% sodium chloride for injection (physiological saline) and given over 15-30 minutes.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION OF THE TEXT

Nov 2017

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2. Qualitative and Quantitative Composition	Addition of information on excipients with known effect
4.2 Posology	Addition of information on posology for special populations
4.3 Contraindications	Additional contraindications - known hypersensitivity to active or excipients, syndrome of inappropriate ADH secretion
4.4 Special warnings and precautions for use	Additional precautions added re bladder dysfunction, increased intracranial pressure, low serum sodium levels, co-administration with other drugs affecting water and/or sodium homeostasis, moderate and severe renal insufficiency, patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease.
4.5 Interaction with other medicines and other forms of interaction	Rewording of this section
4.6 Pregnancy	Updated information regarding use in pregnancy and breastfeeding. Additional statement on fertility.
4.8 Undesirable effects	Reformatting and tabulation. Additional information on selected adverse reactions
5.2 Pharmacokinetic properties	More specific information on pharmacokinetic properties
6.2 Incompatibilities	Statement warning against mixing this product with other medicinal products.