SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Desmopressin Melt 120 micrograms oral lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate contains 120 micrograms desmopressin (as acetate).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral lyophilisate

White, round, oral lyophilisate marked with two drop shaped figures on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Desmopressin Melt is indicated for the treatment of primary nocturnal enuresis.

4.2 Posology and method of administration

Posology

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 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 1 week without Desmopressin Melt.

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 Melt is 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 Melt is indication 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 melt 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Known or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents. Desmopressin Melt 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)
- 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)

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 Melt would be less than normal.

When Desmopressin Melt is 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:

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).

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.

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.

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 of desmopressin plasma concentrations, which may lead to an increased risk of water retention and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased the absorption (rate and extent) of desmopressin tablets. No significant affect was observed with respect to pharmacodynamics (urine production and osmolality).

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

Caution should be exercised when prescribing to pregnant women.

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.

Breastfeeding:

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 Melt 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 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 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 Melt, 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, website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms:
Overdose of Desmopressin Melt 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

Pharmacotherapeutic group: vasopressin and analogues ATC code: H01B A02

Desmopressin Melts contain desmopressin, a 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. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

5.2 Pharmacokinetic properties

Absorption:

The overall mean systemic bioavailability of desmopressin administered sublingually as Melts 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 Melt forms:

Tablet	**Tablet**	**Melt**	**Melt**
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

Distribution:

The distribution of desmopressin is best described by a two-compartment distribution model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg.

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 to 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-live 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 PNE and no significant difference from adults were detected.

5.3 Preclinical safety data

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

Gelatin

Mannitol (E421)

Citric acid, anhydrous

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store in the original package in order to protect from moisture and light

6.5 Nature and contents of container

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester teraphthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 10, 30 and 100 oral lyophilisates.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 03194/0120

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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23/01/2024