SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Desmopressin 120 micrograms Sublingual Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 120 micrograms desmopressin (as desmopressin 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

White or almost white, octagonal, biconvex tablet debossed with 'II' on one side and plain on other side, with 6.5 mm length/width and 2 mm thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Desmopressin Sublingual Tablets are indicated for the treatment of vasopressin-sensitive cranial diabetes insipidus or in the treatment of post-hypophysectomy polyuria/polydipsia.

Desmopressin Sublingual Tablets are also indicated for the treatment of primary nocturnal enuresis.

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.

Primary nocturnal enuresis

The recommended initial dose for children (from 5 years of age) and adults (up to 65 years of age) with normal urine concentrating ability, who have primary nocturnal enuresis, is 120 micrograms at bedtime administered sublingually. If this dose is not sufficiently effective, the dose may be increased up to 240 micrograms, administered sublingually. Fluid restriction should be observed.

Desmopressin Sublingual Tablets are 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 1 week without Desmopressin Sublingual Tablets.

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).

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

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

Contraindications related to the treatment of primary nocturnal enuresis

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.

Known or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents. 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 50ml/min).

Known hyponatremia

Syndrome of inappropriate ADH secretion (SIADH)

Contraindications related to the treatment of diabetes insipidus and posy-hypophysectomy polyuria/polydipsia

When treated for the above conditions Desmopressin Sublingual Tablets are contraindicated in cases of cardiac insufficiency and other conditions requiring treatment with diuretic agents.

Before prescribing Desmopressin Sublingual Tablets, the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.

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 Sublingual Tablets would be less than normal.

Safety warnings specific to the treatment of primary nocturnal enuresis:

When desmopressin 120 or 240 microgram sublingual tablets are used for the treatment of enuresis, the fluid intake must be limited to a minimum from 1 hour before 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).

All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.

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.

Precaution specific to the treatment of primary nocturnal enuresis:

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

Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia.

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

Precautions to avoid hyponatraemia including careful attention to fluid restriction and more frequent monitoring of serum sodium must be taken in case of concomitant treatment with drugs, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, case of concomitant treatment with NSAIDs.

Excipients with known effect

Desmopressin contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per sublingual tablet, that is to say essentially ‘sodium-free’.

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/fetal 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 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
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 Sublingual Tablets leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:

Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the desmopressin treatment, fluid restriction and symptomatic treatment if needed

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: H01B A02

Pharmacotherapeutic group: Vasopressin and analogues

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 Cmax was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms respectively. tmax 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-live of desmopressin is estimated at 2.8 hours. In healthy subjects the fraction excreted unchanged was 52 % (44 % - 60 %).

Linearity/non-linearity

There are no indications of non-linearities 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 SPC.

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 with desmopressin, because it is closely related to the naturally-occurring peptide hormone.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Citric acid (E330)

Croscarmellose sodium (E468)

Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

Blisters

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

HDPE Bottles

Store in the original package. Keep the bottle tightly closed in order to protect from moisture. Do not store above 30°C.

6.5 Nature and contents of container

Carton box containing OPA/Al/PVC/PE-AL standard blisters or unit dose blisters with integrated desiccant layer with 10 tablets each.

Pack sizes:

Blisters: 10, 20, 30, 50, 60, 90 or 100 sublingual tablets (in blisters)

Unit dose perforated blisters: 10, 20, 30, 50, 60, 90, 100

HDPE bottle with PP caps with integrated desiccant containing 30 or 100 sublingual tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/2568

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06/01/2025