Minirin® Melt 60, 120 & 240 mcg

FERRING

NAME OF THE MEDICINAL PRODUCT
Minirin 60 microgram oral lyophilisate
Minirin 120 microgram oral lyophilisate
Minirin 240 microgram oral lyophilisate

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS
Minirin 60 microgram:
One oral lyophilisate contains 60 microgram desmopressin (free base), added as Desmopressin acetate (approximately 67 microgram).
Minirin 120 microgram:
One oral lyophilisate contains 120 microgram desmopressin (free base), added as desmopressin acetate (approximately 135 microgram).
Minirin 240 microgram:
One oral lyophilisate contains 240 microgram desmopressin (free base), added as desmopressin acetate (approximately 270 microgram).

Other excipients see 6.1

3. PHARMACEUTICAL FORM
Oral lyophilisate

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Central diabetes insipidus.
Primary nocturnal enuresis (from 5 years of age)
Symptomatic treatment of nocturia in adults associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

4.2 Posology and method of administration
The dosage of Minirin oral lyophilisates **sublingual tablet** is individually titrated. Minirin oral lyophilisate 60 microgram is calculated correspond to Minirin tablet 0.1 mg. 120 microgram corresponds to 0.2 mg and 240 microgram corresponds to 0.4 mg tablets (see also 5.2).
Desmopressin should always be taken at the same time in relation to food intake, since food intake causes decreased absorption and by that also might influence the effect of desmopressin, see section 4.5.

Central diabetes insipidus:
A suitable initial dose for children and adults is 60 microgram 3 times daily, administered sublingually. The dosage regimen is then adjusted in accordance with the patient's response.
Clinical experience has shown that the daily dose varies between 120 microgram and 720 microgram sublingually. For most patients, the maintenance dose is 60 microgram to 120 microgram sublingually 3 times daily. In the event of signs of water retention/hyponatraemia treatment should be interrupted and the dose should be adjusted.

Primary nocturnal enuresis:
A suitable initial dose is 120 microgram at bedtime, administered sublingually. The dose may be increased up to 240 microgram sublingually if the lower dose is not sufficiently effective.
Fluid restriction shall be enforced. In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and in serious cases convulsions) the treatment should be interrupted until the patient has completely recovered. When the treatment is resumed strict fluid restriction is necessary, see section 4.4.
Evaluation of continued need of treatment should be carried out after three months by means of at least one treatment-free week.

Nocturia:
The recommended initial dose is 60 microgram at bedtime, administered sublingually. If this dose is not sufficiently effective after one week, the dose may be increased up to 120 microgram sublingually and subsequently 240 micrograms sublingually by weekly dose escalations. Fluid restriction should be observed.
In nocturic patients, a frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days and nights before starting treatment. A night-time urine production exceeding the functional bladder capacity or exceeding 1/3 of the 24-hour urine production is regarded as nocturnal polyuria.

The initiation of treatment in the elderly (65 years of age and over) is not recommended.
Should treatment of these patients be considered, serum sodium should be measured before beginning the treatment and 3 days after initiation or increase in dosage and other times during treatment as deemed necessary by the treating physician, see section 4.4.

Should there be signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions) the treatment should be interrupted until the patient has completely recovered. When the treatment is resumed strict fluid restriction is necessary, see section 4.4..
If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration the medication should be discontinued.

4.3 Contraindications
Habitual or psychogenic polydipsia (urine production exceeding 40 ml/kg/24 hours), known or suspected cardiac insufficiency and other conditions that require treatment with diuretics, moderate to severe renal insufficiency (creatinine clearance below 50 ml/min), syndrome of inappropriate ADH secretion (SIADH), known hyponatraemia. Hypersensitivity to desmopressin or to any of the excipients (contain fish gelatine).

4.4 Special warnings and precautions for use
In patients with urgency/urge incontinence, organic causes for increased micturition frequency or nocturia (e.g. benign prostate hyperplasia (BPH), urinary tract infection, bladder stones/tumors), polydipsia and poorly adjusted diabetes mellitus, the specific cause should be treated.
In the treatment of primary nocturnal enuresis and nocturia fluid intake shall be limited to the least possible during the period of one hour before and 8 hours after administration. Treatment without concomitant reduction in fluid intake can lead to water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions).
In clinical trials, higher occurrence of hyponatraemia was found in patients over 65 years.
Therefore, the initiation of treatment in the elderly is not recommended, especially not in patients suffering from other conditions that may increase the likelihood of fluid or electrolyte imbalance. Elderly patients, patients with low serum sodium levels and patients with high 24-hour urine volumes (above 2.8 to 3 litres) have an increased risk for hyponatraemia.
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 serotonine reuptake inhibitors, chlorpromazine and carbamazepine,
- Case of concomitant treatment with NSAIDs.

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

4.5 Interaction with other medicinal products and other forms of interaction
Substances that are known to induce disturbed ADH-secretion, e.g. tricyclic antidepressant substances, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine may cause an additive antidiuretic effect with an increased risk of fluid retention, see section 4.4

NSAID preparations can induce water retention/hyponatraemia, see section 4.4.
Concomitant treatment with loperamide may result in a three-fold increase in desmopressin plasma concentration, which may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.
Concomitant treatment with dimeticone may result in a decreased absorption of desmopressin.
It is unlikely that desmopressin interacts with pharmaceuticals affecting hepatic metabolism, since desmopressin has not been shown to undergo any significant liver metabolism in in vitro studies with human microsomes. However, no formal interaction studies in vivo have been carried out.

A standardised meal with 27% fat taken together with or 1.5 h prior to Desmopressin decreased the extent and rate of absorption of desmopressin by about 40%. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality).
However, it can not be excluded that some patients may have altered effect at concomitant food intake, see section 4.2.

4.6 Pregnancy and lactation
Pregnancy
Data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ foetal development, parturition or postnatal development.
Caution should be exercised when prescribing to pregnant women.

Lactation
Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 µg intranasal), indicate that desmopressin is transferred to the milk but that the amount of desmopressin that can be transferred to the child is low and probably less than the amounts required to influence diuresis. Whether desmopressin will accumulate in breast milk upon repeated doses has not been studied.

4.7 Effects on ability to drive and use machines
Minirin has no effect on the ability to drive vehicles and use machines.

4.8 Undesirable effects
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 serious cases convulsions).

Primary nocturnal enuresis & diabetes insipidus

System organ class	Frequency	Adverse event
Immune system disorders	Isolated reports	Allergic reactions
Metabolism and nutrition disorders	Very rare (<1/10 000)	Hyponatraemia
Psychiatric disorders	Very rare (<1/10 000)	Emotional disturbances
Nervous system disorders	Common (>1/100,<1/10)	Headache
Gastrointestinal disorders	Common (>1/100,<1/10)	Abdominal pain, nausea
Skin and subcutaneous tissue disorders	Very rare (<1/10 000)	Allergic skin reactions

Nocturia:
In clinical trials in the treatment of nocturia about 35% of the patients experienced adverse drug reactions during dose-titration. 8% of the patients interrupted in the dose titration phase due to adverse effects and 2% in the subsequent double-blind phase (0.63% on desmopressin and 1.45% on placebo).

System organ class	Frequency	Adverse event
Metabolism and nutrition disorders	Common (>1/100,<1/10)	Hyponatraemia
Nervous system disorders	Common (>1/100,<1/10)	Headache, dizziness
Cardiac and vascular disorders	Common (>1/100,<1/10)	Peripheral oedema
Urinary tract disorders	Common (>1/100,<1/10)	Micturition frequency
Gastrointestinal disorders	Common (>1/100,<1/10)	Abdominal pain, nausea, dry mouth, weight increase

4.9 Overdose
Overdosage leads to prolonged duration of action with an increased risk of fluid retention and hyponatraemia. The treatment of hyponatraemia must be individual but the following general recommendations may be given.
Hyponatraemia is treated by interrupting the desmopressin treatment and fluid restriction. If the patient has symptoms an infusion of isotonic or hypertonic sodium chloride may be given.
When the fluid retention is severe (convulsions and loss of consciousness) furosomide treatment is given.

Toxicity: Even normal doses can in combination with considerable fluid intake cause water intoxication. Doses from 0.3 µg/kg i.v. and 2.4 µg/kg intranasally have caused hyponatraemia and convulsions in children and adults. On the other hand, 40 µg intranasally administered to a 5-month-old baby and 80 µg intranasally to a 5-year-old gave no symptoms. 4 µg administered parenterally to a newborn caused oliguria and weight gain.
Symptoms: Headache, nausea. Fluid retention, hyponatraemia, oliguria, convulsions, lung oedema.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC code: H01BA02
Pharmacotherapeutic group: Antidiuretic hormone, ADH
Minirin contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in that the amino group in cysteine has been removed and L-arginine has been substituted by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages used clinically.
Clinical trials with desmopressin tablets in the treatment of nocturia showed the following:
- A reduction of at least 50% in the mean number of nocturnal voids was obtained in 39% of patients with desmopressin compared to 5% of patients with placebo (p<0.0001).
- The mean number of voids per night decreased by 44% with desmopressin compared to 15% with placebo (p<0.0001).
- The median duration of first undisturbed sleep period increased by 64% with desmopressin compared to 20% with placebo (<0.0001).
- The mean duration of first undisturbed sleep period increased by 2 hours with desmopressin compared to 31 minutes with placebo (p<0.0001).

5.2 Pharmacokinetic properties
The plasma concentration of desmopressin has been shown to be equivalent after administration of Minirin tablet 2x0.2 mg (0.4 mg) and Minirin oral lyophilisate 240 microgram respectively.
The mean bioavailability of desmopressin administered sublingually as Minirin oral lyophilisate is approximately 0.25%. Concomitant use of food with Minirin tablets decreases the rate and extent of absorption by about 40%. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. The plasma concentration of desmopressin increases proportionally to administered doses and after administration of 200, 400 and 800 microgram was Cmax 14, 30 and 65 pg/mL respectively. Tmax was observed at 0.5– 2.0 hours after dosing. The terminal half-life is 2.8 hours.
The distribution volume of desmopressin after intravenous administration is 33 L (0.41 L/kg). Desmopressin does not cross the blood-brain barrier.

In vitro studies with human liver microsomes have shown that no significant amount of desmopressin is metabolized in the liver. It is therefore unlikely that desmopressin is metabolized in the liver in human beings.

After i.v. injection 45% of the amount of desmopressin could be recovered in the urine within 24 hours.

5.3 Preclinical safety data
There are no pre-clinical data of relevance in addition to those already noted in the summary of the product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Gelatine (from fish)
Mannitol (E421)
Citric acid, anhydrous (E330)

6.2 Incompatibilities
Not applicable

6.3 Shelf-life
See outer carton

6.4 Special precautions for storage
Store in the original package.
Store at room temperature (max 25 C).

6.5 Nature and content of container
Aluminium/Aluminium blisters of 10 oral lyophilisates.
Pack sizes:
60 microgram: 10, 30 and 100 oral lyophilisates
120 microgram: 10, 30 and 100 oral lyophilisates
240 microgram: 10, 30 and 100 oral lyophilisates
Not all pack sizes may be marketed.

6.6 Instructions for use and handling and disposal
The oral lyophilisates are brittle and could not be pressed through the foil since they then are running the risk to break. The oral lyophilisates should be taken out from the blisters by removing the aluminium cover.

7. MARKETING AUTHORISATION HOLDER
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8. DATE OF REVISION OF THE TEXT
2005-07-01