SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCTS

MINIRIN® 60 micrograms oral lyophilisate
MINIRIN® 120 micrograms oral lyophilisate
MINIRIN® 240 micrograms oral lyophilisate

Active ingredient: desmopressin acetate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each oral lyophilisate MINIRIN® 60 micrograms contains 67 µg desmopressin acetate equivalent to 60 µg desmopressin.
Each oral lyophilisate MINIRIN® 120 micrograms contains 135 µg desmopressin acetate equivalent to 120 µg desmopressin.
Each oral lyophilisate MINIRIN® 240 micrograms contains 270 µg desmopressin acetate equivalent to 240 µg desmopressin.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Oral lyophilisate (melt tablet)

Appearance:
60 micrograms: white, round oral lyophilisate imprinted with one drop on one side
120 micrograms: white,round oral lyophilisate imprinted with two drops on one side
240 micrograms: white, round oral lyophilisate imprinted with three drops on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of primary nocturnal enuresis;
  - within an overall therapeutical concept, e.g. in cases of failure of other non-medicinal therapies or with indication of a medicinal therapy,
  - caused by nocturnal ADH deficiency;

- Symptomatic treatment of nocturia (at least twice a night urine production) in adults, in connection with nocturnal polyuria.

- Trauma-induced polyuria and polydipsia in the presence of transient lack of ADH after hypophysectomy, after surgery in the pituitary gland area or cranio-cerebral trauma;

- Central diabetes insipidus

4.2 Posology and method of administration

Sublingual use

Primary nocturnal enuresis
For the therapy of nocturnal enuresis, an initial dosage of 120 micrograms desmopressin before going to bed is recommended. In cases of insufficient therapy success, the dose can be increased to 240 micrograms. Fluid supply should be reduced.
With symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and, in severe cases, cramps), the treatment is to be interrupted until the patient has fully recovered. When continuing treatment, the fluid supply has to be controlled strictly (see section 4.4 Special warnings and precautions for use).

MINIRIN® is intended for a treatment period of up to 3 months. The necessity of additional treatment should be verified following interruption of administration for at least one week.

Nocturia with nocturnal polyuria

For treatment of nocturia, the recommended initial dose is 60 micrograms desmopressin at bedtime. If this dose is not sufficiently effective after one week, it may be increased up to 120 micrograms and subsequently to 240 micrograms by weekly dose escalations. Reduction of nocturnal fluid supply should be observed (see section 4.4).

In nocturia patients, a frequency/volume chart should be used to diagnose nocturnal polyuria for at least 48 hours before starting treatment. A night-time urine production exceeding the functional bladder capacity or 1/3 of the 24-hour urine production is regarded as nocturnal polyuria.

In addition, serum sodium levels should be measured before start of treatment.

The body weight should be checked over several days at the beginning of treatment and after increase of dose.

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

Treatment of elderly patients is not recommended. If, nevertheless, therapy is to be performed, serum sodium levels should be determined before start of treatment, 3 days after start of treatment, 3 days after a dose increase as well as at other time points deemed necessary.

In the event of signs of water retention and/or hyponatraemia (headache, oedemas, nausea/vomiting, weight gain and, in severe cases, cramps), treatment should be interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction and close monitoring of serum sodium levels should be enforced (see section 4.4).

If adequate effect is not achieved within 1 week with appropriate dosage, the medication should be discontinued.

Central diabetes insipidus

Adults and children: in cases of diabetes insipidus, the dosage is to be adapted individually. The daily dose is normally between 120 micrograms and 720 micrograms. The initial dosage for adults and children should be around 60 micrograms, three times daily, and then adapted to the patient's individual reaction. The maintenance dose for most patients is 60 – 120 micrograms, three times daily.

With symptoms of water retention/hyponatraemia, the treatment is to be interrupted, and the dosage is to be adapted.

4.3 Contraindications

MINIRIN® is contraindicated with:

- hypersensitivity to desmopressin or any of the other ingredients of the medicinal product
- habitual or psychogeneous polydipsia (resulting in a urine production exceeding 40 mg/kg/24 hours), polydipsia in alcoholics
- known or suspected cardiac insufficiency
- conditions that require therapy with diuretics
- known hyponatraemia
- renal insufficiency with a creatinine clearance below 50 ml/min
- syndrome of inadequate ADH secretion
- patients aged 65 or more if desmopressin used to treat nocturia

4.4 Special warnings and precautions for use

Warnings

With treatment of primary nocturnal enuresis and nocturia, the fluid supply is to be reduced to a minimum from one hour before administration until the next morning (at least 8 hours following administration). Treatment without simultaneous restriction of fluid supply can lead to water retention and/or hyponatraemia with or without accompanying warning symptoms (headache, nausea/vomiting, weight gain) and, in severe cases, to cerebral oedema sometimes associated with clouding of consciousness up to loss of consciousness.

Precautions for use

Desmopressin should be used with caution in patients with mild renal insufficiency.

Serious bladder function disorders and bladder neck obstruction have to be excluded prior to treatment.

Elderly patients and those with low sodium serum levels may show an increased risk of hyponatraemia.

Treatment with desmopressin should be interrupted in cases of upcoming diseases characterised by fluid and/or electrolyte balance disorders.

Precautions for the avoidance of hyponatraemia have to be taken in cases of:
- accompanying treatment with medicinal products that can induce SIADH, e.g. antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine;

- simultaneous treatment with non-steroidal anti-inflammatory drugs.

4.5 Interactions with other medicinal products and other interactions

Substances known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine and indomethacine, can increase the antidiuretic effect which can lead to an increased risk of water retention/hyponatraemia (see section 4.4).

Non-steroidal anti-inflammatory drugs can induce water retention/hyponatremia (see section 4.4).

Accompanying treatment with loperamide can lead to an increase of the desmopressin plasma concentration to three times the amount, which, in turn, can cause an increased risk of water retention/hyponatremia. Although there are no data on this, other medicinal products which slow down the intestinal transport can have the same effect.

Interactions of desmopressin with substances influencing the liver metabolism are improbable since desmopressin does not show any significant metabolism in the liver in in-vitro studies in human microsomes. In-vivo studies on possible interactions have not been performed so far.

A standardised diet with 27 % fat significantly reduces the absorption (amount and duration) of orally administered desmopressin. With respect to the pharmacodynamic characteristics (urine production or osmolality), no significant effect has been reported. With low desmopressin doses, simultaneous food supply can reduce the effect and duration of the antidiuretic effect.

In case of concomitant use of oxytocin, an increased antidiuretic effect and reduced uterus perfusion should be taken into account.

Clofibrate, indomethacin and carbamazepine may intensify the antiduretic effect of desmopressin whilst glibenclamide may reduce it.

4.6 Pregnancy and lactation

Pregnancy:
The medicinal product should be given with caution to pregnant women and monitoring of blood pressure is recommended.

The available data with a limited number of pregnant women (n = 53) with diabetes insipidus show that desmopressin has no negative effect on pregnancy or the health condition of the fetus or newborn. So far, there are no further relevant epidemiological data. Animal experiments show no direct or indirect harmful effects on pregnancy, the development of the embryo or fetus, birth or postnatal development.

MINIRIN® should only be administered to pregnant women after thoroughly weighing up the risks and benefits.

Lactation:
Examinations of the mother's milk of women who had been administered a high dosage of 300 µg desmopressin (intranasal) showed that the amounts of desmopressin that could be transferred to the child are too low to influence the diuresis.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Treatment without simultaneous limited fluid supply can lead to water retention/hyponatremia with or without accompanying warning symptoms (headache, nausea/vomiting, weight gain and, in serious cases, cramps sometimes associated with somnolence up to prolonged loss

of consciousness). This applies particularly to small children up to one year or elderly people, dependant on their overall condition.

Primary nocturnal enuresis and central diabetes insipidus

System organ class	Common (>1/100, <1/10)	Very rare (<1/10,000)
Immune system disorders		Allergic reactions of the skin, general allergic reactions
Metabolic and nutritional disorders		Hyponatraemia
Psychiatric disorders		Emotional disorders (children)
Nervous system disorders	Headache	
Gastrointestinal disorders	Abdominal pain, nausea	

Nocturia

In clinical studies, 35 % of the patients showed side effects during dose titration and 24 % during long-term treatment. The following table shows the most frequent adverse effects observed in clinical studies (with 632 patients):

System organ class	Very common (>1/10)	Common (>1/100, <1/10)
Metabolic and nutritional disorders		Hyponatraemia
Psychiatric disorders		Sleeplessness
Nervous system disorders	Headache	Dizziness
Vascular disorders		Hypertension
Gastrointestinal disorders		Nausea, abdominal pain, dry mouth, diarrhoea
Renal and urinary disorders		Pollakisuria
General disorders		Tiredness, peripheral oedema
Investigations		Weight gain

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 to:

Bundesinstitut für Arzneimittel und Medizinprodukte
Abt. Pharmakovigilanz
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn
Website: www.bfarm.de

4.9 Overdose

a) Symptoms of intoxication

The symptoms of an overdose may occur under the following conditions:
- if the dose administered is too high.
- if there is excessive fluid intake at the same time or shortly after desmopressin administration.

The symptoms are manifested by weight gain (water retention), headaches, nausea and, in severe cases, water intoxication with convulsions sometimes associated with clouding of consciousness up to loss of consciousness.

An overdose may occur in particular in infants due to an uncautious drug adjustment.

b) Treatment of intoxication

In case of overdose, depending on its severity, the dose should be reduced, the interval between single doses should be increased or the drug should be discontinued. Suspected cerebral oedema requires immediate admittance to intensive care. Convulsions also require intensive measures. There is no known specific antidote to desmopressin. If diuresis is indicated, saluretics such as furosemide can be used under monitoring of serum electrolytes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues
ATC code: H01B A02

MINIRIN® contain desmopressin, a synthetic analogue to natural human L-arginine-vasopressin, and differs formally from the latter by the fact that the amino group of the cystein in position 1 has been removed and the L-arginine has been replaced by the stereoisomer D-arginine. Because of these alterations, the vasopressoric effect of the molecule is (widely) lost while the anti-diuretic effect is prolonged..
Desmopressin has an EC_{50} value of 1.6 pg/ml in relation to the antidiuretic effect. Oral administration leads to an antidiuretic effect between 6 and 14 hours or more with considerable inter- and intra-individual variability.

5.2 Pharmacokinetic properties

The mean systemic bioavailability of sublingually administered desmopressin like MINIRIN® in doses of 200, 400 and 800 µg is 0.25% with a 95% confidence interval of 0.21 – 0.31%. After administration of 200, 400 and 800 µg C_{max} was 14, 30 and 65 pg/ml. t_{max} was observed 0.5 – 2.0 hours after administration. The geometric mean half-life is 2.8 (CV = 24%) hours.

Comparative table of MINIRIN® tablets and MINIRIN® oral lyophilisate:

MINIRIN® tablets	**MINIRIN®** tablets	**MINIRIN®** oral lyophilisate	**MINIRIN®** oral lyophilisate
Desmopressin acetate	Desmopressin free base	Desmopressin free base	Desmopressin acetate
0.1 mg	89 µg	60 µg	approx. 67 µg*
0.2 mg	178 µg	120 µg	approx. 135 µg*
0.4 mg	356 µg	240 µg	approx. 270 µg*

*) calculated for purposes of comparison

The distribution volume of desmopressin after intravenous injection is 33 l (0.41 l/kg). Desmopressin does not pass the blood-brain-threshold. Desmopressin shows a moderate to high inter- and intrapatient variability in bioavailability. Taking desmopressin with food reduces the amount and the extent of absorption by 40%.

In-vitro preparations of human liver microsomes showed that no significant amount of desmopressin is metabolised, and a metabolism in the liver in vivo is thus improbable.

After intravenous injection, 45 % of the desmopressin amount is excreted with the urine within 24 hours.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity in addition to what is already stated in other parts of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin, mannitol (Ph.Eur.), citric acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

MINIRIN® 60 micrograms: 4 years
MINIRIN® 120 micrograms: 4 years
MINIRIN® 240 micrograms: 3 years

6.4 Special precautions for storage

Do not store above 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium/aluminium blister in the following pack sizes:
MINIRIN® 60 micrograms : 10, 30, 90 melt tablets
MINIRIN® 120 micrograms : 10, 30, 90 melt tablets
MINIRIN® 240 micrograms: 10, 30, 90 melt tablets

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Ferring GmbH
Wittland 11
D-24109 Kiel

Codistribution
Ferring Arzneimittel GmbH

Fabrikstraße 7
D-24103 Kiel
Tel.: (0431) - 58 52 - 0
Fax: (0431) - 58 52 - 74

8. MARKETING AUTHORIZATION NUMBERS

MINIRIN® 60 micrograms: 80334.00.00
MINIRIN® 120 micrograms: 80335.00.00
MINIRIN® 240 micrograms: 80336.00.00

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

January 21, 2011 / ---

10. DATE OF REVISION OF THE TEXT

December 2014

11. PRESCRIPTION/PHARMACY STATUS

Prescription only

For further information please feel free to contact us at the following e-mail address: info-service@ferring.de