AUSTRALIAN PRODUCT INFORMATION - MINIRIN® (desmopressin acetate) 10 micrograms/actuation Nasal Spray

1. NAME OF THE MEDICINE

Desmopressin acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MINIRIN Nasal Spray also contains sodium chloride, citric acid monohydrate, dibasic sodium phosphate-dihydrate, benzalkonium chloride solution 50% as preservative and water-purified.

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.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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, and where the oral administration of desmopressin is not feasible.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Note: MINIRIN Nasal Spray is for intranasal administration only. 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

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

Paediatric
2.5 to 20 micrograms 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 post-operative 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.

b. Primary 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 or 0.2 mL solution intranasally at bed time. Adjustment up to 40 micrograms is suggested if the patient does not respond. Some patients may respond to 10 and a downward adjustment to 10 micrograms can be made if the patient responds to 20 micrograms. Note that each actuation of the spray contains 10 micrograms of desmopressin acetate. It is recommended that one half of the dose be administered per nostril. Since the spray cannot deliver less than 10 micrograms, 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

Instructions to be given to patients:

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.

4.3 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.
- Moderate and severe renal insufficiency (creatinine clearance below 50 mL/min).
- Known hyponatraemia.
- Syndrome of inappropriate anti-diuretic hormone secretion (SIADH).
- Hypersensitivity to desmopressin acetate or any of the excipients in MINIRIN Nasal Spray.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

b. Only use MINIRIN Nasal Spray in patients where orally administered formulations are not feasible (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS): Post marketing experience).

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. There is some evidence from post-marketing data for the occurrence of severe hyponatraemia in association with the nasal spray formulation of desmopressin when it is used in the treatment of central diabetes insipidus.

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.

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. When MINIRIN Nasal Spray is prescribed it is recommended to start at the lowest dose, ensure compliance with fluid restriction instructions; increase dose progressively, with caution; ensure adult supervision when a child is administering the drug in order to control the dose intake.
e. Desmopressin acetate should not be administered to dehydrated or overhydrated patients until water balance has been adequately restored.
f. Nasal infections/rhinorrhoea. Intranasal administration may be ineffective and unreliable absorption may result in the presence of local infection or rhinorrhoea. In patients being treated for enuresis, treatment should cease until the nasal condition resolves. Bodyweight should be regularly monitored.
g. Myocardial ischaemia. Desmopressin acetate should be used with caution in patients with cardiovascular disease and the elderly.
h. Hypersensitivity. Patients with a known hypersensitivity to ADH, should be tested for sensitivity to desmopressin acetate before the full dose is given.
i. 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.
j. MINIRIN Nasal Spray 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 of increased intracranial pressure.
l. Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for primary nocturnal enuresis.
m. 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).
n. 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.
o. Due to the presence of benzalkonium chloride, MINIRIN Nasal Spray may cause bronchospasm.

Use in elderly
See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Paediatric use
See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Effects on laboratory tests
See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Table 1. Pharmacodynamics interactions

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

- Use of large doses of intranasal desmopressin with other pressor agents should only be done with careful patient monitoring.
- 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

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

Sub-therapeutic 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

Table 2. *Primary Nocturnal enuresis* - The following table lists the percentage of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for primary nocturnal enuresis.

Adverse Reaction	Placebo (N=59)	Desmopressin 20 mcg (N=60)	Desmopressin 40 mcg (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	0	2	0
Nausea	0	0	2
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

The below table is based on the frequency of adverse drug reactions reported in clinical trials with MINIRIN Nasal Spray, conducted in children and adults for treatment of Central Diabetes Insipidus (CDI), Primary Nocturnal Enuresis (PNE) and Renal Concentrating Capacity Testing (RCCT) (N=745).

Table 3. Adverse reactions with MINIRIN Nasal Spray

MedDRA Organ Class	Very common (>10%)	Common (1-10%)	Uncommon (0.1-1%)
Metabolism and nutrition disorders			Hyponatraemia
Psychiatric disorders		Insomnia, Affect lability[2)], Nightmare[2)], Nervousness[2)], Aggression[2)]	

Nervous system disorders		Headache[1)]	
Respiratory, thoracic and mediastinal disorders	Nasal congestion, Rhinitis	Epistaxis, Upper respiratory tract infection[2)]	
Gastrointestinal disorders		Gastroenteritis, Nausea[1)], Abdominal pain[1)]	Vomiting[1)]
Investigations	Body temperature increased[2)]		

[1)] Reported in connection with hyponatraemia.
[2)] Reported primarily in children and adolescents.

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 nasal spray, distributed by organ class. The frequency of adverse drug reactions occurring in the post-marketing period is unknown.

Table 4. Adverse drug reactions reported in the post marketing period

MedDRA Organ Class	ADR for when frequency is unknown
Immune system disorders	Allergic reaction
Metabolism and nutrition disorders	Dehydration[3)], Water intoxication[4)]
Psychiatric disorders	Confusional state[1)], Emotional disturbances[2)]
Nervous system disorders	Convulsions[1)], Coma[1)], Dizziness[1)], Somnolence, Syncope[4)], Loss of consciousness[4)].
Vascular disorders	Hypertension, Flushing
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Sore throat, Cough
Gastrointestinal disorders	Diarrhoea
Skin and subcutaneous tissue disorders	Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders	Muscle spasms[1)]
General disorders and administration site conditions	Fatigue[1)], Peripheral oedema[1)], Oedema[4)], Chest pain, Chills
Investigations	Weight increased[1)]

[1)] Reported in connection with hyponatraemia.
[2)] Reported primarily in children and adolescents.
[3)] Reported in the CDI indication.
[4)] Reported in the PNE indication.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose of MINIRIN Nasal Spray 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 treatment, instigation fluid restriction and symptomatic treatment, if needed.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: vasopressin and analogues.
ATC code: H01B A02

MINIRIN Nasal Spray contains 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.

Mechanism of action

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 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 V_2-receptor agonist activity.

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.

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)

Clinical trials
Relevant data not documented in this Product Information.

5.2 PHARMACOKINETIC PROPERTIES

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. 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.

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

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

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to **section 2 – QUALITATIVE and QUANTITATIVE COMPOSITION**

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

6.5 NATURE AND CONTENTS OF CONTAINER

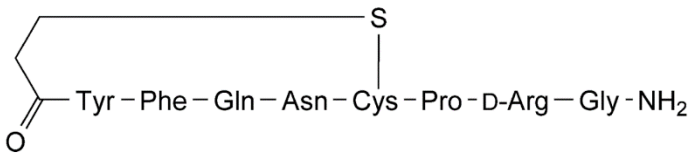
Spray pump of 5 mL delivering 50 doses of 10 micrograms desmopressin acetate.
Spray pump of 6 mL delivering 60 doses of 10 micrograms desmopressin acetate.
Not all pack sizes are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSIOCHEMICAL PROPERTIES

Synonyms of desmopressin:
DDAVP
1-desamino-8-D-Arginine vasopressin.
Desamino-cys-1-D-Arginine-8 vasopressin.



CAS No (base):
16679-58-6

Molecular weight (base): 1069.22

Desmopressin is a white, fluffy powder, soluble in water, alcohol and glacial acetic acid.

7. MEDICINE SCHEDULE (POISONS STANDARD)

(S4) Prescription Only Medicine

8. SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

Toll free: 1800 337 746

9. DATE OF FIRST APPROVAL

21 April 1997

10. DATE OF REVISION

28 August 2019

For the most current approved PI, please refer to https://www.ebs.tga.gov.au/ or http://www.ferring.com.au/

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Summary table of changes

Section Changed	Summary of new information
All	PI reformatted to align with TGA's *Form for Providing Product Information*, March 2018 version.
5.3	Addition of standard text as per TGA's *Form for Providing Product Information*, March 2018 version.
6.2	Addition of standard text as per TGA's *Form for Providing Product Information*, March 2018 version.
6.3	Addition of standard text as per TGA's *Form for Providing Product Information*, March 2018 version.
6.6	Addition of standard text as per TGA's *Form for Providing Product Information*, March 2018 version.