MINIRIN®

Tablet 0.1 mg and 0.2 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION

MINIRIN® 0.1 mg:
Each tablet contains desmopressin acetate 0.1 mg, corresponding to desmopressin (free base) 0.089 mg.

MINIRIN® 0.2 mg:
Each tablet contains desmopressin acetate 0.2 mg, corresponding to desmopressin (free base) 0.178 mg.

Excipients: Lactose monohydrate, potato starch, povidone, magnesium stearate.

PHARMACEUTICAL FORM

Tablet

MINIRIN® 0.1 mg:
White, oval, convex tablet with a single score and marked “0.1” on one side.

MINIRIN® 0.2 mg:
White, round, convex tablet with a single score and marked “0.2” on one side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

THERAPEUTIC INDICATIONS

Central diabetes insipidus. The use of MINIRIN® in patients with an established diagnosis will result in a reduction in urinary output with concomitant increase in urine osmolality and decrease in plasma osmolality. This will result in decreased urinary frequency and decreased nocturia.

Primary nocturnal enuresis in children aged 5 years or more.

Symptomatic treatment of nocturia in adults, associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

POSOLOGY AND METHOD OF ADMINISTRATION

General
The dose of MINIRIN® tablets is individually adapted.
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 Interaction with other medicinal products and other forms of interaction.
In the event of signs of water retention/hyponatraemia (headache, nausea/vomiting, weight gain, and in serious cases convulsions) the treatment should be temporarily interrupted until the patient has completely recovered. When the treatment is resumed strict fluid restriction is necessary, see section Special warnings and precautions for use.

Indication specific
Central diabetes insipidus:
A suitable initial dose for children and adults is 0.1 mg 3 times daily. The dosage regimen is then adjusted in accordance with the patient's response. Clinical experience has shown, that the daily dose varies between 0.2 mg and 1.2 mg. For most patients, the maintenance dose is 0.1-0.2 mg 3 times daily. In the event of signs of water retention/hyponatraemia treatment should be temporarily interrupted and the dose should be adjusted.

Primary nocturnal enuresis:
A suitable initial dose is 0.2 mg at bedtime. The dose may be increased up to 0.4 mg if the lower dose is not sufficiently effective. Fluid restriction shall be enforced. Evaluation of continued need of treatment should be carried out after three months by means of at least one treatment-free week.

Nocturia:
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 recommended initial dose is 0.1 mg at bedtime. If this dose is not sufficiently effective after one week, the dose may be increased up to 0.2 mg and subsequently 0.4 mg by weekly dose escalations. Fluid restriction should be enforced.

Treatment should not be initiated in the elderly (65 years of age and over). Should treatment of these patients be considered, serum sodium should be measured before beginning of treatment and after 3 days of treatment. The same applies at increase in dosage and other occasions during treatment as deemed necessary by the treating physician, see section Special warnings and precautions for use.
If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration the treatment should be discontinued.

Special Populations
Paediatric Population: MINIRIN® tablets are indicated in Central Diabetes Insipidus and Primary Nocturnal Enuresis (see section Pharmacodynamic properties and indication specific information above). Dose recommendations are the same as in adults.

Elderly: Treatment of nocturia should not be initiated in patients >65 years (see dosage section above).
Renal Impairment: see section Contraindications.
Hepatic Impairment: see section Interaction with other medicinal products and other forms of interaction.

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 and severe renal insufficiency (creatinine clearance below 50 ml/min);
- Syndrome of inappropriate ADH secretion (SIADH);
- Known hyponatraemia;
- Hypersensitivity to the active substances or to any of the excipients.

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, urinary tract infection, bladder stone/tumor), polydipsia and poorly adjusted diabetes mellitus, the specific cause should be treated primarily.

At treatment of primary nocturnal enuresis and nocturia, fluid intake should be limited to the least possible during the period of 1 hour before evening dose until at least 8 hours after administration. Treatment without concomitant reduction in fluid intake may lead to water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions).
All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.

In clinical trials, higher occurrence of hyponatraemia was found in patients over 65 years. Therefore, treatment should not be initiated in the elderly, 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 a 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 at:
- concomitant treatment with drugs known to induce syndrome with disturbed ADH secretion (SIADH), e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors (SSRI), chlorpromazine and carbamazepine,
- concomitant treatment with NSAIDs.

Precautions must be taken in patients at risk for increased intracranial pressure.
Treatment with desmopressin should be interrupted during acute illnesses characterised by fluid and/or electrolyte imbalance such as systemic infections, fever, gastroenteritis.

MINIRIN® tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Substances that are known to induce disturbed ADH-secretion, e.g. tricyclic antidepressants, SSRI, chlorpromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group, especially chlorpropamide, may cause an additive antidiuretic effect with an increased risk of fluid retention (see section Special warnings and precautions for use).

NSAID preparations may induce water retention/hyponatraemia (see section Special warnings and precautions for use).

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 and/or hyponatraemia.
Other drugs slowing intestinal transport might have the same effect. However, this has not been investigated.

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.

Concomitant food intake decreased the extent and rate of absorption of desmopressin by 40%. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality). It cannot be excluded that some patients may have decreased antidiuretic effect at concomitant food intake.

FERTILILTY, PREGNANCY AND LACTATION

Fertility

Fertility studies have not been carried out. *In vitro* analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentrations corresponding to recommended dose.

Pregnancy

Data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number (n = 54) of exposed pregnancies in women with von Willebrand disease indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. 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 giving MINIRIN® tablets to pregnant women.

Lactation

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 mcg intranasally), show 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINIRIN® has no or negligible effect on the ability to drive vehicles and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile

The most serious adverse reaction with desmopressin is hyponatraemia, see below under “Description of selected adverse reactions”.

In adults the most commonly reported adverse reaction during treatment was headache (12%). Other common adverse reactions were hyponatraemia (6%), dizziness (3%), hypertension (2%) and gastrointestinal disorders (<10%). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.
In children the most commonly reported adverse reaction was headache (1%). Less common were psychiatric disorders (<1%), which generally abated after treatment discontinuation and gastrointestinal disorders (<1%). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Tabulated summary of adverse reactions

Adults:

The frequency of adverse drug reactions reported in clinical trials with oral desmopressin conducted in adults for treatment of nocturia (N=1557) combined with the post marketing experience for all adult indications (incl. central diabetes insipidus). Reactions only seen post marketing have been added in the 'Not known'-frequency column.

MedDRA Organ Class	**Very common** (≥1/10)	**Common** (≥1/100, <1/10)	**Uncommon** (≥1/1000, <1/100)	**Rare** (≥1/10 000, <1/1000)	**Not known** (cannot be estimated from available data)
Immune system disorders					Anaphylactic reaction

Metabolism and nutrition disorders		Hyponatraemia*			Dehydration**, Hypernatraemia **
Psychiatric disorders			Insomnia	Confusional state*	
Nervous system disorders	Headache*	Dizziness*	Somnolence, Paraesthesia		Convulsions*, Asthenia**, Coma *
Eye disorders			Visual impairment		
Ear and labyrinth 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 tissue disorders			Sweating, Pruritus, Rash, Urticaria	Dermatitis allergic	
Musculoskeletal and connective tissue disorders			Muscle spasms, Myalgia		
Renal and urinary disorders		Bladder and urethral symptoms			
General disorders and administration site conditions		Oedema, Fatigue	Malaise* Chest pain Influenza like symptoms		
Investigations			Weight increased*, Hepatic enzyme increased, Hypokalaemia		

*Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, vertigo and in serious cases convulsions and coma.
** Only seen in the CDI indication

Paediatric Population:
The frequency of adverse drug reactions reported in clinical trials with oral desmopressin conducted in children and adolescents for treatment of primary nocturnal enuresis (N = 1923). Events only seen in post marketing have been added in the 'Not known' frequency column'.

MedDRA Organ Class	**Common** (≥1/100, <1/10)	**Uncommon** (≥1/1000, <1/100)	**Rare** (≥1/10 000, <1/1000)	**Not known** (cannot be estimated from available data)
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders				Hyponatraemia****
Psychiatric disorders		Affect lability**, Aggression***	Anxiety symptoms, Nightmare****, Mood swings****	Abnormal behaviour, Emotional disorder, Depression, Hallucination,

				Insomnia
Nervous system disorders	Headache*		Somnolence	Disturbance in attention, Psychomotor hyperactivity, Convulsions*
Vascular disorders			Hypertension	
Respiratory, thoracic and mediastinal disorders				Epistaxis
Gastrointestinal disorders		Abdominal pain*, Nausea*, Vomiting*, Diarrhoea		
Skin and subcutaneous tissue disorders				Dermatitis allergic, Rash, Sweating, Urticaria
Renal and urinary disorders		Bladder and urethral symptoms		
General disorders and administration site conditions		Oedema peripheral, Fatigue	Irritability	

*Hyponatraemia may cause headache, abdominal pain, nausea, vomiting and in serious cases convulsions
**Post marketing reported equally in children and adolescents (<18years)
***Post marketing almost exclusively reported in children and adolescents (<18years)
****Post marketing reported primarily in children (<12years)

Special populations:
Elderly patients and patients with low serum sodium levels may have an increased risk of developing hyponatraemia (see section Special warnings and precautions for use).

Description of selected adverse reactions:
The most serious adverse reaction with desmopressin is hyponatraemia, which may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, vertigo and in seriuos cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect. 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 adult study subjects treated for nocturia, the majority of those developing low serum sodium, developed this after 3 days of treatment or after dose increase.
Special precautions should be observed in adults as well as in children, see section Special warnings and precautions for use.

OVERDOSE
Toxicity
Overdosage leads to prolonged duration of action with an increased risk of fluid retention and hyponatraemia. Even normal doses may in combination with considerable fluid intake cause water intoxication. Doses from 0.3 mcg/kg i.v. and 2.4 mcg/kg intranasally have caused hyponatraemia and convulsions in children and adults. On the other hand, 40 mcg intranasally administered to a 5-month-old baby and 80 mcg intranasally to a 5-year-old gave no symptoms. 4 mcg administered parenterally to a newborn caused oliguria and weight gain.

Symptoms
The same symptoms as for water intoxication. Headache, nausea. Fluid retention, hyponatraemia, hypoosmolality, oliguria, CNS depression, convulsions, pulmonary oedema. See also side-effects described in the text.

Treatment
The treatment of hyponatraemia should 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 serious (convulsions and loss of consciousness) furosomide treatment is given.

PHARMACODYNAMIC PROPETIES
Pharmacotherapeutic group: vasopressin and analogues
ATC code: H01B A02.

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. After oral administration of desmopressin, the antidiuretic effect could be expected to last 6-14 hours or more.

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 ($p<0.0001$).
- The mean duration of first undisturbed sleep period increased by 2 hours with desmopressin compared to 31 minutes with placebo ($p<0.0001$).

PHARMACOKINETIC PROPERTIES

Absorption

The absolute bioavailability after perorally administered desmopressin is 0.16% (SD=0.17%). Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant food intake decreases the rate and extent of absorption by about 40%.
The maximum plasma concentration is reached after 1-1.5 hours. C_{max} and AUC do not increase in proportion to the administered dose.

Distribution

The distribution volume is 0.2-0.3 l/kg. Desmopressin does not cross the blood-brain barrier.

Metabolism

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.

Elimination

The mean half-life for desmopressin in the elimination phase is 2-3 hours.
52% (44%-60%) of the amount of administered desmopressin is found in the urine.

Paediatric Population

The population pharmacokinetics has been studied in children with PNE and is comparable to that in adults.

INCOMPATIBILITIES

Not applicable.

SHELF LIFE

24 months.

SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.
Keep the container tight closed and do not remove the desiccant capsule from the cap.

NATURE AND CONTENT OF CONTAINER

The tablets are presented in a 30 ml HDPE bottle/PP closure with a desiccant capsule.
Pack sizes:
0.1 mg: 30 tablets
0.2 mg: 30 tablets

MANUFACTURER

Ferring International Center SA
Chemin de la Vergognausaz 50,
CH-1162 St. Prex,
Switzerland

DATE OF REVISION

Dec 2016