

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Desmopressin 60 micrograms sublingual tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 micrograms of desmopressin (as acetate)

Excipient with known effect

Each sublingual tablet contains 62 mg lactose (as monohydrate).

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Sublingual tablet

White or almost white, round, biconvex tablet debossed with 'T' on one side and plain on other side, with 6.5 mm diameter and 2 mm thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of vasopressin-sensitive cranial diabetes insipidus
- Treatment of post-hypophysectomy polyuria/polydipsia

4.2 Posology and method of administration

Posology

Treatment of diabetes insipidus:

Dosage is individual in diabetes insipidus but the total daily sublingual dose normally lies in the range of 120 micrograms to 720 micrograms. A suitable starting dose in adults and children is 60 micrograms 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 micrograms to 120 micrograms sublingually three times daily.

Post-hypophysectomy polyuria/polydipsia:

The dose of desmopressin sublingual tablets should be controlled by measurement of urine osmolality.

Special Populations

Elderly patients (65 years of age and older)

The initiation of treatment in patients over 65 years of age is not recommended (see section 4.3 and 4.4).

Renal impairment

Desmopressin sublingual tablets are contraindicated in patients with moderate and severe renal insufficiency (see section 4.3).

Hepatic impairment

No dose adjustment is needed for patients with hepatic impairment (see section 5.2).

Paediatric population

Desmopressin sublingual tablets are indicated for treatment in this population (see section 4.2 above). Dose recommendations are the same as in adults.

Method of administration

Sublingual use, place the tablet under the tongue where it dissolves without the need for water.

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see section 4.5).

4.3 Contraindications

- Hypersensitivity to desmopressin or any of the excipients listed in section 6.1
- Known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics. Desmopressin sublingual tablets should only be used in patients with normal blood pressure

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours) and alcohol abuse
- Desmopressin should not be prescribed to patients over the age of 65
- Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min)
- Known hyponatremia
- Syndrome of inappropriate ADH secretion (SIADH).

4.4 Special warnings and precautions for use

Special warnings

Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis. In chronic renal disease, the antidiuretic effect of desmopressin would be less than normal.

Precautions

Desmopressin should be used with caution in patients with conditions characterised by fluid and/or electrolyte imbalance.

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

Excipients with known effect

Desmopressin sublingual tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

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 and/or hyponatraemia (see section 4.4).

NSAIDs may induce water retention and/or hyponatraemia.

Pharmacokinetic interactions

Concomitant treatment with loperamide may result in a 3-fold increase in plasma desmopressin concentrations, which may lead to an increased risk of water retention

and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transit might have the same effect.

A standardised 27% fat meal significantly decreased the absorption (rate and extent) of a 0.4mg dose of oral desmopressin tablets. Although it did not significantly affect the pharmacodynamic effect (urine production and osmolality), there is the potential for this to occur at lower doses. If a reduction of the effect is noted, then the effect of food should be considered before increasing the dose.

Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of desmopressin tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Lactation

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 micrograms intranasally) indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis. Therefore it is not considered necessary to stop breastfeeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most serious adverse reaction with desmopressin is hyponatraemia, which is associated with headache, nausea, vomiting, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness 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

Tabulated summary of adverse reactions

The table below is based on the frequency of adverse drug reactions reported in clinical trials with oral desmopressin conducted in children and adolescents for the treatment of Primary Nocturnal Enuresis (PNE) (N = 1923).

System Organ Class	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10000, <1/1000)
Psychiatric disorders		Affect lability Aggression	Anxiety symptoms Nightmare Mood swings
Nervous system disorders	Headache		Somnolence
Vascular disorders			Hypertension
Gastrointestinal disorders		Abdominal pain Nausea Vomiting Diarrhoea	
Renal and urinary disorders		Bladder and urethral symptoms	
General disorders and administration site conditions		Oedema peripheral Fatigue	Irritability

In the case of hyponatraemia, the treatment of hyponatraemia should be individualised (see section 4.9).

Caution should be taken when substances with increased risk of water retention are taken concurrently with desmopressin sublingual tablets, since the concurrent use may increase the risk of hyponatraemia (see section 4.4).

Anaphylactic reactions, Psychomotor hyperactivity and some Psychiatric reactions such as abnormal behaviour, emotional disorder, depression, hallucination & insomnia, have not been seen in clinical trials but spontaneous reports have been received.

In children, psychiatric disorders including affect lability, aggression, anxiety, mood swings & nightmare are generally reversed upon treatment discontinuation.

Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported.

Other special populations:

Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of developing hyponatraemia (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

An overdose of desmopressin leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia

Treatment

Although the treatment of hyponatremia should be individualised, the following general recommendations can be given:

- Hyponatremia is treated by discontinuing the desmopressin treatment and fluid restriction.
- Symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues

ATC code: H01BA02

Desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. In its main biological effects, desmopressin does not differ qualitatively from vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Therefore desmopressin is characterised by a high antidiuretic activity whereas the uterotonic and vasopressor actions are extremely low.

5.2 Pharmacokinetic properties

Absorption

The overall mean systemic bioavailability of desmopressin administered sublingually at doses of 200, 400 and 800 micrograms is 0.25% with a 95% confidence interval of 0.21% - 0.31%. The C_{max} was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms 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.

Correlation table between desmopressin in tablet and sublingual forms:

Tablet	Tablet	Sublingual Tablet	Sublingual Tablet
Desmopressin acetate	Desmopressin free base	Desmopressin free base	Desmopressin acetate
0.1mg	89 micrograms	60 micrograms	Approx. 67 micrograms +
0.2mg	178 micrograms	120 micrograms	Approx. 135 micrograms +
0.4mg	356 micrograms	240 micrograms	Approx. 270 micrograms +

+ calculated for comparative purposes

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

Biotransformation

The in-vivo metabolism of desmopressin has not been studied. In vitro human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolised in the liver by the cytochrome P450 system. Thus human liver metabolism in vivo by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the pharmacokinetics of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug-metabolizing system.

Elimination

The total clearance of desmopressin has been calculated to 7.6 L/hr. The terminal half-life of desmopressin is estimated at 2.8 hours. In healthy subjects the fraction excreted unchanged was 52 % (44 % - 60 %).

Linearity/non-linearity

There is no indication of non-linearity in any of the pharmacokinetic parameters of desmopressin.

Characteristics in specific groups of patients

Renal impairment:

Depending on the degree of renal impairment the AUC and half-life increased with the severity of the renal impairment. Desmopressin is contraindicated in patients with moderate and severe renal impairment (creatinine clearance below 50 ml/min).

Hepatic impairment:

No studies have been performed in this population.

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.

Children:

The population pharmacokinetics of Desmopressin tablets has been studied in children with primary nocturnal enuresis and no significant difference from adults were detected.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

However non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction.

Carcinogenicity studies have not been performed because desmopressin is closely related to the naturally occurring peptide hormone, vasopressin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch
Citric acid (E 330)
Croscarmellose sodium (E 468)
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in the original blister in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Carton containing Al-Al standard blisters or unit dose blisters with integrated desiccant layer with 10 tablets each.

Pack sizes:

30 or 100 sublingual tablets (in blisters)

30 x 1 or 100 x 1 (in unit dose perforated blisters)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aristo Pharma GmbH
Wallenroder Strasse 8-10
13435 Berlin
Germany

8 MARKETING AUTHORISATION NUMBER

PL 40546/0223

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
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06/02/2024

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