

OCTOSTIM SOLUTION FOR INJECTION

Desmopressin acetate

Presentation

OCTOSTIM 15µg/ml solution for injection. 1 ml solution for injection contains desmopressin acetate 15µg equivalent to desmopressin 13.4µg. A clear, colourless solution in an OPC ampoule with two red rings.

Uses

Actions

Pharmacotherapeutic group: Vasopressin and analogues, ATC code: H01B A02.

OCTOSTIM injection contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and 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, 0.3µg/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 substance-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.

Pharmacokinetics

Plasma half-life varies between 3 and 4 hours. The duration of the haemostatic effect is dependent of the half-life for VIII:C which is about 8-12 hours. The bioavailability following subcutaneous injection compared with intravenous administration is about 85%. Maximal plasma concentration after 0.3µg/kg is achieved after approximately 60 minutes and it amounts to 600pg/ml in average.

Indications

OCTOSTIM solution for injection is indicated as follows:

- 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.

Dosage and Administration

Therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation

0.3µg/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.

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.

Contraindications

OCTOSTIM solution for injection is contraindicated in cases of:

- habitual and psychogenic polydipsia
- unstable angina pectoris
- decompensated cardiac insufficiency
- von Willebrand's Disease Type IIB

Warnings and Precautions

OCTOSTIM solution for injection should be used with caution in:

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

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

Special attention must be paid to the risk of water retention/hyponatremia. 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 130mmol/l or plasma osmolality to below 270mOsm/kg body weight, the fluid intake must be reduced drastically and the administration of OCTOSTIM interrupted.

OCTOSTIM does not reduce prolonged bleeding time thrombocytopenia.

Use in pregnancy and lactation

Pregnancy

Reproduction studies performed in rats and rabbits with doses more than 100 times the human dose have revealed no evidence of a harmful action of desmopressin on the foetus. One investigator has reported 3 cases of malformations in children to mothers suffering from diabetes insipidus and receiving desmopressin during pregnancy. However, several other published reports comprising more than 120 cases show that women treated with desmopressin during pregnancy have given birth to normal children. Furthermore a review of a very large data set identifying 29 children who have been exposed to desmopressin during the full pregnancy shows no increase in the malformation rate in the children born.

Lactation

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

Effects on ability to drive and use machines

None.

Adverse Effects

A few per cent of treated patients can be expected to experience side effects such as fatigue, headache, nausea and stomach pain.

Common (>1/100)

General

Headache. At high doses: Fatigue.

Circulation

At high doses: Transient fall in blood pressure with a reflex tachycardia and facial flushing at the time of administration.

GI

Stomach pain, nausea.

Rare (<1/100)

General

At high doses: Dizziness.

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

Post marketing experience

Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported.

Interactions

Substances which are known to release antidiuretic hormone, e.g. tricyclic antidepressants, chlorpromazine and carbamazepine may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatremia.

Indomethacin increases the urine concentrating effect of desmopressin without influencing the duration. The effect is probably without any clinical significance.

Overdosage

Overdose of OCTOSTIM solution for injection can lead to water retention and hyponatremia.

Treatment

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

Pharmaceutical Precautions

List of excipients

Sodium Chloride, Hydrochloric Acid, Water for Injection.

Incompatibilities

Not applicable.

Shelf-life

4years.

Special precautions for storage

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

Medicine Classification

Prescription Medicine.

Package Quantities

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

Pack sizes

10 x 1ml

Instructions for use/handling

The injection is administered by subcutaneous injection or intravenous infusion. For intravenous infusion the dose should be diluted 50-100ml 0.9% sodium chloride for injection (physiological saline) and given over 15-30 minutes.

Further Information

Preclinical safety data

There were no unusual findings during the examination of the safety and safety profile of desmopressin.

Name and Address

Ferring Pharmaceuticals A/S

NZ distributor:
Pharmaco (NZ) Ltd
P O Box 4079
Auckland
Telephone: (09) 377-3336

Date of Preparation

17 March 2008

(CDS 2000/05 Rev 1; May 2000)