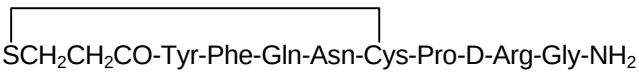
MINIRIN® Melt

Desmopressin

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



SCH_2CH_2CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH_2

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, in alcohol and in glacial acetic acid.

DESCRIPTION

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, anhydrous.

PHARMACOLOGY

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.

Pharmacokinetics

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.

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

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.

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

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}.

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.

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 ADH secretion;
- Hypersensitivity to desmopressin or to any of the excipients of MINIRIN Melt.

PRECAUTIONS

When used for primary nocturnal enuresis, fluid intake must be limited to a minimum, from 1 hour before until 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.

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 (eg 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.

Precautions to avoid hyponatraemia, including careful attention to fluid restrictions and more frequent monitoring of serum sodium, must be taken in:

- conditions characterised by fluid and/or electrolyte imbalances (such as systemic infections, fever, gastronenteritis and syndrome of inappropriate ADH secretion (SIADH))
- conditions requiring concomitant treatment with diuretic agents
- concomitant treatment with drugs known to induce SIADH (see Interactions)
- concomitant treatment with NSAIDs (see Interactions)

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

Children should be closely observed to avoid over ingestion of fluid and to ensure that only the recommended dose of MINIRIN Melt is taken.

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.

Carcinogenicity

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

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

Effects on Fertility

No study has been conducted in animals to examine the potential effects of desmopressin on fertility.

Use in Pregnancy (Category B2)

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate no adverse effects of desmopressin on pregnancy or on the health of the fetus/newborn child. 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 fetus. 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.

Interactions with Other Drugs

- NSAIDs may induce water retention/hyponatraemia.
- Substances which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None

ADVERSE REACTIONS

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.

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 & diabetes insipidus:

Common (>1/100)	General: Headache GI: Abdominal pain, nausea
Very rare (<1/10,000)	Hyponatraemia

Post marketing experience (MINIRIN Tablet)

- Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported.
- Isolated cases of visual abnormalities have been reported.
- Very rare cases of emotional disturbances in children have been reported.

DOSAGE AND ADMINISTRATION

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 Precautions).

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 Precautions).

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.

OVERDOSAGE

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.

PRESENTATION

MINIRIN Melt 60 micrograms desmopressin. White, round, sublingual wafer marked with a drop shaped figure on one side. (Not currently available in Australia).

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

MINIRIN Melt 240 micrograms desmopressin. White, round, sublingual wafer marked with three drop shaped figures on one side. (Not currently available in Australia).

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

MINIRIN Melt is available in cartons of 10*, 30 or 100* each containing 1 to 10 Aluminium/Aluminium blister trays of 10 wafers. (*Not currently available in Australia).

Storage

Store below 25^{o}C. Keep in original container.

POISON SCHEDULE OF THE DRUG

Prescription Medicine

NAME AND ADDRESS OF THE SPONSOR

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

Date of the TGA approval: 21st June 2007

Date of most recent amendment: 15th October 2008