## 1. NAME OF THE MEDICINAL PRODUCT

Desmopressine 1A Pharma 60 microgram, tabletten voor sublinguaal gebruik
Desmopressine 1A Pharma 120 microgram, tabletten voor sublinguaal gebruik
Desmopressine 1A Pharma 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 tablet>*
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 tablet>*
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.
- Symptomatic treatment of primary nocturnal enuresis in patients from 6 years old, with a normal ability to concentrate urine.
- Symptomatic treatment of nocturia in adults, associated with nocturnal polyuria.

## 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 may vary according to age and 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*
[Nationally completed name] is not recommended in children below 6 years old.
The recommended starting dose is 120 micrograms at bedtime in one evening dose. The dose may be increased to 240 micrograms per day if the lower dose is not sufficiently effective, respecting an interval of at least 1 week between each dose adjustment level. Fluid intake should be limited and controlled. The treatment period with desmopressin is always 3 months. After 3 months of treatment at the minimally effective dose determined after dose adjustment, treatment should be discontinued and enuresis reassessed at least one week after discontinuation.

*Nocturia*
Before the diagnosis of nocturnal polyuria, the frequency and volume of urine output should be measured for at least 48 hours. Nocturnal polyuria is said to be nocturnal polyuria if nocturnal urine output is greater than bladder capacity or is more than a third of urine output over 24 hours.
The recommended starting dose is 60 micrograms at bedtime. If the effect is insufficient, the dose can be increased weekly to 120 micrograms and then to 240 micrograms. Fluid intake should be limited and controlled. The treatment period with desmopressin is always 3 months.

*Elderly*
In elderly patients (over 65 years of age), in patients with blood sodium levels below normal and those with a large daily amount of urine (over 2.8 L) have an increased risk of developing hyponatremia (see section 4.4).
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.

Desmopressin treatment requires fluid restriction. In the treatment of primary nocturnal enuresis and nocturia, it is imperative to restrict the intake of fluids for at least 1 hour before and for 8 hours after taking desmopressin (see section 4.4).

Desmopressin causes renal water reabsorption resulting in fluid retention. It is advisable to:
- start treatment at the lowest recommended dosage;
- increase the dosage gradually and cautiously (without exceeding the maximum recommended dosage);
- respect the water restriction;
- ensure that in children, administration is done under adult supervision.

## 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 in which disproportionately high ADH production occurs

## 4.4 Special warnings and precautions for use

*Special warnings*
In the treatment of nocturnal enuresis and nocturia, 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. 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). If these symptoms occur, in the case of nocturnal enuresis in the child and nocturia in adult, treatment should be discontinued and an ionogram performed to measure serum sodium. If treatment is resumed, the water restriction should be stricter.
Cerebral edema has been reported rarely in children and adolescents treated with desmopressin acetate for nocturnal enuresis.

The treatment of the nocturnal enuresis of the child usually begins with lifestyle measures and night-time wetting alarm. If these measures fail or if there are other underlying causes for nocturnal enuresis for which pharmacological treatment cannot be delayed, treatment with desmopressin may be initiated.

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

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. In patients with urge incontinence, organic causes of increased micturition frequency or nocturia (e.g. benign prostatic hyperplasia (BHP), urinary tract infection, bladder stones/tumors, bladder sphincter disorders), polydipsia and insufficiently controlled diabetes mellitus, the specific cause of the problems should be considered as to be treated first, respectively to be excluded.

The elderly and patients with serum sodium levels near the lower limit of normal are at increased risk of hyponatremia. Due to the increased risk of hyponatremia in patients beyond 65 years old, treatment should be initiated with caution. 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).

Desmopressin should be administered with caution, and the dose should be 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. Caution should be exercised in patients with increased risk of intracranial pressure.

At high doses, especially in diabetes insipidus, desmopressin may sometimes cause a slight rise in blood pressure, which disappears with dose reduction.

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 diuretic agents is contraindicated (see section 4.3). 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 (≥1/1 000, <1/100) | Rare (≥1/10 000, <1/1 000) | Frequency not known (cannot be estimated from available data) |
|---|---|---|---|---|---|
| **Immune system** | | | | | Anaphylactic |

| | | | | | |
|---|---|---|---|---|---|
| **disorders** | | | | | 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 disorders** | | Pollakiuria | Urgent urination, 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

Diabetes insipidus and primary nocturnal enuresis

Cases of water intoxication with hyponatremia occur most often at the beginning of treatment, when the dosage is increased, or when the route of administration is changed in the diabetes insipidus indication.

Nocturia

Adverse reactions to desmopressin have been described in patients, including the 65+ year old population, treated for nocturia in clinical trials. In total, approximately 35% of patients experienced adverse events during the titration phase. The majority of cases of clinically significant hyponatremia (natraemia < 130 mmol/L) occurred in patients aged 65 years or older. Hyponatremia has occurred either early in the course of treatment or when the dosage was increased. Adverse reactions other than hyponatremia are mainly minor. During the long-term treatment period, 24% of patients experienced adverse events.

Hyponatremia
Treatment without concomitant reduction in fluid intake may result in water intoxication with hyponatremia. This should be considered when alarm symptoms occur: headache, abdominal pain, nausea, vomiting, anorexia, rapid weight gain, dizziness and vertigo, confusion, memory loss, fainting, falls and, in severe cases, convulsions or even coma. In adults the risk of hyponatremia increases with the dosage and the risk is more frequent in women.

*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 (≥1/1 000, <1/100) | Rare (≥1/10 000, <1/1 000) | 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,** | Abnormal behavior, Emotional |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Mood swings** | disturbances, Depression, Hallucinations, Insomnia |
| **Central and peripheric nervous system disorders** | | Headache* | | Somnolence | Attention Deficit Disorder, Psychomotor hyperactivity, Convulsions* |
| **Vascular disorders** | | | | Hypertension | |
| **Respiratory, thoracic and mediastinal disorders** | | | | | Nasal bleeding |
| **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.

Hyponatremia
Treatment without concomitant reduction in fluid intake may result in water intoxication with hyponatremia. This should be considered when alarm symptoms occur: headache, abdominal pain, nausea, vomiting, anorexia, rapid weight gain, dizziness and vertigo, confusion, memory loss, fainting, falls and, in severe cases, convulsions or even coma. In children, hyponatremia is likely to occur with changes in daily activities that may affect fluid intake or sweating.

*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, unconsciousness, a rapid increase in weight, tachycardia, headache, nausea and vomiting.
In the event of a significant overdose with a major risk of water intoxication, specific measures must be taken in a hospital setting, with strict clinical and biological monitoring.

*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. Compared to the natural hormone, desmopressin is characterized by an increased and prolonged antidiuretic activity, while its vasopressive activity is very reduced. Desmopressin behaves as a selective agonist of the V2 vasopressin receptors, located mainly on the collecting tubule cells of the kidney.
Oral administration of a dose of 60 micrograms and 120 micrograms produces an antidiuretic effect lasting approximately 8 hours with significant inter-individual variation.

Nocturia: Pooled results from randomized, controlled clinical studies in men and women aged 18 to 65 years and older, treated for nocturia, with desmopressin at an individualized dose between 60 micrograms and 240 micrograms per day for 3 weeks show a reduction of at least 50% in the mean number of nocturnal micturitions in 39% of the patients compared to 5% in the patients on placebo ($p<0.0001$).
Due to adverse events, 8% of 448 desmopressin patients discontinued treatment during the titration phase and 2% of 295 patients discontinued treatment during the double-blind period (0.63% desmopressin and 1.45% placebo).

### 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

[For Blisters]
Store in the original blister in order to protect from moisture. This medicinal product does not require any special temperature storage conditions.
[For HDPE containers]
Store in the original package. Keep the bottle tightly closed.

### 6.5 Nature and contents of container

OPA-Al-PVC-PE/Al blisters with integrated desiccant layer.
HDPE containers with PP caps with integrated desiccant.

Pack sizes
Blisters: 30 and 100 sublingual tablets
HDPE containers: 30 and 100 sublingual tablets

Not all pack sizes may be marketed.

### 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

1A Pharma GmbH
Industriestrasse 18
83607 Holzkirchen
Duitsland

## 8. MARKETING AUTHORISATION NUMBER(S)

RVG 129992 - Desmopressine 1A Pharma 60 microgram, tabletten voor sublinguaal gebruik
RVG 129993 - Desmopressine 1A Pharma 120 microgram, tabletten voor sublinguaal gebruik
RVG 129994 - Desmopressine 1A Pharma 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