1. NAME OF THE MEDICINAL PRODUCT

Desmopressine Hexal 60 microgram, tabletten voor sublinguaal gebruik
Desmopressine Hexal 120 microgram, tabletten voor sublinguaal gebruik
Desmopressine Hexal 240 microgram, tabletten voor sublinguaal gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Nationally completed name] <60 micrograms> <sublingual tablets>
Each sublingual tablet contains 67 micrograms desmopressin acetate equivalent to 60 micrograms desmopressin.

[Nationally completed name] <120 micrograms> <sublingual tablets>
Each sublingual tablet contains 133 micrograms desmopressin acetate equivalent to 120 micrograms desmopressin.

[Nationally completed name] <240 micrograms> <sublingual tablets>
Each sublingual tablet contains 267 micrograms desmopressin acetate equivalent to 240 micrograms desmopressin.

Excipient(s) with known effect

[Nationally completed name] <60 micrograms> <sublingual tablets>
Each sublingual tablet contains 65.23 mg lactose (as monohydrate).

[Nationally completed name] <120 micrograms> <sublingual tablets>
Each sublingual tablet contains 65.18 mg lactose (as monohydrate).

[Nationally completed name] <240 micrograms> <sublingual tablets>
Each sublingual tablet contains 65.08 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet

[Nationally completed name] <60 micrograms> <sublingual tablets>
White or almost white, round, tablet, rounded on the upper and lower side, debossed with ‘I’ on one side and plain on other side, with 6.5 mm of length and 2 mm of thickness.

[Nationally completed name] <120 micrograms> <sublingual tablets>
White or almost white, octagonal, tablet, rounded on the upper and lower side, debossed with ‘II’ on one side and plain on other side, with 6.5 mm of length and 2 mm of thickness.

[Nationally completed name] <240 micrograms> <sublingual tablets>
White or almost white, square, tablet, rounded on the upper and lower side, debossed with ‘III’ on one side and plain on other side, with 6.5 mm of length and 2 mm of thickness.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[Nationally completed name] is indicated for:

- Treatment of central diabetes insipidus.
- Treatment of primary nocturnal enuresis in patients from5 years old, with a normal ability to concentrate urine.

4.2 Posology and method of administration

Posology

Generally
If signs or symptoms of fluid retention and/or hyponatremia (headache, nausea/vomiting, weight gain and in severe cases, convulsions and coma) occur, treatment should be discontinued until the patient has fully recovered. When re-initiating treatment, strict adherence to fluid intake restrictions should be maintained and serum sodium levels monitored (see section 4.4). In all cases, a dose adjustment should be progressively performed with respect of a sufficient period between each dosage level.

If the desired clinical effect is not achieved after 4 weeks of treatment with appropriate dose titration, treatment should be discontinued.

Central diabetes insipidus
Starting dose in adults and children is 60 micrograms three times daily. Thereafter, the dose regimen should be adjusted according to the patient's response. Clinical experience has shown that the daily dose varies between 120 micrograms and 720 micrograms. For most patients, the maintenance dose is 60-120 micrograms three times daily.

Primary nocturnal enuresis
The recommended starting dose is 120 micrograms at bedtime. The dose may be increased to 240 micrograms if the lower dose is not sufficiently effective. Fluid intake should be limited and controlled. The treatment period with desmopressin is always 3 months. A treatment-free period of at least one week should be instituted every three months to assess whether further treatment is necessary.

Elderly
Due to an increased risk of hyponatremia, [nationally completed name] should be used with extreme caution in elderly patients.. If treatment is decided, serum sodium should be determined prior to initiation of treatment. In case of hyponatremia, [nationally completed name] treatment should not be started (see also section 4.3). Treatment may be initiated at normal serum sodium concentrations and serum sodium should be monitored three days after initiation of treatment and at each dose increase. It should also be monitored at other times during treatment if deemed necessary by the doctor.

Method of administration

This medicinal product is placed sublingually where it dissolves without fluid.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Habitual or psychogenic polydipsia (leading to a urine output higher than 40 ml/kg/24 hours)
- Cardiac impairment or other conditions requiring treatment with diuretics
- Moderate or severe renal impairment (creatinine clearance <50 ml/min)
- Established hyponatremia
- SIADH- a condition with disproportionately high ADH secretion

4.4 Special warnings and precautions for use

Special warnings
In the treatment of nocturnal enuresis, fluid intake should be limited as much as possible from 1 hour before bedtime administration to the following morning, and in any case for at least 8 hours after administration. It is also recommended to empty the bladder before administration. Treatment without concomitant fluid restriction may lead to fluid retention and/or hyponatremia with or without warning symptoms (headache, nausea/vomiting, weight gain and, in severe cases, convulsions and coma). Cerebral edema has been reported rarely in children and adolescents treated with desmopressin acetate for nocturnal enuresis.

All patients or, if applicable, their caregiver should be properly instructed to adhere to fluid restrictions, including alcoholic beverages.

Fluid retention can be easily monitored by weighing the patient or by determining plasma sodium or osmolality.

Precautions
Severe bladder dysfunction and bladder obstruction should be considered before initiating treatment. The elderly and patients with serum sodium levels near the lower limit of normal are at increased risk of hyponatremia. If disease develops with fluid and/or electrolyte imbalance, treatment with desmopressin should be interrupted (e.g. in case of systemic infections, fever or gastroenteritis).

Caution should be exercised in patients at risk of increased risk of intracranial pressure.

Desmopressin should be administered with caution and the dose reduced if necessary, in patients with cardiovascular impairments or in patients suffering from asthma, cystic fibrosis, epilepsy, migraine or conditions characterized by fluid disturbances and/or electrolyte balance.

Precautions should be taken to avoid hyponatremia, such as fluid restriction and more frequent measurement of serum sodium when desmopressin is used concomitantly with drugs that may cause SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), chlorpromazine, carbamazepine, antidiabetics belonging to the sulfonylureas or when used concomitantly with NSAIDs.

[Nationally completed name] contains lactose and sodium
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine 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

Medicinal products known to cause SIADH, such as tricyclic antidepressants, SSRIs, chlorpromazine and carbamazepine, as well as antidiabetics belonging to the sulphonylureas, may have an additive antidiuretic effect and therefore increase the risk of fluid retention/hyponatremia (see section 4.4).

NSAIDs may cause fluid retention/hyponatremia (see section 4.4).

Concomitant treatment with loperamide may cause a three-fold increase in plasma concentrations of desmopressin, which may lead to an increased risk of fluid retention/hyponatremia. Other drugs that slow intestinal transport may have the same effect. However, this has not been investigated.

Desmopressin acetate is unlikely to interact with drugs that affect hepatic metabolism as *in vitro* studies with human microsomes show no significant hepatic metabolism. However, no *in vivo* interaction studies have been performed.

Concomitant treatment with dimethicone may reduce the absorption of desmopressin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from studies in a limited number (n=53) pregnant women with diabetes insipidus as well as data from a limited number (n=54) exposed pregnancies in women with von Willebrand disease revealed no adverse effects on pregnancy or on fetal health/neonate. To date, no other relevant epidemiological data are available. Animal studies indicate that there are no direct or indirect harmful effects with respect to pregnancy, fetal formation and development, parturition or postnatal development.

Caution should be exercised when prescribing desmopressin acetate to pregnant women and it is recommended that blood pressure should be monitored during pregnancy due to a possible increased risk of preeclampsia.

Breast-feeding

Analysis of the milk of mothers treated with high doses of desmopressin (300 micrograms intranasally) shows that the amount of desmopressin that can pass into the infant is significantly less than the amount needed to affect diuresis.
Desmopressin can be used during breastfeeding.

Fertility

Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines

[Nationally completed name] has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adults
The frequency of adverse reactions reported in the clinical studies conducted with oral desmopressin in adults for the treatment of nocturia (N=1557) combined with post-marketing reports for all indications in adults (including central diabetes insipidus) are presented in Table 1. Post-marketing adverse reactions are presented in the column 'Frequency not known'.

Table 1: Tabulated list of adverse reactions in adults

System Organ Class	Very common (≥1/10)	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10000, <1/1000)	Frequency not known (cannot be estimated from available data)
Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders		Hyponatremia*			Dehydration,** Hypernatremia**
Psychiatric disorders			Insomnia	Confusion state*	
Central and peripheric nervous system disorders	Headache*	Dizziness*	Somnolence, Paresthesias		Convulsions,* Astenia,** Coma*
Eye disorders			Visual disturbances		
Ears and balance organs disorders			Vertigo*		
Cardiac disorders			Palpitations		
Vascular disorders		Hypertension	Orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders			Dyspnoea		
Gastrointestinal disorders		Nausea,* Abdominal pain,* Diarrhoea, Constipation, Vomiting*	Dyspepsia, Flatulence, bloating and distension		
Skin and subcutaneous disorders			Sweating, Pruritus, Rash, Urticaria	Allergic dermatitis	
Musculoskeletal and connective tissue disorders			Muscle spasms, Myalgia		
Renal and urinary		Pollakiuria	Urgent urination,		

disorders			Urinary Disorder		
General disorders and administration site conditions		Oedema, Fatigue	Feeling sick,* Chest pain, Influenza like symptoms		
Investigations			Weight Gain,* Increase in liver enzymes, Hypokalemia		

*hyponatremia may cause headache, abdominal pain, nausea, vomiting, weight gain, dizziness, confusion, malaise, memory impairment, vertigo, falling and in severe cases, convulsions and coma, see also section 4.4
**Only observed in the indication CDI

Paediatric population
The frequency of adverse reactions reported in the clinical studies conducted with oral desmopressin in children and adolescents for the treatment of primary nocturnal enuresis (N = 1923). Post-marketing adverse reactions are presented in the column 'Frequency not known'.

Table 2: Tabulated list of adverse reactions in paediatric population

System Organ Class	**Very common (≥1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1000, <1/100)**	**Rare (≥1/10000, <1/1000)**	**Frequency not known (cannot be estimated from available data)**
Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders					Hyponatremia*
Psychiatric disorders			Affect lability, Aggression	Anxiety symptoms, Nightmares,** Mood swings**	Abnormal behavior, Emotional disturbances, Depression, Hallucinations, Insomnia
Central and peripheric nervous system disorders		Headache*		Somnolence	Attention Deficit Disorder, Psychomotor hyperactivity, Convulsions*
Vascular disorders				Hypertension	
Respiratory, thoracic and					Nasal bleeding

mediastinal disorders					
Gastrointestinal Disorders			Abdominal pain,* Nausea,* Vomiting,* Diarrhoea		
Skin and subcutaneous disorders					Rash, Allergic dermatitis, Sweating, Urticaria
General disorders and administration site conditions			Peripheral oedema, Fatigue	Irritation	

* Hyponatremia may cause headache, abdominal pain, nausea, vomiting, weight gain, dizziness, confusion, malaise, memory impairment, vertigo, falling and in severe cases, convulsions and coma, see also section 4.4.
**Reported mainly in children (< 12 years) in the post-marketing period.

Special population
Elderly patients and patients with low plasma sodium levels may be at increased risk of developing hyponatremia (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 national reporting system listed in Appendix V.

4.9 Overdose

Overdose with desmopressin leads to prolonged duration of action with an increased risk of fluid retention and hyponatremia. Symptoms of severe fluid retention include convulsions and unconsciousness.

Treatment
Although the treatment of hyponatremia should be individualised, the following general recommendations can be given:
- Hyponatremia is treated by discontinuing desmopressin treatment, limiting fluid intake and initiating symptomatic treatment if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues, ATC code: H01BA02

Desmopressin acetate is a synthetic analog of the naturally antidiuretic hormone arginine-vasopressin. Desmopressin acetate differs chemically from the natural hormone in two respects: deamination of 1-

cysteine and substitution of 8-L-arginine with 8-D-arginine. This change significantly prolongs the antidiuretic effect, eliminating the pressor effect at therapeutic doses. Desmopressin acetate is a potent agent with an EC50 value of 1.6 pg/ml for its antidiuretic effect. An effect lasting 6-14 hours or longer can be expected after oral administration.

5.2 Pharmacokinetic properties

Absorption
The mean bioavailability after sublingual use of desmopressin lyophilised tablets 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 65 pg/ml after administration of 200, 400 and 800 micrograms, respectively. The T_{max} was observed 0.5-2 hours after administration. Concomitant food intake has not been studied with desmopressin lyophilised tablet, but food intake with desmopressin tablet reduces the rate and the degree of absorption by 40%.

Distribution
The distribution of desmopressin is best described using a two-compartment distribution model with a volume of distribution during the elimination phase of 0.56 L/kg.

Biotransformation
The *in vivo* metabolism of desmopressin has not been studied. *In vitro* metabolism studies on human liver microsomes performed with desmopressin showed no significant hepatic metabolism by the cytochrome P450 system. Therefore, desmopressin is unlikely to be metabolised *in vivo* by the hepatic cytochrome P450 system in humans. The effect of desmopressin on the pharmacokinetics of other drugs is likely to be minor because desmopressin does not inhibit the cytochrome P450 drug metabolism system.

Elimination
The total clearance of desmopressin was calculated to be 7.6 l/h. The terminal half-life of desmopressin is estimated to be 2.8 hours. In healthy subjects, the fraction excreted in unchanged form was 52% (44% - 60%).

Linearity/non-linearity
There are no indications of non-linearity in any of the pharmacokinetic parameters of desmopressin.

Special patient groups:

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

Liver impairment:
No studies have been performed.

Paediatric population
The population pharmacokinetics of desmopressin tablets were studied in children with PNE. Clearance (Cl/F) was approximately 30% lower compared to adults, however due to the high variability this difference was not significant.

5.3 Preclinical safety data

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

No carcinogenicity studies have been performed with desmopressin as it is very closely related to the natural peptide hormone.

In vitro analysis of human cotyledon models showed no placental transfer of desmopressin when administered at therapeutic concentrations consistent with recommended doses.

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

2 years

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

OPA-Al-PVC-PE/Al blisters with integrated desiccant layer.

Pack sizes
30 sublingual tablets

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestrasse 25
83607 Holzkirchen

Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 129995 - Desmopressine Hexal 60 microgram, tabletten voor sublinguaal gebruik
RVG 129996 - Desmopressine Hexal 120 microgram, tabletten voor sublinguaal gebruik
RVG 129997 - Desmopressine Hexal 240 microgram, tabletten voor sublinguaal gebruik

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 4 juli 2023

10. DATE OF REVISION OF THE TEXT