MINIRIN®

Oral lyophilisates 60 µg, 120 µg and 240ug

Name and Strength of Active Substance
MINIRIN® oral lyophilisate 60 µg:
Each unit contains 60 µg desmopressin (free base), added as desmopressin acetate.

MINIRIN® oral lyophilisate 120 µg:
Each unit contains 120 µg desmopressin (free base), added as desmopressin acetate.

MINIRIN® oral lyophilisate 240 µg:
Each unit contains 240 µg desmopressin (free base), added as desmopressin acetate.

Excipients: Gelatin, mannitol (E421) and citric acid (anhydrous).

Pharmaceutical form
MINIRIN® oral lyophilisate 60 µg: White, round, oral lyophilisate marked with a drop shaped figure on one side.
MINIRIN® oral lyophilisate 120 µg: White, round, oral lyophilisate marked with two drop shaped figures on one side.
MINIRIN® oral lyophilisate 240 µg: White, round, oral lyophilisate marked with three drop shaped figures on one side.

Therapeutic indications
MINIRIN® oral lyophilisate is indicated for the treatment of central diabetes insipidus.
MINIRIN® oral lyophilisate is indicated for the treatment of primary nocturnal enuresis in patients (from 5 years of age) with normal ability to concentrate urine.

Posology and method of administration
General
Method of administration: MINIRIN® oral lyophilisate is placed under the tongue where it dissolves without the need for water.
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:
Dosage is individual in diabetes insipidus but the total daily sublingual dose normally lies in the range of 120 µg to 720 µg. A suitable starting dose in adults and children is 60 µg three times daily, administered sublingually. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 60 µg to 120 µg sublingually three times daily.

Primary nocturnal enuresis:
The recommended initial dose is 120 µg at bedtime, administered sublingually.
If this dose is not sufficiently effective, the dose may be increased up to 240 µg sublingually. Fluid restriction should be observed. MINIRIN® oral lyophilisate is intended for treatment periods of up to 3 months. The need for continued treatment should be reassessed by means of a period of at least one week without MINIRIN® oral lyophilisate.

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® oral lyophilisate 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® oral lyophilisate is 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 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 substances or to any of the excipients

Special warnings and precautions for use
Special warnings:
When used for primary nocturnal enuresis indications, the fluid intake must be limited to a minimum from 1 hour before until 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.
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/hyponatraemia (see section Special warnings and precautions for use).
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.
It has been shown that intake of a standardized meal with MINIRIN® Tablets has no effect on pharmacodynamic parameters (urine production and osmolality) despite some pharmacokinetic influence. The fact that MINIRIN® oral lyophilisate is absorbed initially in the oral mucosa, pharynx and oesophagus implies that it is even less likely that food intake will influence its absorption. Therefore, it is very unlikely that any clinically significant drug-food interaction exists with sublingual administration of MINIRIN® oral lyophilisate.

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, embryonic/foetal development, parturition or postnatal development.
Caution should be exercised when prescribing to pregnant women. In case of prescription to pregnant women, special care is to be taken and blood pressure monitoring is recommended.
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.
Breastfeeding
Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 µg intranasal), 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® oral lyophilisate has no or negligible influence on the ability to drive and use machines.

Undesirable effects
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**, 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 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***	(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					Dermatitis allergic, Rash 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 and in severe cases 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® oral lyophilisate leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment
Although the treatment of hyponatremia should be individualised, the following general recommendations can be given: discontinue the desmopressin treatment and institute fluid restriction and symptomatic treatment if needed.

Pharmacodynamic properties
Pharmacotherapeutic group: vasopressin and analogues.
ATC code: H01B A02.
MINIRIN® oral lyophilisate contains 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.

Pharmacokinetic properties
Absorption: The overall mean absolute bioavailability of desmopressin administered sublingually as MINIRIN® oral lyophilisate at doses of 200, 400 and 800 µg is 0.25% with a 95% confidence interval of 0.21 – 0.31 %. The C_{max} was 14, 30 and 65 pg/mL after administration of 200, 400 and 800 µg, respectively. t_{max} was observed at 0.5 – 2.0 hours after dosing. 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 %).
Linearity/non-linearity:
Linearity (dose-proportional pharmacokinetics) was established for MINIRIN® oral lyophilisate for dose levels from 60 µg to 240 µg.
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.

Shelf Life

3 years.

Storage Condition
Do not store above 30°C.
Store in the original package in order to protect from moisture and light.

Pack Sizes
Aluminium/Aluminium blisters of 10 oral lyophilisates in pack sizes of 30 and 100 oral lyophilisates.
Not all pack sizes may be marketed.

Manufactured by:
Catalent U.K. Swindon Zydis Limited
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