Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nordurine Melt 240 micrograms oral lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral lyophilisate
White, round, oral lyophilisate marked with three drop shaped figures on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. For the diagnosis and treatment of cranial diabetes insipidus including post- hypophysectomy polyuria/polydipsia and for the treatment of primary nocturnal enuresis in patients (from 5 to 65 years of age) with normal ability to concentrate urine.

2. Nordurine Melt is indicated for the symptomatic treatment of nocturia in adults up to 65 years only, associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

4.2 Posology and method of administration

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. In the event of signs of water retention/hyponatraemia treatment should be interrupted until the patient has recovered.

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.
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. The supervising specialist should decide whether or not to restart treatment in such a patient. If restarting treatment strict fluid restriction should be enforced (see 4.4).

Nordurine 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 Nordurine Melt.

Nocturia:
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 by weekly dose escalations. Fluid restriction should be observed.

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

The initiation of treatment in the elderly (patients over 65 years) is contraindicated.

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

4.3 Contraindications

Nordurine 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 50 ml/min).
- Known hyponatraemia.
- Syndrome of inappropriate ADH secretion.
- Hypersensitivity to desmopressin or to any of the excipients of Nordurine Melt.
- Patients over the age of 65 for the treatment of primary nocturnal enuresis**.**
- Patients over the age of 65 for the treatment of nocturia.

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

4.4 Special warnings and precautions for use

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 servere 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 Nordurine Melt during an episode of vomiting and/or diarrhoea until their fluid balance is once again normal.

When used for primary nocturnal enuresis or 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).

Precautions:

- 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 therefore Nordurine Melt is contraindicated in these patients.
- Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterized by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

- 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 Non-Steroidal Ant-inflammatory Drugs (NSAIDs).

4.5 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, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia (see 4.4).

NSAIDs may induce water retention/hyponatraemia (see 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 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 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:
Caution should be exercised when prescribing Nordurine Melt to pregnant women.

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus 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. There have been rare reports of malformations in children born to mothers treated for diabetes insipidus during pregnancy.

Lactation:
Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 micrograms intranasal), 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

None.

4.8 Undesirable effects

Treatment without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain and in severe cases convulsions).

Primary nocturnal enuresis and diabetes insipidus:

System Organ Class	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders					Hypersensitivity (urticaria, rash)
Metabolism and nutrition disorders					Hyponatraemia
Psychiatric disorders					Emotional disorder (nightmare, aggression and abnormal behaviour) – only in children
Nervous system disorders		Headache			Convulsions (due to hyponatraemia)
Gastrointestinal disorders		Nausea, Abdominal pain			
Investigations					Weight increased (due to hyponatraemia)

Nocturia (based on the frequency of adverse drug reactions reported in phase III studies (N=632)).

System Organ Class	Very common	Common	Uncommon	Rare	Very rare
Metabolism and nutrition disorders		Hyponatraemia			
Nervous system disorders	Headache				
Cardiac disorders		Dizziness			
Gastrointestinal disorders		Nausea, Abdominal pain, Dry mouth			
Renal and urinary disorders		Pollakiuria			
General disorders and administration site conditions		Oedema peripheral			
Investigations		Weight increased (due to hyponatraemia)			

Nocturia:

In clinical trials of Desmopressin tablets, about 35% of patients experienced adverse drug reactions during dose-titration. The most frequent adverse drug reactions during dose-titration were headache (15%), nausea (5%), abdominal pain (4%), hyponatraemia (4%), dizziness (3%) and dry mouth (3%). During long-term treatment 24% of patients experienced adverse drug reactions. The most frequent adverse drug reactions in long-term treatment were headache (6%), dizziness (3%), peripheral oedema (3%), micturition frequency (2%), nausea (2%), and weight increase (2%).

4.9 Overdose

Overdose of Nordurine 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 individualised, the following general recommendations can be given - discontinue the desmopressin treatment, fluid restriction, and symptomatic treatment if needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues.
ATC code: H01B A02.

Nordurine 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. The uterotonic and vasopressor actions are extremely low in the dosages clinical used.

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 tablets between 0.1 and 0.4 mg 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

The mean systemic bioavailability of desmopressin administered sublingually as Nordurine 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. The geometric mean terminal half-life is 2.8 (CV=24%) hours.

Correlation table between Desmopressin Tablet and Nordurine Melt:

Desmopressin Tablet	**Desmopressin tablet**	**Nordurine Melt**	**Nordurine Melt**
Desmopressin acetate	**Desmopressin free base**	**Desmopressin Free Base**	**Desmopressin acetate.**
0.1mg	**89micrograms**	**60micrograms**	**Approx 67micrograms***
0.2mg	**178micrograms**	**120micrograms**	**Approx 135micrograms***
0.4mg	**356micrograms**	**240micrograms**	**Approx 270micrograms***

(*) calculated for comparative purposes

The distribution volume of desmopressin after intravenous infusion is 33L (0.41 L/kg). Desmopressin does not cross the blood-brain barrier. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant use of food decreases the rate and extent of absorption by 40%.

In *In-vitro* studies in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolized in the liver, and thus human liver metabolism *in vitro* is not likely to occur. After IV injection 45% of the amount of Desmopressin could be recovered in the urine within 24 hours. Following sublingual administration of Nordurine Melt, maximum plasma concentrations are achieved within one and a half hour. The disappearance of desmopressin from plasma follows an exponential decrease with a half-life of about 3 hours.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)
Citric Acid, anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Store in original package in order to protect from light and moisture.

6.5 Nature and contents of container

The tablets are supplied in a blister card of 10, 30, 90 or 100 oral lyophilisates.
Not all pack sizes are marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Limited
United Drug House
Magna Drive
Magna Business Park
Citywest
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA 1009/17/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30 September 2005

Date of last renewal: 30 September 2010

10 DATE OF REVISION OF THE TEXT

January 2012