NEW ZEALAND DATA SHEET

MINIRIN® MELT

Desmopressin acetate sublingual wafer

1 PRODUCT NAME

MINIRIN® Melt 60 micrograms

MINIRIN® Melt 120 micrograms

MINIRIN® Melt 240 micrograms

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MINIRIN Melt 60 micrograms: Each unit contains 60 micrograms desmopressin (free base), added as desmopressin acetate.

MINIRIN Melt 120 micrograms: Each unit contains 120 micrograms desmopressin (free base), added as desmopressin acetate.

MINIRIN Melt 240 micrograms: Each unit contains 240 micrograms desmopressin (free base), added as desmopressin acetate.

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

MINIRIN Melt 60 micrograms – white, round, oral sublingual wafer marked with a drop shaped figure on one side.

MINIRIN Melt 120 micrograms – white, round, oral sublingual wafer marked with two drop shaped figures on one side.

MINIRIN Melt 240 micrograms – white, round, oral sublingual wafer marked with three drop shaped figures on one side.

Do not halve wafer. Dose equivalence when the wafer is divided has not been established.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIRIN Melt is indicated for the treatment of central diabetes insipidus.

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

MINIRIN Melt is 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

Method of administration

MINIRIN Melt is placed under the tongue where it dissolves without the need for water. Do not halve the wafer. Dose equivalence when the wafer is divided has not been established.

Effect of food

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 the total daily sublingual dose normally lies in the range of 120 micrograms to 720 micrograms. A suitable starting dose in adults and children is 60 micrograms 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 micrograms to 120 micrograms sublingually three times daily.

Primary nocturnal enuresis

The recommended initial dose is 120 micrograms at bedtime, administered sublingually. If this dose is not sufficiently effective, the dose may be increased up to 240 micrograms sublingually. Fluid restriction should be observed.

MINIRIN Melt 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 Melt.

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 60 micrograms at bedtime, administered sublingually. If this dose is not sufficiently effective after one week, the dose may be increased up to 120 micrograms sublingually and subsequently 240 micrograms sublingually by weekly dose escalations. 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 4.3

Hepatic Impairment**:** see Section 4.5

Paediatric Population:

MINIRIN Melt is indicated in Central Diabetes Insipidus and Primary Nocturnal Enuresis (see Section 5.1 and indication specific information in Section 4.2). Dose recommendations are the same as in adults.

4.3 Contraindications

MINIRIN Melt is 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 substances or to any of the excipients of MINIRIN Melt.

4.4 Special warnings and 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 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 low 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 of 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/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 medicines slowing intestinal transport might have the same effect.

It is unlikely that desmopressin will interact with medicines 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.

A standardised 27% fat meal significantly decreased absorption (rate and extent) of MINIRIN tablets. 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 tablet.

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, 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.

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 known available.

4.7 Effects on ability to drive and use machines

MINIRIN Melt 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 (including 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	-	-	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 (<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.

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 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
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 Melt 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.

Clinical trials with MINIRIN tablet 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 MINIRIN tablet 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 overall mean systemic bioavailability of desmopressin administered sublingually as MINIRIN Melt at doses of 200, 400 and 800 micrograms 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 micrograms, respectively. t_{max} was observed at 0.5-2.0 hours after dosing.

Correlation table between MINIRIN tablet and MINIRIN Melt:

MINIRIN Tablet	**MINIRIN Tablet**	**MINIRIN Melt**	**MINIRIN Melt**
Desmopressin acetate	Desmopressin free base	Desmopressin free base	Desmopressin acetate
0.1 milligrams	89 micrograms	60 micrograms	Approx. 67 micrograms*
0.2 milligrams	178 micrograms	120 micrograms	Approx. 135 micrograms*
0.4 milligrams	356 micrograms	240 micrograms	Approx. 270 micrograms*

* 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 be 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 (see Section 4.3).

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

- Gelatin
- Mannitol
- Citric acid, anhydrous

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
48 months.

6.4 Special precautions for storage
Store below 25°C. Store in the original pack in order to protect from moisture and light.

6.5 Nature and contents of container
Aluminium/aluminium blisters of 10 oral sublingual wafers in pack sizes of 10, 30 and 100 oral sublingual wafers. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

7 MEDICINE SCHEDULE
Prescription Medicine.

8 SPONSOR
Pharmaco (NZ) Ltd
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9 DATE OF FIRST APPROVAL
17/09/2009

10 DATE OF REVISION OF THE TEXT
10 September 2018
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MINIRIN® is a trademark of Ferring B.V

SUMMARY TABLE OF CHANGES

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