NEW ZEALAND DATA SHEET

MINIRIN® tablets 0.1mg
MINIRIN® tablets 0.2mg

Desmopressin acetate

1 PRODUCT NAME

MINIRIN® tablets 0.1mg

MINIRIN® tablets 0.2mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient(s) with known effect: lactose

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

MINIRIN 0.1mg: White, oval and convex tablets with a single score and marked "0.1" on one side.

MINIRIN 0.2mg: White, round and convex tablets 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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIRIN tablets are indicated for the treatment of central diabetes insipidus.

MINIRIN tablets are indicated for the treatment of primary nocturnal enuresis in patients (from 5 years of age) with normal ability to concentrate urine.

MINIRIN tablets are indicated for the symptomatic treatment of nocturia in adults, associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

4.2 Dose and method of administration

General

The tablet may be divided to ease the intake but both tablet halves must be taken at the same occasion.

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see Section 4.5).

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 4.4).

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

Central diabetes insipidus

Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 0.2 to 1.2mg. A suitable starting dose in adults and children is 0.1mg three times daily. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 0.1mg to 0.2mg three times daily.

Primary nocturnal enuresis

The recommended initial dose is 0.2mg at bedtime. If this dose is not sufficiently effective, the dose may be increased up to 0.4mg. Fluid restriction should be observed. MINIRIN tablets are 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 tablets.

Nocturia

In nocturia patients, a frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days 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 0.1mg at bedtime. If this dose is not sufficiently effective after one week, the dose may be increased up to 0.2mg and subsequently 0.4mg by weekly dose escalations. Fluid restriction should be observed.

Special Populations

Elderly Patients:

The initiation of treatment in the elderly 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 4.3

Hepatic Impairment*:* See Section 4.4

Paediatric Population:

MINIRIN tablet is indicated in Central Diabetes Insipidus and Primary Nocturnal Enuresis (see Section 4.1). Dose recommendations are the same as in adults.

4.3 Contraindications

MINIRIN tablets are contraindicated in cases of:

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40ml/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 50ml/min)
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

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 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 medicines, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, cases of concomitant treatment with NSAIDs.

4.5 Interaction with other medicines 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/hyponatremia (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 agents slowing intestinal transport might have the same effect.

It is unlikely that desmopressin will interact with agents 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.

4.6 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 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 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.

Breastfeeding

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

Fertility

No information available.

4.7 Effects on ability to drive and use machines

MINIRIN tablets have 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 the 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 (including 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*

MedDRA Organ Class	Very Common (>10%)	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.1-0.01%)	Not known
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

MedDRA Organ Class	Very Common (>10%)	Common (1-10%)	Uncommon (0.1-1%)	Rare (0.1-0.01%)	Not known
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 (<18 years)

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

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

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, memory impairment, vertigo, falls and in severe cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect. The 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 within the first days of treatment or in relation to dose increase.

In both adults and children special attention should be paid to the precautions addressed in Section 4.4.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

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 necessary.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 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 EC50 value of 1.6pg/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 0.4mg during 3 weeks, compared with placebo (pooled data)

	Desmopressin	Placebo	Statistical significance vs 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

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%.

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 vitro* 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 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.

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, toxicity to reproduction.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Potato starch
- Povidone
- Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

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

6.5 Nature and contents of container

The tablets are presented in a 30ml HDPE bottle/PP closure with a desiccant capsule in a pack size of 30 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

20 October 1995

10 DATE OF REVISION OF THE TEXT

10 September 2018

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new SPC format