AUSTRALIAN PRODUCT INFORMATION - MINIRIN® (desmopressin) Melt

1. NAME OF THE MEDICINE

Desmopressin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MINIRIN Melt, a sublingual wafer, contains the active substance, desmopressin, (present as the hydrated acetate), a synthetic structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. MINIRIN Melt also contains gelatin, mannitol and citric acid.

Desmopressin free base represents approximately 89% of the desmopressin acetate content. This is due to the presence of acetic acid/acetate, water and impurities.

Excipients with known effect: contains sulfites and fish products.

3. PHARMACEUTICAL FORM

A white, fluffy powder, soluble in water, in alcohol and in glacial acetic acid.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MINIRIN Melt is indicated for the treatment of

- cranial diabetes insipidus
- primary nocturnal enuresis in patients from 6 years of age with normal ability to concentrate urine, who are refractory to an enuresis alarm or in whom an enuresis alarm is contraindicated or inappropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

MINIRIN Melt is placed under the tongue where it dissolves without the need for water.

If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration the medication should be discontinued.

Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of MINIRIN tablets (see **section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**).

Cranial Diabetes Insipidus
Dosage is individual in diabetes insipidus but the total daily sublingual dose normally lies in the range of 120 μg to 720 μg. A suitable starting dose in adults and children is 60 μg three times daily, administered sublingually. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 60 μg to 120 μg sublingually three times daily.

In the event of signs of water retention/hyponatraemia, treatment should be interrupted and the dose should be adjusted (see **section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Primary Nocturnal Enuresis
The recommended initial dose is 120 μg at bedtime, administered sublingually. If this dose is not sufficiently effective, the dose may be increased up to 240 μg sublingually. Fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration.

In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be interrupted until the patient has fully recovered. When restarting treatment strict fluid restriction should be enforced (see **section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

MINIRIN Melt is intended for treatment periods of up to 3 months. The need for continued treatment should be reassessed by means of a period of at least one week without MINIRIN Melt.

4.3 CONTRAINDICATIONS

MINIRIN Melt is contraindicated in:

- Habitual or 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 or to any of the excipients of MINIRIN Melt.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

When used for primary nocturnal enuresis, the fluid intake must be limited to a minimum from 1 hour before administration, until the next morning (at least 8 hours) after administration. Treatment without concomitant reduction of fluid intake may lead to water retention and/or hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions). In the event of signs or symptoms of water retention and/or hyponatraemia, treatment should be interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction should be enforced. All patients and, when applicable, their guardians, should be carefully instructed to adhere to the fluid restrictions.

In the event of signs or symptoms of water retention/hyponatraemia in cranial diabetes insipidus patients, treatment should be interrupted and the dose should be adjusted.

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.

Caution should be exercised in patients with other causes of urinary frequency (e.g. multiple sclerosis or urge incontinence), and in diabetes mellitus and renal impairment, since the use of desmopressin has not been well studied in these populations.

Elderly patients and patients with low serum sodium levels may have an increased risk of hyponatraemia (see **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - USE IN THE ELDERLY**).

Precautions to avoid hyponatraemia must be taken in:

- conditions characterised by fluid and/or electrolyte imbalances (such as systemic infections, fever, gastroenteritis and syndrome of inappropriate ADH secretion (SIADH)) (see **section 4.3 - CONTRAINDICATIONS**)
- conditions requiring concomitant treatment with diuretic agents

- concomitant treatment with drugs known to induce SIADH (see **section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**) including careful attention to fluid restrictions and more frequent monitoring of serum sodium
- concomitant treatment with NSAIDs (see **section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**)

Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Precautions must be taken in patients at risk of increased intracranial pressure.

For each approved indication the lowest effective dose should be used. Patient dosage should be reassessed periodically.

MINIRIN Melt should not be administered to dehydrated or overhydrated patients until water balance has been adequately restored.

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

Use in the elderly

The initiation of treatment in patients over 65 years of age is not recommended. Should physicians decide to initiate Minirin treatment in these patients then serum sodium should be measured before beginning the treatment and 3 days after initiation or dosage increase, and at other times during treatment as deemed necessary by the treating physician.

Paediatric use

Dose recommendations are the same as in adults. Children should be closely observed to avoid over ingestion of fluid and to ensure that only the recommended dose of MINIRIN Melt is taken.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

- NSAIDs may induce water retention/hyponatraemia (see **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**)
- Substances which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group particularly chlorpropamide, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia
- Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect
- 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
- A standardised 27% fat meal significantly decreased absorption (rate and extent) of MINIRIN tablets. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality). Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of MINIRIN tablets.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Fertility studies have not been done. *In vitro* analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentration corresponding to recommended dose.

Use in Pregnancy

(Category B2)

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number (n=54) of exposed pregnancies in women with von Willebrand disease indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available.

However, these findings are based on case report data and should be interpreted with caution. No reproduction study has been conducted in animals using oral administration. Studies performed in rats and rabbits with cutaneous doses up to 50ng/kg/day and 10µg/kg/day, respectively, revealed no evidence for a harmful effect on the foetus.

Caution should be exercised when prescribing to pregnant women.

Use in Lactation

No study has been conducted in animals to examine the effects of desmopressin on postnatal development.

There have been no controlled studies in nursing mothers. In a single dose study in 6 lactating women administered 300µg desmopressin intranasally, the concentration of desmopressin was less in breast milk than in plasma. However, until further evidence is available for its safe use during lactation, desmopressin should not be used in breast feeding mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINIRIN Melt has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Treatment with and without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain, and in severe cases, convulsions). The risk appears to be dose-related and the elderly (>60 years) are at increased risk.

The most serious adverse reaction with desmopressin is hyponatraemia, which may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls and in severe cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect. The hyponatraemia is reversible and in children it is often seen to occur in relation to changes in daily routines affecting fluid intake and/or perspiration. In both adults and children special attention should be paid to the precautions addressed in **section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

Clinical Trials

Cranial diabetes insipidus - During clinical trials with desmopressin in diabetes insipidus the following adverse events have been reported more than once: headache, cold, weight gain, dizziness, sore throat, and depressed mood.

Primary nocturnal enuresis - Based on the frequency of adverse drug reactions reported in clinical trials with oral desmopressin conducted in children and adolescents for treatment of Primary Nocturnal Enuresis (N = 1923), the following adverse events have been listed:

MedDRA Organ Class	Very common (>10%)	Common (≥1 % & <10 %)	Uncommon (≥0.1 % & <1 %)	Rare (≥0.01 % & < 0.1 %)
Immune system disorders	-	-	-	-
Metabolism and nutrition disorders	-	-	-	-
Psychiatric disorders	-	-	Affect lability, Aggression,	(HLT) Anxiety symptoms Nightmare, Mood swing
Nervous system disorders	-	Headache[1)]	-	Somnolence
Vascular disorders	-	-	-	Hypertension
Respiratory, thoracic and mediastinal disorders	-	-	-	-
Gastrointestinal disorders	-	-	Abdominal pain [1)], Nausea [1)], Vomiting [1)], Diarrhoea	-
Skin and subcutaneous tissue disorders	-	-	-	-
Renal and urinary disorders	-	-	(HLT) Bladder and urethral symptoms	-
General disorders and administration site conditions	-	-	Oedema peripheral, Fatigue	Irritability

[1)] Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma

Post marketing experience

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

MedDRA Organ Class	Frequency not known
Immune system disorders	Anaphylactic reaction
Metabolism and nutrition disorders	Hyponatraemia[1)], Dehydration [2)], Hypernatraemia [2)]

Psychiatric disorders	Abnormal behaviour [3)], Emotional disorder [3)], Depression [3)], Hallucination [3)], Insomnia [3)]
Nervous system disorders	Disturbance in attention [3)], Psychomotor hyperactivity [3)], Convulsions [1)], Asthenia [2)], Coma [1)]
Vascular disorders	-
Respiratory, thoracic and mediastinal disorders	Epistaxis [3)]
Gastrointestinal disorders	-
Skin and subcutaneous tissue disorders	Rash [3)], Dermatitis allergic [3)], Sweating [3)],Urticaria [3)]
Renal and urinary disorders	-
General disorders and administration site conditions	-

[1)] Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma.
[2)] Post marketing reporting in the CDI indication.
[3)] Post marketing reporting in children/adolescents for 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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose of MINIRIN Melt leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment: Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given: discontinue the desmopressin treatment, fluid restriction, and symptomatic treatment if needed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: vasopressin and analogues.

Compared to vasopressin, desmopressin has a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Clinical Trials

Results of a bioequivalence study comparing desmopressin 240 µg administered sublingually as MINIRIN Melt versus a single oral 400 µg dose of MINIRIN Tablets are summarised below:

*Ratio**	*Point estimate*	*90% CI*	*Equivalence criteria*
AUC	1.0561	[0.9179, 1.2150]	0.80 – 1.25
AUC_t	1.0581	[0.9137, 1.2252]	0.80 – 1.25
C_{max}	0.8296	[0.7385, 0.9320]	0.75 – 1.33

**Melt/Tablets*

The relative bioavailability of the oral lyophilisate versus MINIRIN Tablet, based on dose adjusted values, was estimated to be 1.57 for both AUC and AUC_t and 1.23 for $C_{max.}$

5.2 PHARMACOKINETICS PROPERTIES

Absorption

The overall mean systemic bioavailability of desmopressin administered sublingually as MINIRIN Melt at doses of 200, 400 and 800 µg is 0.25%. The C_{max} was 14, 30 and 65 pg/mL after administration of 200, 400 and 800 µg, respectively. t_{max} was observed at 0.5 – 2.0 hours after dosing. The geometric mean terminal half-life is 2.8 (CV = 24%) hours.

Concomitant intake of food decreases the rate and extent of absorption by 40 %.

Distribution

The distribution volume of desmopressin after intravenous administration is 33 L (0.41 L/kg). Desmopressin does not cross the blood-brain barrier. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects.

Metabolism

In *in-vitro* studies 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.

Elimination

After iv injection 45 % of the amount of desmopressin could be recovered in the urine within 24 hours.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of desmopressin has not been adequately investigated, although *in vitro* studies in bacterial and mammalian cells revealed no mutagenicity of the drug.

Carcinogenicity

The carcinogenic potential of desmopressin has not been investigated in pre-clinical studies.

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^{o}C. Keep in original container to protect from moisture and light.

6.5 NATURE AND CONTENTS OF CONTAINER
MINIRIN Melt 60 micrograms desmopressin (as desmopressin acetate). White, round, sublingual wafer marked with a drop shaped figure on one side.

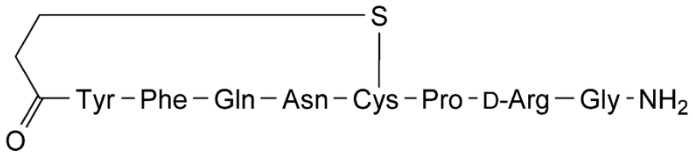
MINIRIN Melt 120 micrograms desmopressin (as desmopressin acetate). White, round, sublingual wafer marked with two drop shaped figures on one side.

MINIRIN Melt 240 micrograms desmopressin (as desmopressin acetate). White, round, sublingual wafer marked with three drop shaped figures on one side.

MINIRIN Melt is available in cartons of 30 or 100 each containing 3 to 10 Aluminium/Aluminium blister trays of 10 wafers. Not all strengths/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 PHYSICOCHEMICAL PROPERTIES
Chemical Structure



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

CAS number

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

Molecular weights:

Desmopressin base	1069.22

Desmopressin acetate 1183.34

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

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

28 June 2007

10 DATE OF REVISION

13 March 2024

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	Minor editorial changes
2	Excipients with known effect: contains sulfites and fish products.
6.5	Deletion of 10 pc pack size