

MINIRIN® Nasal Spray

NAME OF THE MEDICINE:

Desmopressin Acetate

Synonyms:

DDAVP

1-desamino-8-D-Arginine vasopressin.

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

CAS No. 62357-86-2 (trihydrate)

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

SCH₂CH₂CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH₂

Minirin Nasal Spray contains desmopressin acetate, sodium chloride, citric acid monohydrate, sodium phosphate-dibasic dihydrate, benzalkonium chloride solution 50% as preservative 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.

Pharmacokinetics

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. The extent of absorption is similar for the spray and the rhinyle with a trend towards higher absorption associated with the spray. Mean C_{max} and AUC values are approximately 40% higher with the spray than with the rhinyle; however, there is considerable intra and inter individual variability in plasma levels of desmopressin.

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 acetate from the enzyme which inactivates ADH.

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

Half-Life No information is available for intranasal administration. For i.v. administration of labelled desmopressin acetate, 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 acetate 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 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 0.3-0.4µg/kg desmopressin acetate 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 V₂-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.

PRODUCT INFORMATION

INDICATIONS:

Diabetes Insipidus

The treatment of ADH-sensitive cranial diabetes insipidus, including treatment of post-hypophysectomy polydipsia and polyuria. Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus. 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. Note: Minirin Nasal Spray is for intranasal administration only.

Nocturnal Enuresis

Minirin Nasal Spray is indicated for the symptomatic treatment of primary nocturnal enuresis in patients who have normal ability to concentrate urine. Minirin Nasal Spray should be used only in patients who are refractory to the enuresis alarm or in patients in whom enuresis alarm is contraindicated or inappropriate.

Renal Concentrating Capacity

By intranasal administration to adults and children as a diagnostic test to establish renal concentrating capacity.

CONTRAINDICATIONS:

Habitual and psychogenic polydipsia.

Cardiac insufficiency and other conditions requiring treatment with diuretic agents.

Hypersensitivity to desmopressin acetate or any of the components of Minirin Nasal Spray.

SIADH; syndrome of inappropriate anti-diuretic hormone secretion.

Known Hyponatraemia.

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

PRECAUTIONS:

a. Only use nasal spray in patients where orally administered formulations are not feasible (See – Post Marketing Experience).

b. 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 desmopressin acetate 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 (see Precautions – Hyponatraemia and Precautions – Fluid Intake) and to ensure that only the recommended dose of Minirin is taken

c. Laboratory Tests: For the healthy patient with primary nocturnal enuresis, it is advisable to check serum electrolytes at least once if therapy is continued beyond seven days.

d. Hyponatraemia: Treatment without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain, and, in serious cases, convulsions). The risk of hyponatraemia seems to be greater during the first weeks following initiation of therapy.

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

When used for the treatment of nocturnal enuresis the fluid intake must be limited to a minimum and only to satisfy thirst from one hour before until eight hours after administration.

f. In the control of diabetes insipidus the lowest effective dose should be used. Patient dosage should be reassessed periodically.

g. Desmopressin acetate should not be administered to dehydrated or overhydrated patients until water balance has been adequately restored.

h. Nasal infections/rhinorrhoea. Intranasal administration may be ineffective and unreliable absorption may result in the presence of local infection or rhinorrhoea. Treatment should cease until condition resolves in patients being treated for enuresis. Bodyweight should be regularly monitored.

i. Myocardial ischaemia. Desmopressin acetate should be used with caution in patients with cardiovascular disease and the elderly.

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

k. 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.

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

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

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

o. Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for primary nocturnal enuresis.

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

q. Additional information. High doses of desmopressin such as those used to treat bleeding are contraindicated in patients with Type IIB von Willebrand's disease. Use of Minirin Nasal Spray in this patient group is not approved or recommended. At high doses, intravenously administered desmopressin has a vasodilatory effect and may cause a minor decrease in systolic or diastolic blood pressure. In haemophilia where high doses are given extreme care is paid to water balance.

r. Ensure adult supervision when a child is administering the drug.

s. Increase dose progressively and with caution.

PRODUCT INFORMATION

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 anti-diuretic 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 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.

CARCINOGENICITY/MUTAGENICITY:

See Use In Pregnancy.

INTERACTIONS WITH OTHER MEDICINES:

- NSAIDs may induce fluid retention/hyponatraemia.
- 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.
- Use of large doses of intranasal desmopressin with other pressor agents should only be done with careful patient monitoring.

ADVERSE EFFECTS:

Infrequently, high dosages of Minirin Nasal Spray or Minirin Intranasal Solution have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported. The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

Adverse Reaction	Placebo (N=59)	Desmopressin 20mcg (N=60)	Desmopressin 40mcg (N=61)
	%	%	%
Body as a Whole			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
Nervous System			
Depression	2	0	0
Dizziness	0	0	3
Respiratory System			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
Cardiovascular System			
Vasodilation	2	0	0
Digestive System			
Gastrointestinal Disorder			
Nausea	0	2	0
	0	0	2

PRODUCT INFORMATION

Adverse Reaction	Placebo (N=59)	Desmopressin 20mcg (N=60)	Desmopressin 40mcg (N=61)
Skin & Appendages			
Leg Rash	2	0	0
Rash	2	0	0
Special Senses			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

Post marketing experience

A worldwide survey of adverse reactions following the spray in patients with nocturnal enuresis reported the infrequent occurrence of hyponatraemia, water intoxication oedema, convulsions, syncope and unconsciousness.

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.

Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Isolated cases of emotional disturbances in children have been reported.

DOSAGE AND ADMINISTRATION:

a. For ADH-sensitive Cranial Diabetes Insipidus

Adult. The average daily dose is 10 to 40 micrograms intranasally. 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, 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.

Paediatric

Intranasal. 2.5 to 20 micrograms daily.

b. Nocturnal Enuresis

Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 micrograms (μg) or 0.2 mL solution intranasally at bed time. Adjustment up to 40 μg is suggested if the patient does not respond. Some patients may respond to 10 and a downward adjustment to 10 μg can be made if the patient responds to 20 μg . Note that each actuation of the spray contains 10 μg of desmopressin acetate. It is recommended that one half of the dose be administered per nostril. Since the spray cannot deliver less than 10 μg , smaller doses should be delivered by the rhinyle delivery system. A restricted fluid intake is recommended overnight after administration. (See Precautions: Fluid Intake). Patients should be treated for an initial period of 1-3 months followed by a withdrawal of 1 week to assess cure rate. Relapsed patients should be continued for a further 1-3 months at the standard dose.

c. As a diagnostic test of renal concentrating capacity (See Precautions: Overhydration and Fluid Intake)

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 (See Precautions)

INSTRUCTIONS TO BE GIVEN TO PATIENTS:

Spray

The physician should carefully explain the use of the spray device and advise the patient not to inhale. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use. Prime the spray before using it for the first time by pressing it at least four times, or until an even spray is obtained. If the spray has not been used during the last 7 days it is necessary to prime it again by pressing it a couple of times until an even spray is obtained before placing the nozzle in the nostril.

OVERDOSAGE:

LD50 for animals has not been established but no untoward reactions were observed in mice which received 2 milligrams/kg by intravenous injection. Overdosage of Minirin can lead to water retention and hyponatraemia. Treatment is based on restoration of fluid and electrolyte balance. Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Asymptomatic hyponatraemia 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 frusemide should be added.

PRODUCT INFORMATION

PRESENTATION AND STORAGE CONDITIONS:

Spray pump of 5 mL delivering 50 doses of 10 µg desmopressin acetate (Not marketed in Australia).

Spray pump of 6 mL delivering 60 doses of 10 µg desmopressin acetate.

Desmopressin free base represents 89% of the desmopressin acetate content. This is due to the difference in molecular weight as well as the presence of acetic acid/acetate, water and impurities.

Store below 25°C. Protect from light. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR:

Ferring Pharmaceuticals Pty Ltd, Suite 2B, Level 2, 802 Pacific Highway, Gordon, NSW, 2072, AUSTRALIA

POISON SCHEDULE OF THE MEDICINE:

Prescription Medicines

[Therapeutic Goods Administration Approved: 11 April 1997].

[Date of most recent notification 28 November 2008]