

**NAME OF THE MEDICINE:** Desmopressin Acetate

**Synonyms:**

DDAVP

1-desamino-8-D-Arginine vasopressin.

Desamino-cys-1-D-Arginine-8 vasopressin.

**TRADE NAME:** **MINIRIN**  
**OCTOSTIM**

**DESCRIPTION:**

The active substance is a synthetic structural analogue of the natural hormone arginine vasopressin. Early treatment of central diabetes insipidus used a more or less purified extract from bovine or porcine posterior pituitaries. These caused unpleasant complications of use. When vasopressin became known, two forms were found - Arginine Vasopressin (found in humans) and lysine vasopressin (found in pig pituitaries).

Two chemical changes have been made to the natural hormone:

a. desamination of the N-terminal of cysteine-1

b. substitution of 8-D-arginine for 8-L-arginine

Minirin Injection 4µg/mL and Octostim Injection 15 µg/mL contain desmopressin acetate, sodium chloride, hydrochloric acid and Water for Injections.

Minirin Intranasal Solution contains desmopressin acetate, sodium chloride, chlorbutol as preservative, hydrochloric acid and purified water.

**PHARMACOLOGY:**

According to results from antidiuretic and pressor tests in rats these changes increase antidiuretic activity three to five fold while pressor activity is reduced to 0.1% of that of antidiuretic hormone.

a. Absorption: Using i.v. or i.m. doses, 100% is available. Used intranasally, it is estimated that 10% is available. Thus i.v. or i.m. doses are one tenth that of the intranasal route.

b. Distribution: It is believed to be similar to ADH. No information is available on protein binding.

c. Metabolism: It is thought that the presence of the D-isomer in position eight protects DDAVP from the enzyme which inactivates ADH.

d. Excretion: The excretion of DDAVP is similar to that of ADH but considerably slower. Clinically intranasal DDAVP is effective for approximately 10-12 hours.

Half-Life No information is available for intranasal administration. For i.v. administration of labelled DDAVP, biexponential half lives of 7.8 minutes and 75.5 minutes were recorded. The duration of drug effect is 8-20 hours, with much individual variation.

**CLINICAL IMPLICATIONS OF PHARMACOKINETIC DATA**

DDAVP is thought to be resistant to the inactivation that occurs with ADH. Intravenous or intramuscular doses should be about one tenth the intranasal dose for equivalent efficacy.

In some patients, the duration of effect may be sufficiently long to permit once daily dosage if the single dose can be tolerated.

**ACTIONS:**

The actions of Minirin can be summarised as follows:

Antidiuretic Action

Minirin acts at a receptor site in the renal collecting tubule to increase permeability to water reabsorption.

Effect on factor-VIII

High doses of DDAVP produce marked and sustained increases of factor-VIII coagulant activity (VIII:C) as well as of the von Willebrand factor (vWF). At the same time plasminogen activator is released.

Effect on Bleeding Time

At doses of 0.3-0.4 µg /kg DDAVP results in a normalisation of, or marked reduction in the prolonged skin (template) bleeding time. The exact mechanism of this effect is not known.

It is not known whether the effects of Minirin are direct or act through a mediator or second messenger.

There is a temporal correlation between a reduction in bleeding time and the presence in plasma of high molecular weight monomers of the von Willebrand factor which are thought to be released from storage sites. It is thought likely that Minirin exerts its effect through its V<sub>2</sub>-receptor agonist activity.

**OTHER EFFECTS:**

Oxytocic Effect

A slight in vitro oxytocic effect has been reported in animals. A slight stimulatory effect on uterine activity in non-pregnant women has been noted at doses of 15 and 20 micrograms intranasally. See use in pregnancy.

Vasodilatory Effect

At doses used to treat bleeding, Minirin has a vasodilatory effect causing a minor decrease in systolic or diastolic blood pressure.

## **INDICATIONS:**

### Diabetes Insipidus

#### By Intranasal and Parenteral Administration .

The treatment of ADH-sensitive cranial diabetes insipidus, including treatment of post-hypophysectomy polydipsia and polyuria. DDAVP is ineffective for the treatment of nephrogenic diabetes insipidus.

Parenteral administration may be used when the intranasal route is inconvenient.

Caution: The parenteral dose is about one tenth of the intranasal dose.

Renal Concentrating Capacity. By intranasal administration to adults and children or intramuscular administration to adults only, as a diagnostic test to establish renal concentrating capacity.

Mild and Moderate Haemophilia A and von Willebrand's Disease. By intravenous Infusion only, for the increase of factor VIII levels in patients undergoing dental or minor surgery. Not to be used in type IIB von Willebrand's disease since platelet aggregation may be induced.

#### Bleeding in Patients with Platelet Dysfunction.

Treatment of excessive bleeding in patients with congenital or acquired clinical conditions associated with platelet dysfunction which is characterised by a prolonged bleeding time except Glanzmann's thrombasthenia or platelet cyclo-oxygenase deficiency.

Examples are patients with uraemia, congenital or drug induced platelet dysfunction and patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aorto-coronary bypass grafting especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. DDAVP offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure.

There is no definite evidence of efficacy in bleeding associated with cirrhosis of the liver and such use is not recommended.

## **CONTRAINDICATIONS:**

Type IIB von Willebrand's disease.

Habitual and psychogenic polydipsia

Cardiac insufficiency and other conditions requiring treatment with diuretic agents

Known Hyponatraemia

Hypersensitivity to desmopressin acetate or any components of the products.

*Additionally, For Minirin Intranasal Solution;*

SIADH syndrome of inappropriate anti-diuretic hormone secretion

Moderate and severe renal insufficiency (creatinine clearance below 50mL/min)

## **WARNINGS:**

Overhydration. The risk of overhydration including cardiac failure should be borne in mind, especially in children or the elderly or in chronic use and when DDAVP is being used to test renal concentrating capacity or the patient is on fluid supplements either orally or parenterally. Children should be closely observed to avoid overingestion of fluid. Excessive water intake can produce hyponatraemia with associated effects. (See Overdosage).

Blood Pressure: There is a risk that DDAVP may cause a minor reduction in blood pressure.

Hyponatraemia: There is a risk that DDAVP may produce hyponatraemia especially with chronic use.

Fluid Intake: When used for diagnostic purposes the fluid intake must be limited and not exceed 0.5L from 1 hour before until 8 hours after administration.

## **PRECAUTIONS:**

a. Only use intranasal solution in patients where orally administered formulations are not feasible (See ADVERSE REACTIONS)

b. In the control of diabetes insipidus the lowest effective dose should be used. When using the intranasal solution, increase dose progressively and with caution. Patient dosage should be reassessed periodically.

c. DDAVP should not be administered to dehydrated or overhydrated patients until water balance has been adequately restored. In haemophilia where high doses are given, extreme care must be paid to the water balance. Fluid intake should be restricted as much as possible and the patient should be weighed regularly.

d. Nasal infections/rhinorrhoea. Intranasal administration may be ineffective in the presence of local infection or rhinorrhoea.

e. Vasodilator effect.

At doses used to treat bleeding, Minirin has a vasodilator effect, causing a minor decrease in diastolic or systolic blood pressure.

f. Myocardial ischaemia. DDAVP should be used with caution in patients with cardiovascular disease and the elderly.

g. Hypersensitivity. Patients with a known hypersensitivity to ADH, should be tested for sensitivity to DDAVP before the full dose is given.

h. Post-operative use. For polyuria and polydipsia developing in the immediate post-operative period, desmopressin should only be given in minute doses, as extreme sensitivity to it may be present and over-hydration can be very damaging at that time. The maintenance of fluid intake in the light of serial weights, fluid losses, serum electrolytes and serum and urine osmolalities, rather than giving desmopressin may often be a safer course in the early post-operative course of such cases in childhood.

i. In patients with platelet dysfunction. Skin bleeding time should be monitored: i. before surgery with marked prolongation indicating high risk of increased blood loss. ii. during treatment with DDAVP.

j. Minirin should be used with caution in patients with cystic fibrosis because of impaired water handling and increased risk of hyponatraemia.

k. Precautions to prevent fluid overload must be taken in patients at risk for increased intracranial pressure.

l. Renal concentrating capacity testing in children below the age of 1 year should only be performed under carefully supervised conditions in hospital.

m. Treatment with desmopressin should be reassessed during acute intercurrent illness and the fluid and electrolyte balance should be carefully monitored

#### **USE IN PREGNANCY:**

Category B2. Reproduction studies performed in rats and rabbits with subcutaneous doses up to 50ng/kg/day and 10µg/kg/day, respectively, have revealed no evidence of harm to the foetus due to desmopressin.

There are several publications on the management of diabetes insipidus in pregnant women with no harm to the foetus reported, however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormone, MINIRIN in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

#### **USE IN LACTATION:**

Subtherapeutic levels of DDAVP have been detected in the breast milk of lactating women. Until further evidence of its safe use during lactation is available, it is not to be administered to lactating women.

#### **INTERACTION WITH OTHER MEDICINES:**

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

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

Glibenclamide. Glibenclamide inhibits the anti-diuretic effect of DDAVP.

Clofibrate. Clofibrate has potentiated and prolonged DDAVP effect in a few patients.

Chlorpropamide. Chlorpropamide has been reported to potentiate endogenous ADH and therefore may react similarly with DDAVP.

NSAIDS may induce fluid retention / hyponatraemia

#### **ADVERSE EFFECTS:**

Common reactions - Nil with low doses.

Less common or dose related reactions - Tachycardia, fall in diastolic blood pressure by 10-20%, headache, nausea, mild abdominal cramp, vomiting, nasal congestion, facial flushing, vulval pain, water intoxication from overhydration. Hyponatraemia is an infrequent but serious adverse event, which has been reported at a rate of approximately 15 cases per 100,000 patient years of exposure for intranasal formulations and 6 cases per 100,000 years for oral formulations.

#### **DOSAGE AND ADMINISTRATION:**

a. For ADH-sensitive Cranial Diabetes Insipidus

##### **Adult.**

The average daily dose is 10 to 40 micrograms intranasally, or 1 to 4 micrograms by injection. The daily dose is usually given as two divided doses separately adjusted if necessary for an adequate diurnal rhythm of water turnover. A single daily dose may be appropriate if it is tolerated and also satisfactorily controls the diabetes insipidus. About one third of patients may be controlled on a small daily dose. For immediate postoperative polyuria and polydipsia, the dose should be controlled by measurement of the urine osmolality.

##### Mode of Administration:

Intranasal. The required dose is first loaded from the dropper bottle into the plastic catheter following the manufacturer's detailed instructions. One end of the catheter is placed into the mouth and the other end into a nostril; and the contents of the catheter are blown into the nasal cavity.

Parenteral. Desmopressin acetate injection may be administered intramuscularly or intravenously when the intranasal route is inconvenient.

When using doses of less than 4 micrograms the dose should be drawn up from the ampoule as a fraction of a millilitre using a diabetic syringe and not prepared by dilution or given by infusion. This is necessary because of the tendency of peptides to adhere to glass surfaces when in very dilute solutions.

##### **Paediatric**

Intranasal. 2.5 to 20 micrograms daily.

Parenteral. Up to 400 nanograms daily.

The intranasal or parenteral daily doses are usually given as 2 divided doses separately adjusted if necessary. A single daily dose may be appropriate if it is tolerated and also satisfactorily controls the diabetes insipidus.

b. As a diagnostic test of renal concentrating capacity. (See Warnings: Overhydration)

##### Intranasal

**Adults:** Single dose of up to 40 micrograms

**Children:** Single dose of up to 20 micrograms

**Infants:** Single dose of up to 10 micrograms

##### Intramuscular

**Adults:** Single dose of up to 4 micrograms

**Paediatric:** Due to lack of safety data, paediatric use is not recommended.

**c. Mild to Moderate Haemophilia A and von Willebrand's disease**

**Parenteral Administration only**

VIII:C assays should be undertaken regularly during treatment. When surgery or dental extractions are to be undertaken, tranexamic acid should be given intravenously (10 mg tranexamic acid/kg) unless contraindicated. Then 25 mg/kg orally 3-4 times daily until healing is complete.

Within 1/2 hour before surgery 0.4 micrograms DDAVP/kg diluted to 10-100mL in isotonic saline is given as slow intravenous infusion over 15-20 min. Before and 20 min. after the infusion, VIII:C assays and in the case of von Willebrand's disease determination of VIIIIR:Ag and bleeding time should also be carried out unless the patient's response is known from pretesting. The critical haemostatic level for dentistry or surgery should be judged by the same criteria as if the patient were being managed with blood products, except that the level may be expected to continue to rise for 1-2 hours after the infusion rather than beginning to fall immediately.

If a sufficient response was obtained with the initial dose of DDAVP, further doses may be given at 12-hourly intervals so long as cover is required. VIII:C levels must be monitored regularly since some patients have shown a diminishing response to successive infusions.

If a sufficient level has not been reached to cover the intended surgical procedure, a supplementary dose of factor-VIII concentrate should be given to make up the deficit.

**d. Treatment of bleeding in subjects with inherited and acquired platelet function defects.** Minirin is given at a dose of 0.3 µg/kg diluted to 50mL in isotonic saline as a slow intravenous infusion over 30 minutes. Further doses may be given at 12 hourly intervals as long as cover is required. In some patients a 12 hourly injection for 3-4 days may result in clinically significant fluid retention. In some studies combined therapy consisting of Minirin and a fibrinolytic inhibitor was used. **General surgery (except cardiac surgery)** Half an hour prior to surgery, Minirin is given as a slow intravenous infusion over 30 minutes.

**Cardiac surgery** Minirin is to be administered in patients with a prolonged bleeding time when cardiopulmonary bypass has been completed and immediately after protamine has been given to neutralise the effect of heparin or at any time thereafter.

**Non-surgical use** In patients with epistaxis, menorrhagia, or other bleeding episodes, Minirin is given as a slow intravenous infusion over 30 minutes.

Red blood cell transfusion is of value in improving haemostasis in uraemic patients.

**INSTRUCTIONS TO BE GIVEN TO PATIENTS:**

Patient using intranasal DDAVP for the first time should be adequately instructed by their physician to ensure that the dose is correct. Patients should be warned not to inhale the drug.

Physicians should base their instruction on the manufacturer's patient leaflet which also gives information on cleaning the catheter and storing the solution. **Parenteral:** DDAVP is not intended for self administration.

**OVERDOSAGE:**

LD 50 for animals has not been established but no untoward reactions were observed in mice which received 2 milligrams/kg by intravenous injection.

Treatment is based on restoration of fluid and electrolyte balance. The dose should be reduced, the frequency of administration decreased, or the drug withdrawn according to the severity of the overdose. Diuretics and electrolyte therapy may be given as appropriate. There is no specific antidote for DDAVP.

**PRESENTATION AND STORAGE CONDITIONS:**

**Intranasal:** Minirin Intranasal Solution: Dropper bottles of 2.5mL containing 100 micrograms/mL supplied with plastic rhinyle (catheter).

**Parenteral:** Minirin injection **4µg/mL:** Box of 10 ampoules of 1 mL.

Octostim injection **15µg/mL** (for intravenous administration only): Box of 10 ampoules of 1 mL.

Store protected from light between 2 to 8°C. Do not freeze.

**NAME AND ADDRESS OF THE SPONSOR:**

Ferring Pharmaceuticals Pty Ltd  
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AUSTRALIA

**POISON SCHEDULE OF THE MEDICINE:**

Prescription Medicine

[Therapeutic Goods Administration Approved: 28 September 1993]

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