

1. NAME OF MEDICINAL PRODUCT

MINIRIN Tablets 0.1 mg

MINIRIN Tablets 0.2 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Minirin 0.1mg tablets - each tablet of contains desmopressin acetate 0.1 mg equivalent to desmopressin (free base) 89 micrograms.

Also contains Lactose monohydrate, 123.7 mg per tablet.

For the full list of excipients, see section 6.1

Minirin 0.2mg tablets - each tablet of contains desmopressin acetate 0.2 mg equivalent to desmopressin (free base) 0.178 mg.

Also contains Lactose monohydrate, 123.7 mg per tablet.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Minirin 0.1mg tablets

Tablets. White, oval, convex tablet with a single score. Engraving 0.1.

The scoreline is to facilitate breaking for ease of swallowing and not to divide into equal halves.

Minirin 0.2mg tablets

Tablets. White, oval, convex tablet with a single score. Engraving 0.2.

The scoreline is to facilitate breaking for ease of swallowing and not to divide into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Minirin tablets are indicated for Central Diabetes Insipidus, Nocturnal Enuresis (in patients from 5 years of age with normal ability to concentrate the urine) and for symptomatic treatment of nocturia in adults associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

The treatment must be started before the age of 65.

4.2 Posology and Method of Administration

Central Diabetes Insipidus:

Tablets administration. A suitable initial dose for children and adults is 0.1 mg three times daily. The dose is than adjusted according to the response of the patient. The average daily dose is between 0.2 and 1.2 mg with tablet administration. For most patients, 0.1 – 0.2 mg three times daily is the optimal dose regimen.

Nocturnal Enuresis:

Tablets administration. 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.

If treatment continues over the long-term, a treatment-free week should be introduced every three months, in order to ascertain whether the condition has resolved spontaneously.

If the desired clinical effect has not been achieved after 4 weeks of dose titration, treatment should be discontinued.

Nocturia:

The recommended initial dose is 0.1 mg at bedtime. If this does not sufficiently effective after one week it can be increased to 0.2 mg and then to 0.4 mg by means of weekly increases. Fluid restriction is to be enforced.

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.

Serum sodium must be measured before beginning the treatment and 3 days after initiation or increase in dosage and other times during treatment as seemed necessary by the treating physician.

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

Assessment of the necessity of continued treatment should be made after three months -during one drug-free week.

Fluid restriction should be observed, (see Special Warnings and Special Precautions for use). In the event of signs of water retention/hyponatraemia treatment should be interrupted.

4.3 Contraindications

Minirin tablets are contra-indicated in cases of:

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours);
- Syndrome of inappropriate ADH secretion;
- Known hyponatraemia;
- A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics;
- Moderate and severe renal insufficiency (creatinine clearance below 50 ml/min) ;
- Hypersensitivity to desmopressin or to any of the excipients;
- Patients over the age of 65 for the treatment of primary nocturnal enuresis.
- Patients over the age of 65 for the treatment of nocturia.

Before prescribing Minirin tablets the diagnosis of psychogenic polydipsia and alcohol abuse should be excluded.

4.4 Special Warnings and Special Precautions for use*Special warnings:*

When used for primary nocturnal enuresis and nocturia indications, 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 lactose deficiency or glucose-galactose malabsorption should not take this medicine.

Use of the product should be under specialist supervision with appropriate facilities available for monitoring and interpretation of response.

All patients on desmopressin therapy should be observed for the signs of symptoms associated with hyponatraemia (headache, nausea/vomiting, weight increased and, in severe cases, convulsions). Care should be taken with patients who have reduced renal function (see section 4.2) and/or cardiovascular disease or cystic fibrosis (see section 4.3).

Patients being treated for primary nocturnal enuresis or nocturia should discontinue Minirin Tablets during an episode of vomiting and/or diarrhoea until their fluid balance is once again normal.

Precautions

- Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.
- Older patients and patients with low serum sodium levels may have an increased risk of hyponatraemia therefore Minirin Tablets are contraindicated in patients being treated for primary nocturnal enuresis and nocturia.
- Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and 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 serotonin reuptake inhibitors, chlorpromazine and carbamazepine, case of concomitant treatment with NSAIDs

4.5 Interactions with other medicinal products and other forms of interaction

Substances, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin 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/hyponatraemia (see section 4.4).

NSAIDs may induce water retention/hyponatraemia (see section 4.4).

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 Nordurine 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 desmopressin (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 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. 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 Nordurine tablets 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 concentrations corresponding to recommended dose.

Lactation:

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction with desmopressin is hyponatraemia, which may cause headache, abdominal pain, nausea, vomiting, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls and in severe cases convulsions and coma. The majority of adults treated for nocturia who develop hyponatraemia have developed low serum sodium after three days of dosing. In adults the risk of hyponatraemia increases with increasing dose of desmopressin and the risk has been found to be more prominent in women.

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 (nausea (4%), vomiting (1%), abdominal pain (3%), diarrhoea (2%) and constipation (1%)). Less common is an influence of the sleep pattern/consciousness level presenting itself as e.g. insomnia (0.96%), somnolence (0.4%) or asthenia (0.06%).

Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received. In children the most commonly reported adverse reaction during treatment was headache (1%), less common were psychiatric disorders (affect lability (0.1%), aggression (0.1%), anxiety (0.05%), mood swings (0.05%), nightmare (0.05%)) which generally abated after treatment discontinuation and gastrointestinal disorders (abdominal pain (0.65%), nausea (0.35%), vomiting (0.2%) and diarrhoea (0.15%)). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

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 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*			Dehydration**, Hyponatraemia**
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			Sweating,	Dermatitis	

subcutaneous tissue disorders			Pruritus, Rash, Urticaria	allergic	
Renal and urinary disorders		Bladder and urethral symptoms			
General disorders and administration site conditions		Oedema Fatigue	Malaise*, Chest pain, Influeza 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 and in severe cases convulsions and coma

** Only seen in the CDI indication

Children and Adolescents:

Based on the frequency of adverse drug reactions reported in clinical trials conducted in children and adolescents with oral desmopressin for treatment of Primary Nocturnal Enuresis (N = 1923). Reactions 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***	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* Diarrhoea Vomiting*,		
Skin and subcutaneous tissue					Dermatitis allergic, Rash,

disorders					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, weight increase, dizziness, confusion, malaise, memory impairment, vertigo, falls, convulsions and coma

** Post marketing reported equally in children and adolescents (<18 years)

*** Post marketing almost exclusively reported in children and adolescents (<18 years)

****Post marketing reported primarily in children (<12 years)

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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

4.9 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 hyponatraemia should be individualised, the following general recommendations can be given - discontinue the desmopressin treatment and institute fluid restriction, and symptomatic treatment if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: vasopressin and analogues.

ATC code: HO1B 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 EC50 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.

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)

Effect of treatment with individual oral dose of desmopressin between 0.1 and 0.4 mg during 3 weeks, compared with placebo (pooled data).

	Desmopressin	Placebo	Statistical significance vs.
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					placebo
Variable	Mean baseline value	Mean value during 3 weeks of treatment	Mean baseline value	Mean value during 3 weeks of treatment	
Number of nocturnal voids	2.97 (0.84)	1.68(0.86)	3.03 (1.10)	2.54 (1.05)	p<0.0001
Nocturnal diuresis rate (ml/min)	1.51 (0.55)	0.87 (0.34)	1.55(0.57)	1.44 (0.57)	p<0.0001
Duration of first undisturbed sleep period (min)	152 (51)	270 (95)	147 (54)	178 (70)	p<0.0001

Eight percent of the patients interrupted in the desmopressin dose titration phase due to adverse effects, and 2 % in the subsequent double-blind phase (0.63 % on desmopressin and 1.45 % on placebo). **5.2**

Pharmacokinetic properties

The absolute bioavailability of desmopressin 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%.

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-life of desmopressin is estimated to be 2.8 hours. In healthy subjects the fraction excreted unchanged was 52% (44%-60%).

Linearity/non-linearity:

There are no indications of non-linearities in any of the pharmacokinetic parameters of desmopressin.

Characteristics in specific groups of patients:

Renal Impairment:

Depending on the degree of renal impairment the AUC and half-life increased with the severity of the renal impairment. In patients with moderate and severe renal impairment (creatinine clearance below 50ml/min) desmopressin is contraindicated.

Hepatic Impairment: No studies performed.

Children: The population pharmacokinetics of desmopressin tablets has been studied in children with PNE and no significant differences from adults were detected.

5.3 Preclinical Safety Data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Potato starch, Povidone, Mg Stearate.

6.2 Incompatibilities: Not applicable

6.3 Shelf Life

The expiry date of each product is indicated on the packaging materials.

6.4 Storage Conditions

Store bellow 25°C.

6.5 Nature and contents of container: HDPE bottles

6.6 Manufacturer: Ferring Switzerland

6.7 License Holder

Ferring Pharmaceuticals Ltd

8, Hashita Street, Industrial Park, Caesarea 3088900 Israel

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