NAME OF THE MEDICINAL PRODUCT
MINIRIN® Tablet 0.1 mg

QUALITATIVE AND QUANTITATIVE COMPOSITION
MINIRIN® 0.1 mg:
Each tablet contains desmopressin acetate 0.1 mg equivalent to desmopressin (free base) 0.089 mg.

List of excipients: lactose monohydrate, potato starch, povidone and magnesium stearate.

PHARMACEUTICAL FORM
Oral Tablet.

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

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

THERAPEUTIC INDICATIONS
MINIRIN® tablets are indicated for the treatment of 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.

MINIRIN® tablets are indicated for the treatment of primary nocturnal enuresis in children aged 5 years or more.

POSOLOGY AND METHOD OF ADMINISTRATION
General
Optimal dose of MINIRIN® tablets is individually adjusted.

Effect of food: Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see section Interaction with other medicinal products and other forms of interaction).

In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be interrupted until the patient has fully recovered. When restarting treatment strict fluid restriction should be enforced (see section Special warnings and precautions for use).

If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration the medication should be discontinued.

Indication Specific
Central diabetes insipidus:
A suitable initial dose for children and adults is 0.1 mg three times daily. The dose is then adjusted according to the response of the patient. According to clinical experience gained so far, the daily dose lies in the range of 0.2 mg and 1.2 mg. For most patients, 0.1-0.2 mg three times daily is the optimal dose regimen.

In the event of signs of water retention/hyponatremia treatment should be 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. The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without MINIRIN® treatment. Fluid restriction should be observed.

Special Populations
Elderly:
The initiation of treatment in patients > 65 years is not recommended. Should physicians decide to initiate desmopressin treatment in these patients then serum sodium should be measured before beginning the treatment and 3 days after initiation or increase in dosage and at other times during treatment as deemed necessary by the treating physician.

Renal Impairment: see section Contraindications

Hepatic Impairment: see section Interaction with other medicinal products and other forms of interaction

Paediatric Population:
MINIRIN® Tablet is indicated in Central Diabetes Insipidus and Primary Nocturnal Enuresis (see section Pharmacodynamic properties and indication specific information in Posology and method of administration above). Dose recommendations are the same as in adults.

CONTRAINDICATIONS
MINIRIN® tablets are contraindicated in cases of:
- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours);
- A history of known or suspected cardiac insufficiency and other conditions that requiring treatment with diuretics;
- Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min);
- Known hyponatraemia;
- Syndrome of inappropriate ADH secretion (SIADH);
- Hypersensitivity to the active substance or to any of the excipients

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Special Warnings
When used for primary nocturnal enuresis indication, the fluid intake must be limited to a minimum from 1 hour before, until the next morning (at least 8 hours) after administration. 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 severe cases, convulsions).

All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.

This product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions
Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.

Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia.

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

Precautions must be taken in patients at risk for increased intracranial pressure.

Desmopressin should be used with caution in patients with conditions characterized by fluid and/or electrolyte imbalance

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Substances, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine, as well as some antidiabetics of the sulfonylurea group particularly Chlorpropamide, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatremia (see section Special warnings and precautions for use).

Indomethacin increases the urine concentrating effect of desmopressin without influencing the duration. The effect is probably without any clinical significance.

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

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in in vitro studies with human microsomes. However, formal in vivo interaction studies have not been performed.

The concomitant use of food decreases the rate and extent of absorption of MINIRIN® tablets by 40 %. No significant effect was observed with respect to pharmacodynamics (urine production or osmolality).

Food intake may reduce the intensity and duration of the antidiuretic effect at low oral doses of MINIRIN® tablets.

FERTILITY, PREGNANCY AND LACTATION

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 bleeding complications 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, embryonic/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

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

Lactation

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 µg intranasally), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINIRIN® tablets has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Tabulated Summary of Adverse Reactions

Adults:

Based on 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 (>10%)**	**Common (1-10%)**	**Uncommon (0.1-1%)**	**Rare (0.1-0.01%)**	**Not known**
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, (HLT) 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		(HLT) Bladder and urethral symptoms			
General disorders and administration site conditions		(HLT) Oedema, Fatigue	Malaise*, Chest pain, Influenza like illness		
Investigations			Weight increased*, Hepatic enzyme increased, Hypokalaemia		

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

Children and adolescents:
Based on 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	Very common (>10%)	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.1-0.01%)	Not known
Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders					Hyponatraemia****
Psychiatric disorders			Affect lability**, Aggression***	(HLT) 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					Rash, Dermatitis allergic, Sweating, Urticaria
Renal and urinary disorders			(HLT) Bladder and urethral symptoms		
General disorders and administration site conditions			Oedema peripheral, Fatigue	Irritability	

*Hyponatraemia may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma
**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)

Other Special Populations
Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of developing hyponatraemia (see section Special warnings and precautions for use).

OVERDOSE
Overdose of MINIRIN® tablets leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment
Although the treatment of hyponatremia should be individualized, the following general recommendations can be given. Asymptomatic hyponatremia is treated with discontinuing the desmopressin treatment and fluid restriction. Infusion of isotonic or hypertonic sodium chloride

may be added in cases with symptoms. When the water retention is severe (convulsions and unconsciousness) treatment with furosemide should be added.

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

MINIRIN® tablets contain desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used. Desmopressin is a potent compound with an EC_{50} value of 1.6 pg/mL, for the antidiuretic effect. After oral administration, an effect lasting from 6 to 14 hours or more, can be expected.

PHARMACOKINETIC PROPERTIES
Absorption:
The absolute bioavailability of MINIRIN® tablets is 0.16 % with an SD of 0.17%. Mean maximum plasma concentration is reached within 2 hours.

Concomitant use of food decreases the rate and extent of absorption by 40%.

Correlation table between MINIRIN® tablet and MINIRIN® oral lyophilisate:

MINIRIN® tablet	**MINIRIN® tablet**	**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 comparative purposes

Distribution
The distribution of desmopressin is best described by a two-compartment distribution model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg

Biotransformation
The *in-vivo* metabolism of desmopressin has not been studied. *In vitro* human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolized in the liver by the cytochrome P450 system. Thus human liver metabolism *in vivo* by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolizing system.

Elimination
The total clearance of desmopressin has been calculated to 7.6 L/hr. The terminal half-live of desmopressin is estimated to 2.8 hours. In healthy subjects the fraction excreted unchanged was 52% (44% - 60%).

Characteristics in specific groups of patients
Renal Impairment:
Depending on the degree of renal impairment the AUC and half-live increased with the severity of the renal impairment in patients with moderate and severe renal impairment (creatinine clearance below 50 ml/min) desmopressin is contraindicated.

Hepatic impairment:
No studies performed.

Children:

The population pharmacokinetics of MINIRIN® tablets has been studied in children with PNE and no significant difference from adults were detected.

PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction.

Carcinogenicity studies have not been performed with desmopressin, because it is very closely related to the naturally-occurring peptide hormone.

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
36 months.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C.

Keep the container tight closed and do not remove the desiccant capsule from the cap.

NATURE AND CONTENTS OF CONTAINER
The tablets are packed in a 30 ml HDPE bottle and polypropylene cap with desiccant insert (LDPE capsule with silica gel).

Pack sizes:
0.1 mg: 30 tablets

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
No special requirements.

MANUFACTURER
Ferring International Center SA
St. Prex, Switzerland

DATE OF REVISION
15 July 2022