1.*NAME OF MEDICINAL PRODUCT*

MINIRIN Melt 60 micrograms

MINIRIN Melt 120 micrograms

2.*QUALITATIVE AND QUANTITATIVE COMPOSITION*

Minirin Melt 60 mcg: each unit contains 60 micrograms desmopressin (free base), present as desmopressin acetate.

Minirin Melt 120 mcg: each unit contains 120 micrograms desmopressin (free base) present as desmopressin acetate.

3.*PHARMACEUTICAL FORM*

Oral lyophilizate

White, round, oral lyophilisate marked with one (60mcg) or two drop (120mcg) shaped figures on one side.

4. *CLINICAL PARTICULARS*

4.1 THERAPEUTIC INDICATIONS

Minirin Melt is indicated Nocturnal Enuresis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Nocturnal Enuresis*:*

Oral lyophilisate administration

Children over 5 years:

The recommended initial dose is 120 microg at bedtime, administered sublingually. If this dose is not sufficient effective, the dose may be increased up to 240 microg sublingually.

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.

4.3 CONTRA-INDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents. Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours)
- Patients over the age of 65
- Moderate and severe renal insufficiency (creatinine clearance below 50ml/min)
- Known hyponatremia
- Syndrome of inappropriate ADH secretion (SIADH)

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

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Special warnings:

When Minirin Melt is used for the treatment of enuresis, 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 in fluid intake can lead to water retention and/or hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain and in serious cases convulsions).
All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.
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 and/or cardiovascular disease or cystic fibrosis.
Patients being treated for primary nocturnal enuresis or nocturia should discontinue Minirin Melt 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.
Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia, therefore Minirin Melt is contraindicated in patients being treated for primary nocturnal enuresis.
Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).
Desmopressin should be used with caution in patients with conditions characterised by fluid and/or electrolyte imbalance.
Precautions must be taken in patients at risk for increased intracranial pressure.
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 Syndrome of Inappropriate Antidiuretic Hormone (SIADH), e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, case of concomitant treatment with Non steroidal Anti-Inflammatory Drugs NSAIDs.

4.5 ITERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Substances, which are suspected to induce SIADH, eg. 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 4.4).
NSAIDs may induce fluid retention and/or hyponatraemia.
Concomitant treatment with loperamide may result in a three-fold increase in desmopressin plasma concentration, 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.

A standardized 27% fat meal significantly decreased the absorption (rate and extent) of 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
Data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus as well as data on a limited number 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 concentrations corresponding to recommended dose.

Breastfeeding

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 μg intranasally), 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 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, nausea, vomiting, , weight increase, malaise, memory impairment, vertigo, falls, dizziness, confusion, 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**, 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, Flatulence, bloating and distension		
Skin and subcutaneous tissue disorders			Sweating, Pruritus, Rash, Urticaria	Dermatitis 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 disorders					Dermatitis allergic, Rash, 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 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) *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 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 Minirn Melt leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment:
Although the treatment of hyponatraemia should be individualized, the following general recommendations can be given: discontinue the desmopressin treatment, fluid restriction and symptomatic treatment is needed.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: vasopressin and analogues.
ATC code: HO1B 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The overall mean absolute bioavailability of desmopressin administered sublingually as Melts at doses of 200, 400 and 800 micrograms is 0.25% with a 95% confidence interval of 0.21% - 0.31%. The Cmax was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms respectively. Tmax was observed at 0.5 – 2.0 hours after dosing. The geometric mean terminal half-life is 2.8 (CV = 24%) hours.

Correlation table between desmopressin in Tablet and Melt forms:

Tablet	Tablet	Melt	Melt
Desmopressin acetate	Desmopressin free base	Desmopressin free base	Desmopressin acetate
0.1mg	89 micrograms	60 micrograms	Approx. 67 micrograms*
0.2mg	178 micrograms	120 micrograms	Approx. 135 micrograms*
0.4mg	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 metabolised 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 pharmacokinetics 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
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-live increased with the severity of the renal impairment. Desmopressin is contraindicated in patients with moderate and severe renal impairment (creatinine clearance below 50 ml/min).

Hepatic impairment:
No studies have been performed.
Children:
The population pharmacokinetics of desmopressin tablets has been studied in children with PNE and no significant difference from adults were detected.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data revealed 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

Minirin Melt: Gelatin, Mannitol, Citric acid (anhydrous).

6.2 INCOMPATABILITIES

Not applicable

6.3 SHELF LIFE

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

6.4 STORAGE CONDITIONS

Store at room temperature not above 25°C and in dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester terephthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 30 oral lyophilisates.

7. *MANUFACTURER*

Ferring GmbH, Germany

8. *LICENSE HOLDER*

Ferring Pharmaceuticals Ltd

8, Hashita Street, Industrial Park, Caesarea 3088900, Israel

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