SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MINIRIN® Melt 60 µg sublingual tablet

MINIRIN® Melt 120 µg sublingual tablet

MINIRIN® Melt 240 µg sublingual tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MINIRIN® Melt 60 µg: Each unit contains 60 µg desmopressin acetate (60 µg free base)

MINIRIN® Melt 120 µg: Each unit contains 120 µg desmopressin acetate (120 µg free base)

MINIRIN® Melt® 240 µg: Each unit contains 240 µg desmopressin acetate (240 µg free base)

Excipient with known effect:

Contains sugar alcohol (mannitol 10,25 mg per dosage unit).

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablets

MINIRIN® Melt 60 µg: White, round, oral lyophilisate marked with a drop shaped figure on one side.

MINIRIN® Melt 120 µg: White, round, oral lyophilisate marked with two drop shaped figures on one side.

MINIRIN® Melt 240 µg: White, round, oral lyophilisate marked with three drop shaped figures on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIRIN® Melt is indicated for:

1. Management of central diabetes insipidus.
2. The symptomatic short-term (4 - 8 weeks) treatment of primary nocturnal enuresis in children older than 5 years who have normal ability to concentrate urine.

4.2 Posology and method of administration

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.

Posology

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 children and in adults 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. In the event of signs of water retention/hyponatraemia treatment should be interrupted and the dose should be adjusted (see section 4.4).

Primary nocturnal enuresis

The recommended initial dose is 120 µg at bedtime, administered sublingually. If this is not sufficiently effective, the dose may be increased up to 240 µg sublingually. Fluid restriction should be observed. MINIRIN® Melt is intended for treatment periods of up to 4-8 weeks. The need for continued treatment should be reassessed by means of a period of at least one week without MINIRIN® Melt.

The recommended dose may only be administered once in every 24 hours.

Special populations

Elderly:

The initiation of treatment in patients > 65 years is not recommended. Should medical practitioners decide to initiate MINIRIN® Melt 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 the treatment as deemed necessary by the treating medical practitioners.

Renal impairment:

See section 5.2

Hepatic impairment:

See section 5.2

Paediatric population

MINIRIN® Melt is indicated in Central Diabetes Insipidus and Primary Nocturnal Enuresis. Dose recommendations are the same as in adults.

Method administration

MINIRIN® Melt is placed under the tongue where it dissolves without the need for water.

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of MINIRIN® Melt (see section 4.5).

4.3 Contraindications

MINIRIN® Melt is contraindicated in cases of:

- Hypersensitivity to desmopressin or to any of the excipients listed in section 6.1.
- Nephrogenic diabetes insipidus is insensitive to ADH. Desmopressin is not effective.
- A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics.
- Moderate or severe renal insufficiency (creatinine clearance below 50 mL/min); including glomerulonephritis/ nephrotic syndrome.
- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 mL/kg/24 hours).
- Known hyponatraemia.
- Syndrome of inappropriate ADH secretion (SIADH).
- All oedematous states not associated with an endogenous vasopressin deficiency.

4.4 Special warnings and precautions for use

Excessive water intake (water intoxication) can produce hyponatraemia with associated effects, including convulsions.

When used for primary nocturnal enuresis indication, 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, if applicable, their guardians should be carefully instructed to adhere to the fluid restrictions while in treatment with MINIRIN® Melt.

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

Elderly patients and patients with low serum sodium levels may have an increased risk of hyponatraemia.

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

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

MINIRIN® Melt should be used with caution in patients with conditions characterised 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, and also in the case of concomitant treatment with NSAIDs.

Pressor effects: MINIRIN® Melt has infrequently produced changes in blood pressure; either as a transient fall in blood pressure in combination with a transient compensatory increase in heart rate or when given in high dosage, as a slight elevation in blood pressure, which disappeared with dose reduction.

Precautions to avoid hyponatraemia must be taken in:

- Conditions characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and syndrome of inappropriate ADH secretion).
- Conditions requiring concomitant treatment with diuretic medicines.
- Case of concomitant treatment with medicine, which are known to induce the syndrome of inappropriate ADH secretion, e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine (see section 4.5).
- Case of concomitant treatment with non-steroid anti-inflammatory drugs (NSAIDs).

4.5 Interaction with other medicines and other forms of interaction

Substances, which are known to induce syndrome of inappropriate ADH secretion (SIADH), e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, as well as antidiabetic medicines of the sulfonylurea group, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia (see section 4.4).

Carbamazepine may prolong the action of MINIRIN® Melt.

Non-steroid anti-inflammatory drugs (NSAIDs) may induce water retention/hyponatraemia (see section 4.4).

Pressor medicines: Large doses of MINIRIN® Melt together with other pressor medicines should only be given with careful monitoring.

Concomitant treatment with loperamide may result in a 3-fold increase of MINIRIN® Melt 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 MINIRIN® Melt will interact with medicine 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 has not been studied with MINIRIN® Melt, but for the desmopressin tablet dosage form. A standardised 27 % fat meal significantly decreased absorption (rate and extent) of oral desmopressin 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 desmopressin tablets.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety during pregnancy has not been established.

Breastfeeding

It is not known whether or not MINIRIN® Melt enters the mother's milk but absorption from the child's gastrointestinal tract is unlikely.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

MINIRIN® Melt may cause somnolence and dizziness and may affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction 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.

Adults:

Immune system disorders

Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Nervous system disorders

Frequent: Headache, dizziness

Less frequent: Influence of the sleep pattern / consciousness level presenting itself as e.g. insomnia, somnolence or asthenia.

Vascular disorders

Frequent: Hypertension

Gastrointestinal Disorders

Frequent: Nausea, vomiting, abdominal pain, diarrhoea and constipation

Metabolism and Nutrition Disorders

Frequent: Hyponatraemia

Children:

Immune system disorders

Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Nervous system disorders

Frequent: Headache

Psychiatric disorders

Less frequent: Lability, aggression, anxiety, mood swings, nightmare.

These side effects generally abated after treatment discontinuation.

Gastrointestinal Disorders

Less frequent: Abdominal pain, nausea, vomiting and diarrhoea.

Tabulated summary of adverse reactions

Adults:

Based on the frequency of side effects reported in clinical trials with oral desmopressin conducted in adults combined with the post-marketing experience for all adult indications (including central diabetes insipidus). Reactions only seen post-marketing have been added in the 'Post-marketing data' column.

MedDRA system Organ Class	**Very common (≥10 %)**	**Common (≥1 %; <10 %)**	**Uncommon (≥0,1 %; <1 %)**	**Rare (≥0,01 %; <0,1 %)**	**Post-marketing data**
Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders		Hypo-natraemia*	Hypo-kalaemia		Dehydration**, Hyper-natraemia**
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		
Gastro-intestinal disorders		Nausea* Abdominal pain*, Diarrhoea, Constipation Vomiting*	Dyspepsia, (HLT) Flatulence, bloating and distension		
Skin and subcutaneous tissue disorders			Sweating, Pruritus, Rash, Urticaria	Allergic dermatitis	

Musculo-skeletal 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*, increased hepatic enzyme		

* 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 side effects reported in clinical trials conducted in children and adolescents with oral desmopressin for treatment of primary nocturnal enuresis (N = 1923). Reactions only seen post-marketing have been added in the 'Post-marketing data column'

MedDRA System Organ Class	**Very common (≥10%)**	**Common (≥1 %; <10 %)**	**Uncommon (≥0,1 %; <1%)**	**Rare (≥0,01 %; <0,1 %)**	**Post-marketing data**

Immune system disorders					Anaphylactic reaction
Metabolism and nutrition disorders					Hypo-natraemia*
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

Gastro-intestinal disorders			Abdominal pain*, Nausea*, Vomiting*, Diarrhoea		
Skin and subcutaneous tissue disorders					Allergic dermatitis, Rash, Sweating, Urticaria
Renal and urinary disorders			(HLT) Bladder and urethral symptoms		
General disorders and administration site conditions			Peripheral oedema, 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 (<18years)

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

Description of selected adverse reactions:

The most serious adverse reaction with MINIRIN® Melt 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 both adults and children special attention should be paid to the precautions addressed in the Warnings section.

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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse drug reactions to SAHPRA via the SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no known antidote for MINIRIN® Melt.

Treatment is symptomatic and supportive.

Overdose of MINIRIN® Melt leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia. Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given:

- discontinue the treatment of desmopressin
- fluid restriction
- symptomatic treatment if needed

Note: Laboratory tests for monitoring the patient include urine volume and osmolality. In some cases, plasma osmolality may be required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.2 Genito-urinary system - Antidiuretics

Pharmacotherapeutic group: Vasopressin and analogues.

ATC code: H01BA02

Mechanism of action

Desmopressin is 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.

5.2 Pharmacokinetic properties

The overall mean systemic bioavailability of desmopressin administered sublingually as desmopressin acetate 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/m**[l]**L after administration of 200, 400 and 800 µg desmopressin acetate, respectively. t_{max} was observed at 0,5 – 2,0 hours after dosing.

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 metabolised in the liver by the cytochrome P450 system.

The effect of desmopressin on the pharmacokinetics of other medicines is likely to be minimal due to its lack of inhibition of the cytochrome P450 metabolising system.

Elimination

The total clearance of desmopressin has been calculated to 7,6 **[**~~l~~**]**L/hr. The terminal half-life of desmopressin is estimated to 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.

Specific patient groups

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.

Paediatric population

The population pharmacokinetics of MINIRIN® Melt has been studied in children (6-12 years) with primary nocturnal enuresis and no significant difference from adults were detected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

Gelatin

Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C in its original package.

Protect from moisture and light.

6.5 Nature and contents of container

MINIRIN® Melt sublingual tablets are packed in white oriented polyamide aluminium (bottom foil) and silver aluminium (top foil) blister strips containing 10 tablets per strip.

Pack sizes: 10, 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

FERRING (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene Ext 30

Pretoria

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8. REGISTRATION NUMBER

MINIRIN® Melt 60 µg: A42/18.2/0345

MINIRIN® Melt 120 µg: A42/18.2/0346

MINIRIN® Melt 240 µg: A42/18.2/0347

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 06 March 2014

10. DATE OF REVISION OF THE TEXT

Type IA_{IN} Clinical Implemented 9 February 2026

NAMIBIA	NS2	Reg. No/Nr: 18/18.2/0085 (60 microgram) Reg. No/Nr: 16/18/0156 (120 microgram) Reg. No/Nr: 16/18/0157 (240 microgram)