SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DDAVP® Melt 60 micrograms oral lyophilisate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit contains 60 micrograms desmopressin (as acetate).

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Oral lyophilisate

White, round, oral lyophilisate marked with a drop shaped figure on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DDAVP Melt is indicated for the treatment of vasopressin-sensitive cranial diabetes insipidus or in the treatment of post-hypophysectomy polyuria/polydipsia.

4.2. Posology and method of administration

DDAVP Melt is for sublingual use.

Treatment of 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.

Post-hypophysectomy polyuria/polydipsia:
The dose of DDAVP Melt should be controlled by measurement of urine osmolality.

4.3. Contraindications

DDAVP Melt is contraindicated in cases of cardiac insufficiency and other conditions requiring treatment with diuretic agents.

Before prescribing DDAVP Melt, the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.

4.4. Special warnings and precautions for use

Care should be taken with patients who have reduced renal function and/or cardiovascular disease. In chronic renal disease the antidiuretic effect of DDAVP Melt would be less than normal.

Precautions to prevent fluid overload must be taken in:
- conditions characterised by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure.

4.5. Interactions with other medicinal products and other forms of interaction

Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatraemia.

NSAIDs may induce water retention and/or hyponatraemia.

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 and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased the absorption (rate and extent) of a 0.4mg dose of oral desmopressin tablets. Although it did not significantly affect the pharmacodynamic effect (urine production and osmolality), there is the potential for this to occur at lower doses. If a diminution of effect is noted, then the effect of food should be considered before increasing the dose.

4.6. Pregnancy and lactation

Pregnancy:
Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

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

None

4.8 Undesirable effects

Side-effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disorders including aggression in children have been reported. Treatment with desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

4.9. Overdose

An overdose of DDAVP Melt leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:
Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing 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

In its main biological effects, DDAVP does not differ qualitatively from vasopressin. However, DDAVP is characterised by a high antidiuretic activity whereas the uterotonic and vasopressor actions are extremely low.

5.2. Pharmacokinetic properties

The overall mean systemic 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 C_{max} was 14, 30 and 65pg/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 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

The distribution volume of desmopressin after intravenous administration is 33 L (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 vitro, in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolised in the liver and thus human liver metabolism *in vivo* is not likely to occur.

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.

5.3. Preclinical safety data

There are no pre-clinical 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
Citric acid, anhydrous

6.2. Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

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

6.5. Nature and contents of container

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester teraphthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 10, 30 and 100 oral lyophilisates.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

None.

7 MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Ltd
Drayton Hall
Church Road
West Drayton
UB7 7PS
UK

8. MARKETING AUTHORISATION NUMBER

PL 03194/0091

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 January 2006

10 DATE OF REVISION OF THE TEXT

07/09/2017