

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DDAVP 4 micrograms/ml Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains Desmopressin acetate 4 micrograms per ml

3. Pharmaceutical Form

Solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DDAVP 4 micrograms/ml Injection is indicated as follows:

Diagnosis and treatment of cranial diabetes insipidus.

To increase Factor VIII:C and Factor VIII:Ag in patients with mild to moderate haemophilia or von Willebrand's disease undergoing surgery or following trauma.

3. To establish renal concentration capacity.

4. To treat headache resulting from a lumbar puncture.

5. To test for fibrinolytic response.

4.2 Posology and method of administration

Treatment of Cranial Diabetes Insipidus:
By subcutaneous, intramuscular or intravenous injection

Adults: The usual dose is 1 to 4 micrograms given once daily.

Children and infants: Doses from 0.4 micrograms (0.1ml) may be used.

Diagnosis of Cranial Diabetes Insipidus:

The diagnostic dose in adults and children is 2 micrograms given by subcutaneous or intramuscular injection. Failure to elaborate a concentrated urine after water deprivation, followed by the ability to do so after the administration of Desmopressin confirms a diagnosis of cranial diabetes insipidus. Failure to concentrate after the administration suggests nephrogenic diabetes insipidus.

Mild to moderate haemophilia and von Willebrand's disease:

By intravenous administration.

The dose for adults, children and infants is 0.4 micrograms per kilogram body weight administered by intravenous infusion. Further doses may be administered at 12 hourly intervals so long as cover is required. As some patients have shown a diminishing response to successive doses, it is recommended that monitoring of Factor VIII levels should continue. The dose should be diluted in S0mI of 0.9% sodium chloride for injection and given over 20 minutes. This dose should be given immediately prior to surgery or following trauma. During administration of intravenous Desmopressin, vasodilation may occur resulting in decreased blood pressure and tachycardia with facial flushing in some patients.

Increase of Factor VIII levels are dependent on basal levels and are normally between 2 and 5 times the pretreatment levels. If results from a previous administration of Desmopressin are not available then blood should be taken pre-dose and 20 minutes post-dose for assay of Factor VIII levels in order to monitor response.

Unless contraindicated, when surgery is undertaken, tranexamic acid may be given orally at the recommended dose from 24 hours beforehand until healing is complete.

Renal Function Testing:

By subcutaneous or intramuscular injection.

Adults and children can be expected to achieve urine concentrations above 700mOsm/kg in the period of 5 to 9

Hours following a dose of 2 micrograms

DDAVP 4 micrograms/ml Injection. It is recommended that the bladder should be emptied at the time of administration.

In normal infants, a urine concentration of 600mOsm/kg should be achieved in the five hour period following a dose of 0.4 micrograms DDAVP 4 micrograms/ml Injection. The fluid intake at the two meals following the administration should be restricted to 50% of the ordinary intake to avoid water overload.

Post Lumbar Puncture Headache:

By subcutaneous or intramuscular injection.

Where a headache is thought to be due to a lumbar puncture, an adult patient can be given a dose of 4 micrograms DDAVP 4 micrograms/ml Injection which may be repeated 24 hours later if necessary. Alternatively, a prophylactic dose of 4 micrograms can be given immediately prior to the lumbar puncture and repeated 24 hours later.

Fibrinolytic Response Testing:

By intravenous administration:

The dose for adults and children is 0.4 micrograms per kilogram body weight administered by intravenous infusion.

The dose should be diluted in 50ml of 0.9% sodium chloride for injection and given over 20 minutes. A sample of venous blood should be taken 20 minutes after the infusion. In patients with a normal response the sample should show fibrinolytic activity of euglobulin clot precipitate on fibrin plates of at least 240mm².

4.3 Contraindications

DDAVP 4 micrograms/ml Injection is contraindicated in cases of:

GENERAL:

-habitual and psychogenic polydipsia

RENAL FUNCTION TESTING, TREATMENT OF LUMBAR PUNCTURE HEADACHE OR FIBRINOLYTIC RESPONSE TESTING:

-should not be carried out in patients with hypertension, heart disease, cardiac insufficiency and other conditions requiring treatment with diuretic agents

FOR HAEMOSTATIC USE:

-unstable angina pectoris

-decompensated cardiac insufficiency

-von Willebrand's Disease Type IIB where the administration of Desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation.

4.4 Special warnings and precautions for use

Precautions:

GENERAL:

Precautions to prevent fluid overload must be taken in

-conditions characterised by fluid and/or electrolyte imbalance

-patients at risk for increased intracranial pressure

Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.

When DDAVP 4 micrograms/ml Injection is used for diagnostic purposes, fluid intake must be limited and not exceed 0.5 litres 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 under carefully supervised conditions in hospital.

FOR HAEMOSTATIC USE:

When repeated doses are used to control bleeding in haemophilia or von Willebrand's disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or by determining plasma sodium or osmolality.

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

Special warnings:

Special attention must be paid to the risk of water retention. 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, the fluid intake must be reduced drastically and the administration of DDAVP 4 micrograms/ml Injection interrupted.

During infusion of DDAVP 4 micrograms/ml Injection for haemostatic use, it is recommended that the patient's blood pressure is monitored continuously.

DDAVP 4 micrograms/ml Injection does not reduce prolonged bleeding time in thrombocytopenia.

4.5 Interactions with other Medicaments and other forms of Interaction

Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatremia.

NSAIDs may induce water retention and/or hyponatraemia.

4.6 Pregnancy and Lactation

Pregnancy

Data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. 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. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Lactation

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

4.7 Effects on Ability to Drive and Use Machines

None

4.8 Undesirable effects

Side-effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disorders including aggression in children have been reported. Treatment with Desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

4.9 Overdose

An overdose of DDAVP 4 micrograms/ml Injection leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment

Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the desmopressin treatment, fluid restriction and symptomatic treatment if needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Desmopressin is a structural analogue of vasopressin in which the antidiuretic activity has been enhanced by the order of 10, while the vasopressor effect has been reduced by the order of 1500. The clinical advantage of this highly changed ratio of antidiuretic to vasopressor effect is that clinically active antidiuretic doses are far below the threshold for a vasopressor effect.

Like vasopressin, Desmopressin also increases concentrations of Factor VIII:C, Factor VIII:Ag and Plasminogen Activator.

5.2 Pharmacokinetic Properties

Following intravenous injection, plasma concentrations of Desmopressin follow a biexponential curve. The initial fast phase of a few minutes duration and with a half life of less than 10 minutes is thought mainly to represent the diffusion of Desmopressin from plasma to its volume of distribution. The second phase with a half life of 51-158 minutes represents the elimination rate of Desmopressin from the body.

As a comparison, the half life of vasopressin is less than 10 minutes.

In vitro, in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolised in the liver and thus human liver metabolism *in vivo* is not likely to occur.

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. However, formal *in vivo* interaction studies have not been performed.

5.3 Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride EP

Hydrochloric Acid EP
Water for Injection EP

6.2 Incompatibilities

None known

6.3 Shelf life

Shelf life of unopened ampoule: 48 months.

6.4 Special precautions for storage

To be stored in a refrigerator at 2°C to 8°C.

6.5 Nature and Contents of Container

Carton containing 10 x 1 ml clear Type I glass ampoules.
Each ampoule contains 1 ml of a sterile, clear, colourless solution for injection.

6.6 Instruction for Use/Handling

As indicated under the posology and method of administration section

7 MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Ltd
Drayton Hall
Church Road
West Drayton
UB7 7PS
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 03194/0002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

02/12/2008

10 DATE OF REVISION OF THE TEXT

07/09/2017