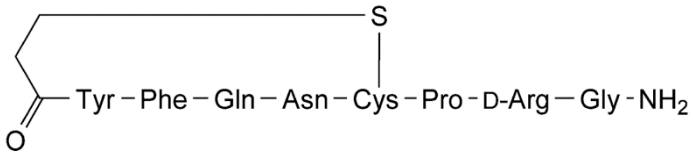
MINIRIN® Nasal Drops
MINIRIN®/OCTOSTIM® Injections

NAME OF THE MEDICINE

Desmopressin Acetate

Synonyms of desmopressin:

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



CAS Nos:

Desmopressin base	16679-58-6
Desmopressin acetate	62288-83-9

Molecular weights:

Desmopressin base	1069.22
Desmopressin acetate	1183.34

Physical and chemical characteristics:
A white, fluffy powder, soluble in water, alcohol and glacial acetic acid.

DESCRIPTION

MINIRIN Injection 4 micrograms/mL and OCTOSTIM Injection 15 micrograms/mL, and MINIRIN Nasal Drops contain desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin, also known as antidiuretic hormone (ADH). 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 to form desmopressin:
a. desamination of the N-terminal of cysteine-1
b. substitution of 8-D-arginine for 8-L-arginine

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 ADH.

MINIRIN and OCTOSTIM Injections also contain, sodium chloride, hydrochloric acid and water for injections. MINIRIN Nasal Drops also contains sodium chloride, chlorobutanol hemihydrate as preservative, hydrochloric acid and purified water.

PHARMACOLOGY

Pharmacotherapeutic group: vasopressin and analogues
ATC code: H01B A02

Pharmacokinetics

a. Absorption: Using i.v. or i.m. doses, 100% of desmopressin is systematically 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 desmopressin from the enzyme which inactivates ADH.
d. Excretion: The excretion of desmopressin is similar to that of ADH but considerably slower. Clinically intranasal desmopressin is effective for approximately 10-12 hours.

Half-Life: No information is available for intranasal administration. For i.v. administration of labelled desmopressin, 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

Desmopressin 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 (0.3 micrograms/kg intravenously) of desmopressin acetate 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 micrograms/kg intravenously, desmopressin 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_2-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 (MINIRIN Nasal Drops and MINIRIN Injection)

By Intranasal and Parenteral Administration.

The treatment of ADH-sensitive cranial diabetes insipidus, including treatment of post-hypophysectomy polydipsia and polyuria.

Renal Concentrating Capacity (MINIRIN Nasal Drops and MINIRIN Injection)
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 Haemophillia A and von Willebrand's Disease (MINIRIN and OCTOSTIM Injections)
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 (MINIRIN and OCTOSIM Injections)
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. Desmopressin acetate 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

- Habitual and psychogenic polydipsia (resulting in a urine production exceeding 40 mL/kg/24 hours)
- A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatraemia
- Hypersensitivity to desmopressin acetate or any of the excipients.

Additionally, For MINIRIN/OCTOSTIM Injection;
- History of unstable angina pectoris*
- von Willebrand's disease type IIB

Additionally, For MINIRIN Nasal Drops;
- Syndrome of inappropriate anti-diuretic hormone secretion (SIADH)
- Moderate and severe renal insufficiency (creatinine clearance below 50 mL/min).

PRECAUTIONS

Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus.

MINIRIN Nasal Drops and MINIRIN/OCTOSTIM Injections

a. MINIRIN Nasal Drops and MINIRIN/OCTOSTIM Injections should be used with caution in patients at risk for increased intracranial pressure; and in patients with conditions characterised by fluid and/or electrolyte imbalance.
b. Desmopressin acetate 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.

c. **Hyponatraemia and Hydration**

Hyponatraemia in the context of the use of desmopressin is generally due to fluid overload, thus careful attention to fluid balance is needed. Other causes of hyponatraemia which may need excluding depending on the clinical situation include renal salt wasting due to central lesions, renal disorders or adrenal disorders.

Central Diabetes Insipidus

- The aim of fluid therapy is to replace urinary fluid loss.
- Children, patients with cognitive impairment, and patients with inadequate thirst sensation need close monitoring of fluid intake.
- Regular monitoring of serum and urinary sodium and osmolality is recommended at the discretion of the clinician.

* Please note changes in Product Information.

Primary Nocturnal Enuresis

- When used for the treatment of primary nocturnal enuresis the fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration.
- Check serum electrolytes at least once if therapy is continued beyond 7 days.

Testing of renal concentrating capacity

- When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 L to satisfy thirst from 1 hour before until at least 8 hours after administration. Renal concentrating capacity testing in children below the age of 1 year should only be performed under carefully supervised conditions in hospital.

d. Vasodilator effect. At doses used to treat bleeding, MINIRIN has a vasodilatory effect, causing a minor decrease in diastolic or systolic blood pressure.
e. Myocardial ischaemia. Desmopressin acetate should be used with caution in patients with cardiovascular disease and the elderly.
f. Hypersensitivity. Patients with a known hypersensitivity to ADH, should be tested for sensitivity to desmopressin acetate before the full dose is given.
g. Post-operative use. The use of desmopressin in a post-operative setting should only occur after the diagnosis of diabetes insipidus has been confirmed. Small doses should be administered with strict fluid balance and regular clinical assessment.
h. 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 desmopressin acetate.
i. MINIRIN should be used with caution in patients with cystic fibrosis because of impaired water handling and increased risk of hyponatraemia.

MINIRIN Nasal Drops

j. Only use MINIRIN Nasal Drops in patients where orally administered formulations are not feasible.
k. Infants, elderly and patients with serum sodium levels in the lower range of normal may be at an increased risk of hyponatraemia.* Treatment with desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).
l. When MINIRIN Nasal Drops is prescribed it is recommended to start at the lowest dose, ensure compliance with fluid restriction instructions, increase dose progressively, with caution. Patient dosage should be reassessed periodically. Ensure adult supervision when a child is administering the drug in order to control the dose intake.
m. All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.
n. Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.*
o. Nasal infections/rhinorrhoea. Intranasal administration may be ineffective in the presence of local infection or rhinorrhoea.

MINIRIN/OCTOSTIM Injections

p. MINIRIN/OCTOSTIM Injections should be used with caution in very young and elderly patients.
q. *For Haemostatic Use*. Measures to prevent fluid overload must be taken in patients requiring treatment with diuretic agents.*
r. Special attention must be paid to the risk of fluid retention/hyponatraemia. 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, 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 MINIRIN/OCTOSTIM Injections interrupted.
s. MINIRIN/OCTOSTIM Injection does not reduce prolonged bleeding time in thrombocytopenia.*

* Please note changes in Product Information.

t. MINIRIN/OCTOSTIM Injection should be used with caution in moderate and severe renal insufficiency (creatinine clearance below 50 mL/min).
u. Treatment with desmopressin should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Use in Pregnancy (Category B1)*

Caution should be exercised when prescribing to pregnant women.

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number of exposed pregnancies in women with bleeding complications (n=216) indicate no adverse effects of desmopressin on pregnancy or on the health of the fetus/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, embryonic/fetal development, parturition or postnatal development.

Embryofetal development studies performed with desmopressin in rats and rabbits given subcutaneous doses up to 50 ng/kg/day and 200 µg/kg/day, respectively, and in rats given intravenous doses up to 241 µg/kg/day, revealed no evidence for a harmful effect on the fetus.

Use in Lactation

Subtherapeutic levels of desmopressin acetate 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.

INTERACTIONS WITH OTHER MEDICINES

Drug Class	Action	Impact of Concomitant use of MINIRIN
Tricyclic antidepressants, selective serotonin reuptake inhibitor, chlorpromazine	Induce SIADH	Water retention and hyponatraemia
Anti-epileptic - carbamazepine		
Sulphonylurea antidiabetics (e.g. chlorpropamide)		
Non-steroidal anti-inflammatories (NSAID)	-	Fluid retention/hyponatraemia

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.

ADVERSE EFFECTS

The below table is based on the frequency of adverse reactions reported with MINIRIN Nasal Drops and MINIRIN/OCTOSTIM Injections, conducted in children and adults.

MedDRA Organ Class	Very common (>10%)	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.1-0.01%)
Metabolism and nutrition disorders			Hyponatraemia[1)]	

* Please note changes in Product Information.

			Water intoxication (from overhydration)[2)]	
Psychiatric disorders		Insomnia[3)], Affect lability[4)], Nightmare[4)], Nervousness[4)], Aggression[4)]		
Nervous system disorders		Headache[5)]		Dizziness[6)]
Cardiac disorders		Tachycardia[2)]		
Vascular disorders		Transient fall in blood pressure with a reflex tachycardia and facial flushing at the time of administration[6)]		
Respiratory, thoracic and mediastinal disorders	Nasal congestion[3)], Rhinitis[3)]	Epistaxis[3)], Upper respiratory tract infection[4)]		
Gastrointestinal disorders		Gastroenteritis, Nausea[5)], Abdominal pain[5)]	Vomiting[5)]	
General disorders and administration site conditions		Fatigue[6)]		
Investigations	Body temperature increased [4)]			

[1)] Hyponatraemia is reported as 'Very Rare (<1/10 000)' for the injection only.
[2)] Reported for the injection only
[3)] Reported for the nasal only
[4)] Reported primarily in children and adolescents for nasal only
[5)] Reported in connection with hyponatraemia
[6)] Reported for injections at high doses

Post marketing experience*

The table below lists additional adverse drug reactions reported in the post marketing period in children, adolescents and adults treated with desmopressin, distributed by organ class. The frequency of adverse drug reactions occurring in the post marketing period is regarded as unknown.

MedDRA Organ Class	**ADR for when frequency is unknown**
Immune system disorders	Allergic reaction
Metabolism and nutrition disorders	Dehydration[1)]
Psychiatric disorders	Confusional state[2)]
Nervous system disorders	Convulsions[2)], Coma[2)], Dizziness[2)], Somnolence
Vascular disorders	Hypertension
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Diarrhoea

* Please note changes in Product Information.

Skin and subcutaneous tissue disorders	Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders	Muscle spasms[2)]
General disorders and administration site conditions	Fatigue[2)], Peripheral oedema[2)], Chest pain, Chills
Investigations	Weight increased[2)]

[1)] Post marketing reporting in the CDI indication
[2)] Post marketing reporting in connection with hyponatraemia

DOSAGE AND ADMINISTRATION

Administration of desmopressin acetate by intravenous or intramuscular injection may be used when the intranasal route is inconvenient. Caution: The intravenous or intramuscular dose is about one tenth of the intranasal dose.

a. For ADH-sensitive Cranial Diabetes Insipidus (MINIRIN Nasal Drops and MINIRIN Injection)

Adult.
The average daily dose is 10 to 40 micrograms intranasally, or 1 to 4 micrograms by injection.

Paediatric
Intranasal: 2.5 to 20 micrograms daily.
Parenteral: Up to 400 nanograms daily.

The daily dose is usually given as two divided doses. The dosage must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, but not excessive, water turnover. In the event of signs of water retention/hyponatraemia, treatment should be interrupted and the dose adjusted. 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. Monitoring in a high dependency setting is recommended. If there is doubt that a dose has been administered, a second dose should not be given until diuresis has occurred.

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 then 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.

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 (MINIRIN Nasal Drops and MINIRIN Injection). (See PRECAUTIONS: 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 (MINIRIN and OCTOSTIM Injections).

VIII: C assays should be undertaken regularly during treatment.
Within 1/2 hour before surgery 0.4 micrograms desmopressin acetate/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 VIIIR: 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 desmopressin acetate, 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 and OCTOSTIM Injections).

Desmopressin acetate is given at a dose of 0.3 micrograms/kg diluted to 50 mL 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 desmopressin acetate and a fibrinolytic inhibitor was used.
General surgery (except cardiac surgery). Half an hour prior to surgery, desmopressin acetate is given as a slow intravenous infusion over 30 minutes.
Cardiac surgery. Desmopressin acetate 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, desmopressin acetate 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:

Nasal Drops: Patient using intranasal desmopressin acetate 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: Desmopressin acetate is not intended for self-administration.

OVERDOSAGE

Overdose of MINIRIN Nasal Drops and MINIRIN/OCTOSTIM Injections leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment: Treatment of hyponatraemia should be individualised. Treatment should include discontinuing desmopressin, instigation fluid restriction and symptomatic treatment if needed.

PRESENTATION AND STORAGE CONDITIONS

Intranasal:
MINIRIN Nasal Drops: Dropper bottles of 2.5mL containing 100 micrograms/mL supplied with plastic rhinyle (catheter).

Parenteral:
MINIRIN Injection **4 micrograms/mL**: Box of 10 ampoules of 1 mL.
OCTOSTIM Injection **15 micrograms/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
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

4/10/1991 (MINIRIN Nasal Drops)
21/08/1992 (MINIRIN 4µg/mL Injection)
15/02/1994 (OCTOSTIM 15 µg/mL Injection)

DATE OF MOST RECENT AMENDMENT

12 January 2017

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