PRODUCT MONOGRAPH

PrDDAVP® MELT

Desmopressin acetate

60 µg, 120 µg and 240 µg

Oral Disintegrating Tablets

Antidiuretic

Ferring Inc.
200 Yorkland Boulevard
Suite 500
North York, Ontario
M2J 5C1

Date of Revision:
May 2, 2017

Submission Control No: 187742

Table of Contents

DDAVP® MELT

Desmopressin Acetate Oral Disintegrating Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Sublingual	Oral Disintegrating Tablets 60 µg, 120 µg, 240 µg	Gelatin, Mannitol, Citric Acid *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DDAVP MELT is indicated for

- treatment of Central Diabetes Insipidus
- treatment of Primary Nocturnal Enuresis

Central Diabetes Insipidus

DDAVP MELT (60 µg, 120 µg and 240 µg desmopressin) is indicated for the management of vasopressin sensitive central diabetes insipidus, and for the control of temporary polyuria and polydipsia following head trauma, hypophysectomy or surgery in the pituitary region.

Primary Nocturnal Enuresis

DDAVP MELT (60 µg, 120 µg and 240 µg desmopressin) is indicated in the management of nocturnal enuresis in patients 5 years of age and older who have normal ability to concentrate urine. DDAVP MELT should be used in conjunction with non-medicinal therapy, such as motivational counselling and bladder exercises.

CONTRAINDICATIONS

- Hypersensitivity to desmopressin or any of the tablet constituents.

- Patients with type IIB or platelet-type (pseudo) Willerbrand disease, because of the risk of platelet aggregation and thrombocytopenia

- Any condition associated with impaired water excretion, such as:
  - Hyponatremia
  - Severe liver disease
  - Nephrosis
  - Cardiac insufficiency
  - Chronic renal insufficiency
  - Congestive heart failure
  - Habitual or psychogenic polydypsia

- Any medical conditions which lead to sodium losing states such as:
  - Vomiting
  - Diarrhoea
  - Bulimia
  - Anorexia nervosa
  - Adrenocortical insufficiency
  - Salt losing nephropathies

WARNINGS AND PRECAUTIONS

General

In general, by adequate treatment with DDAVP MELT, thirst is automatically reduced. However, there is potential risk of water intoxication if, during treatment, excessive liquid is consumed. Fluid intake should be adjusted to reduce the possibility of water intoxication and hyponatremia especially in the very young and elderly patients (See DOSAGE AND ADMINISTRATION). Particular attention should be paid to the risk of extreme decrease in plasma osmolality and resulting seizures in young children.

Treatment with desmopressin should be interrupted during acute inter-current illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and gastroenteritis).

In patients with Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) or with high intra-cranial pressure, it is necessary that extra care be exercised with liquid intake.

Desmopressin should not be administered to dehydrated patients until water balance has been adequately restored.

Desmopressin is not effective in controlling polyuria caused by renal disease, nephrogenic diabetes insipidus, psychogenic diabetes insipidus, hypokalemia or hypercalcemia.

Cardiovascular

Desmopressin acetate can occasionally produce a slight elevation of blood pressure, which disappears with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible tachycardia and changes in blood pressure.

Genitourinary

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

Respiratory

Desmopressin should be used with caution in patients with cystic fibrosis because these patients are prone to hyponatremia.

Special Populations

Pregnant Women:
No controlled studies in pregnant women have been carried out. The physician should weigh possible therapeutic advantages against potential risks in each case.

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 fetus or newborn child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Nursing Women:
There have been no controlled studies in nursing mothers. Results from analysis of milk from nursing mothers receiving high doses of desmopressin (300 μg intranasal), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

Paediatrics:
Use of desmopressin in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water retention due to over ingestion of fluids.

Geriatric:
Geriatric patients should be closely observed for possible hyponatremia and water retention due to over ingestion of fluids.

Monitoring and Laboratory Tests

Central Diabetes Insipidus

Continued response to desmopressin acetate is monitored by urine volume and osmolality.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Five pharmacokinetic and pharmacodynamic (PK/PD) studies were conducted. Four studies enrolled healthy volunteers and one study was conducted in children with primary nocturnal enuresis (PNE). Comparison of the methodologies of the five studies is presented in Table 1.

Table 1: Study Design of the Pharmacokinetic and Pharmacodynamic Studies

Study No.	Type of Study	Formulation & Dosage	Number, Age & Sex of Patients
Study 1	Single-center, open-label, randomized, balanced, 4-way cross-over study	DDAVP MELT 200, 400, 800 µg sublingually Desmopressin 2 µg IV	24 healthy male volunteers (18-55 years)
Study 2	Open-label, randomized, 2-period cross-over study	DDAVP MELT 240 µg sublingually DDAVP Tablets 2x 200 µg orally	14 male and 14 female healthy volunteers (18–55 years)
Study 3	Single-center, open- label, randomized, balanced, 6-sequence, 3-period cross-over study	DDAVP MELT 60, 120, 240 µg sublingually	15 male and 10 female healthy volunteers (18–55 years)
Study 4	Single-center, open-label, replicated, randomized, 2-sequence, 4-period, , cross-over study	DDAVP MELT 240 µg sublingually DDAVP tablets 2x 200 µg orally	32 male and 33 female healthy volunteers (18- 55 years)
Study 5	Double-blind, randomized, placebo-controlled, parallel group study	DDAVP MELT 30, 60, 120, 240, 360, 480 µg sublingually Placebo sublingually	64 males and 20 females with PNE (6-12 years) 72 DDAVP MELT 12 Placebo

A total of 214 subjects were treated with DDAVP MELT in the PK/PD studies. Of these, 172 were also administered DDAVP tablets: 28 in Study 2, 65 in Study 4 and 79 patients in the open-label part of Study 5. Twenty-four (24) subjects were also administered desmopressin intravenously. One hundred and forty two subjects were healthy volunteers and 72 were PNE children.

Sixty-one subjects (29%) of the 214 subjects exposed to desmopressin from DDAVP MELT reported 96 adverse events, all of which were mild to moderate in intensity.

Sixty-five subjects (38%) of the 172 subjects exposed to desmopressin from DDAVP Tablets reported 82 adverse events, all of which were mild to moderate in intensity.

The most frequently reported adverse events (>3%) in subjects in the PK/PD studies are presented by body system in Table 2 for the Safety Population (received at least one dose of study medication) of each study.

Table 2: Number of Subjects Reporting AEs in the PK/PD Studies
(Frequency >3%).

Adverse Event	**DDAVP MELT**		**DDAVP Tablets**	
	No.	%	No.	%
No. subjects exposed	214	–	172	–
No. subjects with adverse events	61	29	65	38
No. adverse events	96	–	82	–
Nervous System				
Headache	26	12.1	27	15.7
Gastrointestinal				
Nausea	7	3.3	5	2.9

The most commonly reported adverse events in the PK/PD studies were headache and nausea. Overall, numbers of adverse events reported were low, and were generally reported with similar frequency between the DDAVP MELT and DDAVP Tablets, desmopressin i.v. and/or placebo.

Headache, nausea and vomiting are known adverse drug reactions to desmopressin, and may be signs and symptoms of water retention and hyponatremia which are recognized sequelae of unrestricted fluid intake during desmopressin administration.

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

Serum SGOT levels were elevated in 4/16 patients, 6 months after commencing oral desmopressin acetate therapy (200 to 600 µg/day). Two of these patients had exhibited baseline levels of SGOT that were above the normal range and all four patients had normal SGOT levels on repeat test at 9 months, even though desmopressin acetate administration continued. The possibility that desmopressin acetate has an adverse effect on serum enzymes is therefore remote.

Primary nocturnal enuresis & diabetes insipidus

Common (>1/100)	General: headache Gastrointestinal: Abdominal pain, nausea
Very rare (< 1/10,000)	Hyponatremia

Post Marketing Experience (DDAVP® Tablet):

Very rare cases of emotional disturbances in children have been reported.

Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

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.

Potential Drug-Drug Interactions

Proper name	Clinical comment
Clofibrate Chlorpropamide Carbamazapine	May potentiate the antidiuretic activity of desmopressin
Demeclocycline Lithium Norepinephrine	May decrease the antidiuretic activity of desopressin
Other Pressor agents	Although the pressor activity of desmopressin acetate is very low compared with the antidiuretic activity, use of large doses of desmopressin with other pressor agents should be done only with careful patient monitoring.
Drugs known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine	May cause an additive antidiuretic effect leading to an increased risk of water intoxication.
Non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors	May induce water retention and hyponatremia.

Proper name	Clinical comment
Opiates, such as loperamide	May result in a 3-fold increase of plasma desmopressin concentrations, which may lead to water retention and hyponatremia. Although not investigated, other drugs slowing intestinal transport might have the same effect

Drug-Food Interactions

It has been previously shown that intake of a standardized meal with DDAVP MELT has no effect on pharmacodynamic parameters (urine production and osmolality) despite some pharmacokinetic influence.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Central Diabetes Insipidus

To institute desmopressin therapy, patients should be withdrawn from previous medication and allowed to establish a baseline polyuria and polydipsia. The stable polyuria is used as a baseline to determine the magnitude and duration of the response to medication.

Primary Nocturnal Enuresis

A restricted fluid intake is recommended a few hours before administration, especially one hour before bedtime. In the event that the child wakes up during the night, liquid intake should be restricted.

Recommended Dose and Dosage Adjustment

Central Diabetes Insipidus

The recommended initial dose in adults and children is 60 µg three times daily administered sublingually. This dosage regimen should then be adjusted in accordance with the patient's response. The recommended daily dose range is 120- 720 µg divided equally into 2 or 3 doses a day.

The lowest effective dose should be used and the effective dosage, as determined by urine volume and osmolality and in some cases, plasma osmolality, should be assessed periodically.

In children, the evening dose is usually 2x higher than the morning and midday dose to ensure sufficient antidiuresis during sleep. This is generally not a requirement for adult patients, presumably because adults sleep for shorter periods of time.

Primary Nocturnal Enuresis

The dosage of DDAVP MELT must be determined for each individual patient and adjusted according to response as follows:

- The recommended initial dose is 120 μg 1 hour before bedtime.
- If the patient experiences a wet night after three days on an initial dose of 120 μg increase the dose by 120 μg.
- The dose may be titrated up to 360 μg to achieve the desired response.

The physician should be consulted if enuresis persists at the maximal dose of 360 μg.
DDAVP MELT is intended for treatment periods of up to three months. The need for continued treatment should be reassessed by means of period of at least one week without DDAVP MELT. If the patient is still wetting the bed, then reintroduce DDAVP MELT at the same dosage prior to discontinuing treatment for another three months and reassess.

Missed Dose

Central Diabetes Insipidus

If the patient misses a dose, the patient should be advised to take the missed dose as soon as possible. However if it is almost time for the next dose, the patient should be advised to skip the missed dose, to return to the regular dosing schedule and to **not** double dose.

Primary Nocturnal Enuresis

If the patient misses a dose, the patient should be advised not to take the missed dose.

OVERDOSAGE

Overdosage will increase the risk of fluid retention and symptoms which include headaches, abdominal cramps, nausea, and facial flushing. Dosage and frequency of administration should be reduced, or the drug withdrawn, according to severity of the condition.

If hyponatremia occurs following medication or excessive fluid intake, treatment should be discontinued and fluid intake restricted until serum sodium is normalized. In most cases this is sufficient. In cases with severe symptoms, (e.g., those associated with the central nervous system (CNS) such as unconsciousness), admission to hospital and a slow normalization of serum sodium is required to avoid additional complications.

For management of a suspected drug overdose, contact your regional Poison Control Centre

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Desmopressin is a synthetic structural analogue of the antidiuretic hormone, arginine vasopressin, which alters the permeability of the renal tubule to increase resorption of water. The increase in the permeability of both the distal tubules and collecting ducts appears to be mediated by a stimulation of the adenylcyclase activity in the renal tubules.

The synthetic analogue exhibits a greater antidiuretic potency, as well as a longer half-life and duration of action, as compared to vasopressin.

Pharmacodynamics

Clinical studies have demonstrated that perioral administration of desmopressin is active in eliciting an antidiuretic effect in humans, be they normal subjects, or adults and children suffering from central diabetes insipidus (CDI) of various etiologies, or from nocturnal enuresis.

The only recognized pharmacodynamic actions detected after orally administered desmopressin are reduction in urine flow and increase in urine osmolality. A number of studies have examined dose, and concentration-effect relationships of desmopressin with respect to its antidiuretic effects. Some studies show clear dose- and concentration-effect relationships, while others do not.

Pharmacokinetics

Human pharmacokinetic studies have been conducted on desmopressin using the oral and intravenous formulations.

Absorption:

Due to the rapid disintegration of DDAVP MELT, desmopressin is immediately available for absorption via the membranes of the mouth, followed by the pharynx, the oesophagus and the stomach.

Pharmacokinetic Parameter (1x240 µg DDAVP MELT)

1 x 240 µg DDAVP MELT	
Parameter	**Test*** **DDAVP MELT**
AUC_T (pg.h/mL)	73.2 85.7 (61.9 %)
AUC_I (pg.h/mL)	79.0 91.5 (59.0%)
C_{max} (pg/mL)	18.0 21.1 (59.5%)
§T_{max} (h)	1.5 (0.5-4.0)
§$T_{1/2}$ (h)	3.19 (1.51-5.25)

* DDAVP MELT Tablets (Ferring Inc, Canada)

§ Expressed as the median and (range)

It is known that the efficacy of desmopressin is not influenced by C_{max}, but by total exposure over time, i.e. AUC.

Distribution:

The distribution of desmopressin has not been fully characterized. It is not known if desmopressin crosses the placenta, but small quantities have been shown to be distributed into milk.

Metabolism:

The metabolic fate of desmopressin is unknown. Unlike vasopressin, desmopressin apparently is more resistant to metabolism by aminopeptidases or other peptidases.

In vitro human liver microsome metabolism of desmopressin has shown that no significant amount is metabolised in the liver, and thus human liver metabolism *in vivo* is not likely to occur. Furthermore, no *in vitro* inhibition on any of the nine human Cytochrome P450 enzyme subtypes could be demonstrated.

Excretion:

Urinary clearance in 6 hydrated volunteers administered DDAVP oral tablets was calculated to be 0.514 mL/min/kg body weight and the amount of peptide excreted in the urine during the 6-

hour observation period constituted 16.4% of the amount absorbed from the intestine over the same period of time.

Special Populations

Pediatrics:

The pharmacokinetic parameters (AUC and C_{max}) obtained in children were comparable to those obtained in adults. However, for children with PNE, little is known about the actual plasma levels of desmopressin required to obtain a maximal antidiuretic effect for a relevant time period.

STORAGE AND STABILITY

DDAVP MELT should be stored in the original package in a dry place at a temperature between 15º C to 25º C.

DDAVP MELT is stable for 48 months.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms:

DDAVP MELT

- 60 μg is a white, round tablet marked with a drop shape figure on one side.
- 120 μg is a white, round tablet marked with two drop shape figures on one side.
- 240 μg is a white, round tablet marked with three drop shape figures on one side.

Composition:
Medicinal ingredients: 60 μg, 120 μg or 240 μg desmopressin

Non medicinal ingredients: gelatin, mannitol and citric acid

Packaging:

DDAVP MELT is packaged in a blister pack. Each blister pack contains 10 tablets in boxes of 10 and 30.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proprietary Name: Desmopressin Acetate

Chemical names: 1-Desamino-8-D-arginine vasopressin acetate trihydrate

1-(3-mercaptopropanoic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate

Molecular formula and molecular mass:

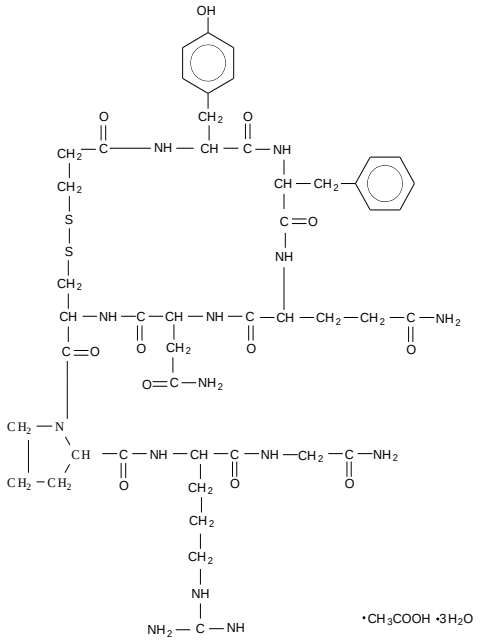
$C_{48}H_{74}N_{14}0_{17}S_2$ (acetate trihydrate)

MW = 1183.2

$C_{46}H_{64}N_{14}O_{12}S_2$ (free base)

MW = 1069.2

Structural formula:



Physicochemical Properties:

Desmopressin acetate is a white lyophilized powder which is soluble in water, methanol, ethanol, and acetic acid, and sparingly soluble in chloroform and ethyl acetate. An aqueous solution of 1 mg/mL at 24°C has a pH of 4.8.

CLINICAL TRIALS

Study demographics and trial design

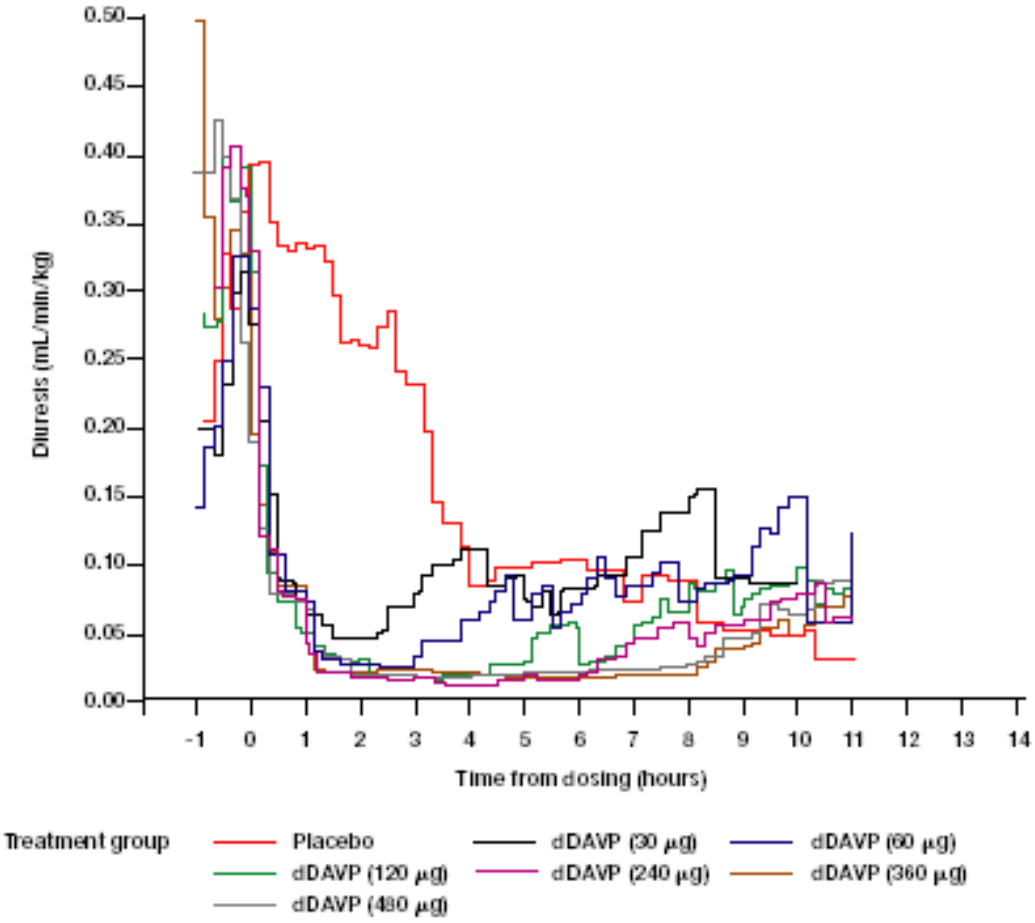
Summary of patient demographics for clinical trials in the treatment of Primary Nocturnal Enuresis (PNE).

Study	Trial Design	Dosage, route of administration and duration	Number of study subjects	Mean age (range)	Gender
Study 5	Double-Blind, Randomized, Placebo-controlled, Parallel Group Study	DDAVP MELT 30, 60, 120, 240, 360, 480 ug sublingually and placebo sublingually	84 children	8.0 -9.4 (6-12 yrs)	64 Male 20 Female

A double-blind, randomized, placebo-controlled, parallel group study in children with PNE was conducted. The primary objective of this study was to determine the pharmacodynamic properties of desmopressin (in single doses of 30, 60, 120, 240, 360 or 480 µg) as DDAVP MELT in children with known PNE. The aim of this study was to identify doses that could provide duration of action corresponding to a typical length of night-time sleep in children with PNE.

The result of the study showed that urinary output fell markedly within the first hour after dosing for all patients in all desmopressin treatment groups; no such change was observed in the placebo group. Little difference was apparent between the creatinine-adjusted diuresis data (Figure 1) and the non-adjusted data. In the higher dose groups (240, 360 and 480 µg desmopressin) the same minimum level of urinary output was reached, suggesting that the maximum antidiuretic effect had been achieved.

Figure 1: Mean diuresis adjusted for creatinine over time following dosing.



The change in mean osmolality over time showed onset of action within one hour following desmopressin dosing but no real change was apparent following placebo dosing (Figure 1). The urinary concentrating capacity of all six doses of desmopressin is indicated by the mean maximum osmolality achieved, which ranged from 515 to 957 mOsm/kg for the six different dose groups (see Table 1), and generally occurred between 1 and 4 hours after dosing.

Figure 2: Mean osmolality over time following dosing.

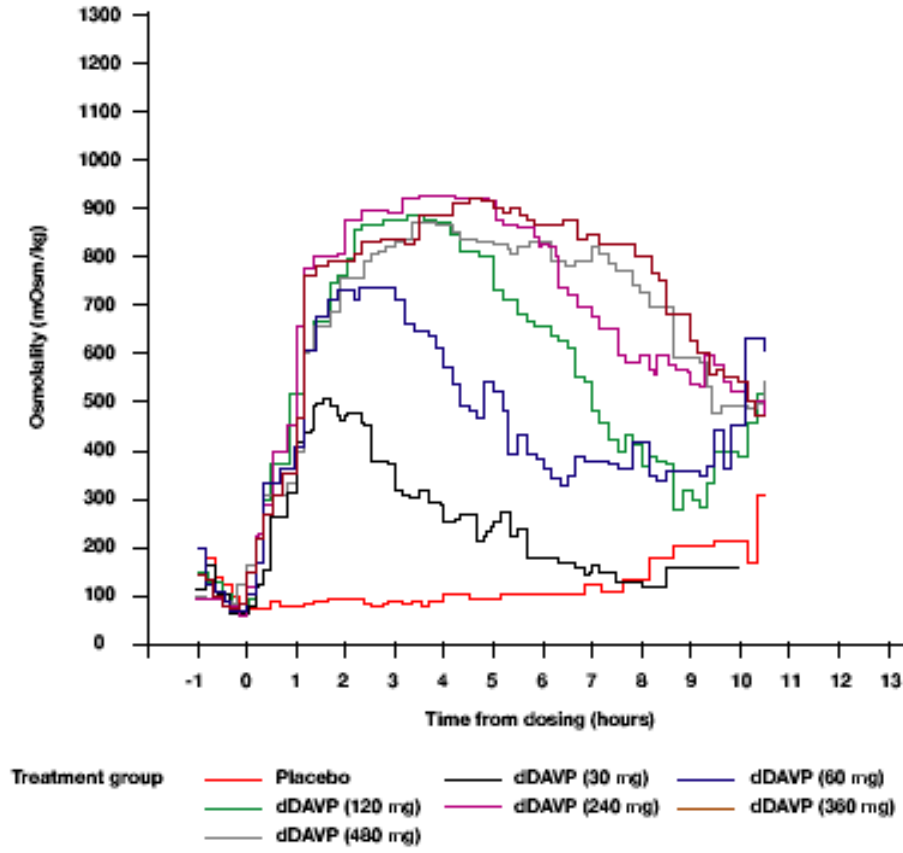


Table 1: Average osmolality during action, and maximum osmolality achieved; mean (SD)

Parameter	**DDAVP MELT (dose)**						**Placebo**
	30 µg	**60 µg**	**120 µg**	**240 µg**	**360 µg**	**480 µg**	
Number	12	12	11	12	13	12	12
Average mOsm/kg during action (SD)	277 (129)	464 (153)	576 (104)	671 (97)	680 (109)	647 (108)	50 (56)
Maximum mOsm/kg (SD)	515 (239)	804 (188)	899 (83)	957 (105)	945 (119)	943 (125)	164 (150)

Threshold levels of 125, 200 and 400 mOsm/kg were used to determine duration of urinary concentrating action. In the placebo group, osmolality measurements never exceeded the highest

threshold for any patient; the intermediate 200 mOsm/kg threshold was exceeded by one patient only and the lowest (125 mOsm/kg) by five patients. At the lowest threshold, mean duration of action increased as the desmopressin dose increased, ranging from 3.6 hours following 30 µg desmopressin to 10.6 hours following the 480 µg dose (Table 2). A similar pattern was apparent for the two higher threshold levels.

Table 2: Duration of action of desmopressin using three osmolality thresholds (125, 200 and 400 mOsm/kg)

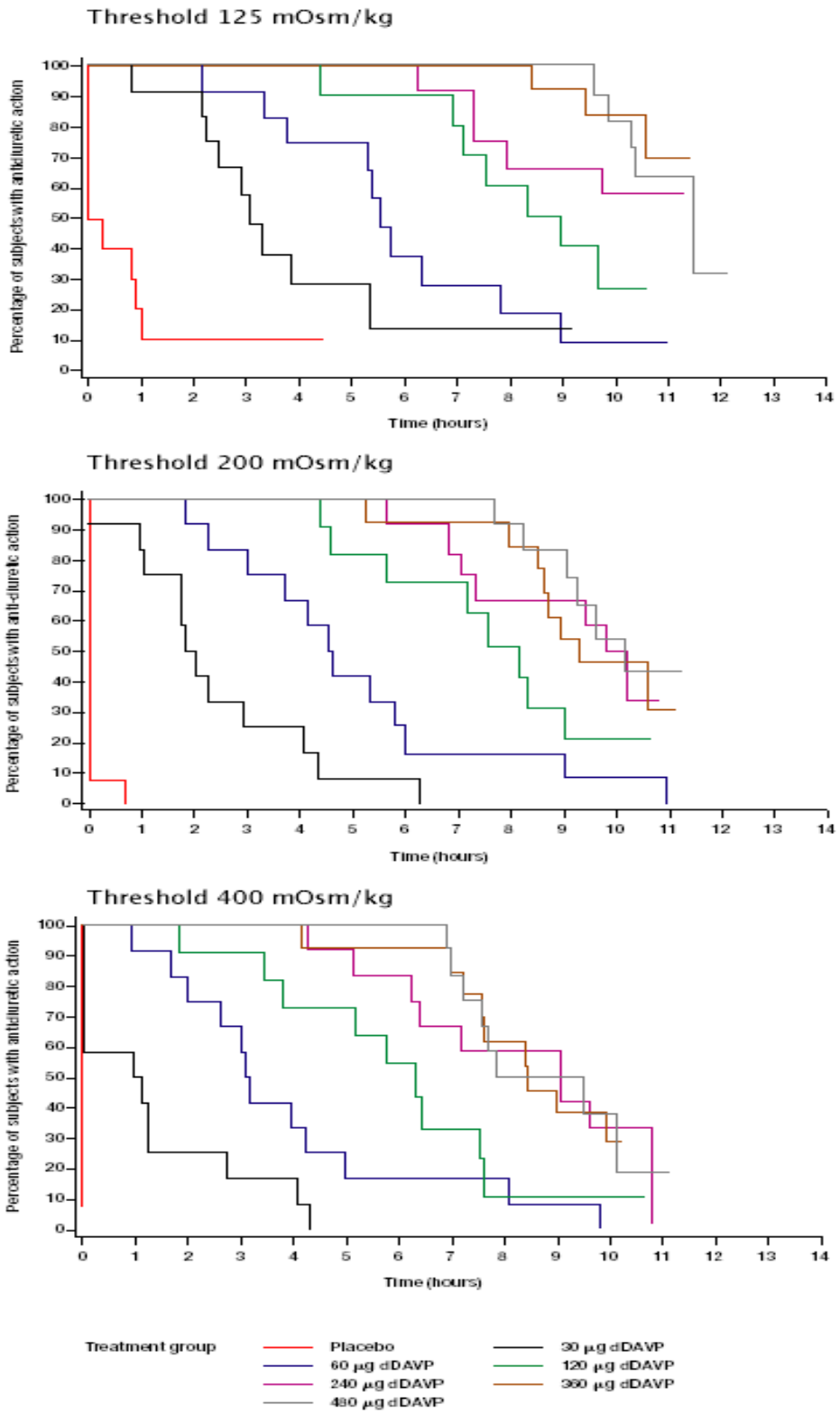
	DDAVP MELT (dose)						Placebo
	(30 µg)	(60 µg)	(120 µg)	(240 µg)	(360 µg)	(480 µg)	
Number	**12**	**12**	**11**	**12**	**13**	**12**	**12**
125 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	3 3.6 (2.1) 3.0 0.8–9.2	2 5.8 (2.4) 5.4 2.2–10.9	4 8.1 (1.9) 8.3 4.4–10.6	7 9.7 (1.9) 10.8 6.2–11.6	10 10.2 (1.0) 10.6 8.4–11.4	7 10.6 (0.9) 10.5 8.9–12.3	2 0.6 (1.3) 0.0 0.0–4.4
200 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	0 2.4 (1.7) 1.9 0.0–6.3	0 5.1 (2.6) 4.6 1.8–10.9	3 7.5 (2.1) 7.6 4.4–10.6	5 9.0 (1.8) 9.8 5.6–10.8	5 9.2 (1.6) 9.3 5.3–11.1	6 9.7 (1.2) 9.6 7.7–11.3	0 0.1 (0.2) 0.0 0.0–0.7
400 mOsm/kg (hours)							
Censored* Mean (SD) Median Min – Max	0 1.3 (1.6) 1.1 0.0–4.4	0 4.0 (2.6) 3.1 1.0–9.8	2 5.9 (2.3) 6.3 1.9–10.5	3 8.2 (2.3) 9.1 4.3–10.8	4 8.4 (1.8) 8.4 4.2–10.3	4 8.6 (1.4) 8.4 6.9–11.3	1 0.0 (0.0) 0.0 0.0–0.0

* Number of patients with no 'end' of action; measurements were censored at the time the over hydration procedure was stopped.

The relationship between dose and duration of action is shown by the Kaplan-Meier plots in Figure 3. For all threshold levels of osmolality, particularly in the higher dose groups, the calculated duration of action is likely to be an underestimate. This is because for some children urine collections were stopped (censored) before urine osmolality had fallen below the threshold level. This may partially account for the apparent similarity between the higher dosage groups (240, 360 and 480 µg desmopressin).

Maximum urinary concentrating ability was thus observed at the doses of 120 µg and above, but this effect occurred over different time courses (Figure 2). Increasing the dose above 360 µg served to increase the duration of action which, for PNE children, would extend the period of antidiuresis into the daytime following the previous night's dose. A dose range between 120 µg and 360 µg is therefore shown to be clinically relevant.

Figure 3: Relationship between duration of action and dose of desmopressin using osmolality thresholds of 125, 200 and 400 mOsm/kg, respectively



There was a marked fall in urinary output within 1 hour of dosing of DDAVP MELT and an increase in mean urinary osmolality in all hydrated children with PNE. The length of time for which this antidiuretic effect was observed increased as the dose increased. A clear dose-response relationship for the duration of urinary concentrating action was demonstrated at all three threshold levels of osmolality. For the lowest of the chosen thresholds (125 mOsm/kg) duration of action ranged from about 3 hours to 10.5 hours, according to dose. It is likely that the actual duration of action was somewhat longer than this for the higher doses of desmopressin (240, 360 and 480 µg) as urinary collections ceased for about half the children in these groups before the osmolality had returned to below this threshold. The data clearly indicate that if higher doses are administered in the evening there is a need to follow the diuresis rate the next morning to avoid risk of water intoxication.

The predictable fast-reaching maximum concentrating ability observed in this study suggests a constant antidiuretic response for DDAVP MELT. After 60 minutes, a mean maximum osmolality above 800 mOsm/kg was achieved following all doses of desmopressin, with the exception of the lowest dose (30 µg). Even with the 30 µg dose the maximum effect was observed after 60 minutes, but maximum concentrating capacity was not obtained. This demonstrates that the time to peak activity is very predictable, even at low doses (± 60 min).

Fifty percent of the patients receiving the 60 µg dose had a maximum osmolality above 800 mOsm/kg. This is close to the maximum urinary concentrating capacity in children, and suggests that 60 µg desmopressin as DDAVP MELT could be an adequate dose in some children. The required duration of maximum activity *versus* speed of maximum diluting capacity is an important consideration, as this balance will determine the maximal effectiveness and the risk of side effects during the day.

Approximately 50% of enuretic episodes in children occur during the early hours of the night. A pharmacological action lasting for three hours may be sufficient for some patients. If a longer duration of action is needed, doses of 120 µg desmopressin or greater would be required. Even at the highest threshold, the 120 µg dose maintained a urinary concentrating effect for approximately six hours. It therefore appears to be possible, even in a prediluted child, to control diuresis for 7–11 hours, a period similar to the sleeping time for children, with DDAVP MELT at a dose in the region of 120–360 µg. In clinical practice, children should be advised to restrict fluid intake one hour before taking DDAVP MELT.

The data suggest that a 60 µg dose could be appropriate for some children. However for bioactivity throughout the night, 120 µg is preferable. For a few children treated with 120 µg the urinary concentrating effect did not last for 11 hours, suggesting that the dose of desmopressin was suboptimal. In these patients a dose increase to 240 or 360 µg ensures antidiuresis will be obtained for the whole night.

The apparent similarity between the three highest doses of desmopressin in terms of duration of action, minimum level of urinary output and maximum osmolality following dosing suggests that the maximum dose response had been achieved. Therefore, a dose in excess of 360 µg desmopressin may not be necessary. It would also reduce the risk of adverse events, as all but one adverse event reported in this study occurred in the 480 µg dose group. In general, DDAVP

MELT was well tolerated with the type of adverse events being the same as has been reported for desmopressin tablets.

This study revealed that DDAVP MELT causes a marked fall in urinary output in hydrated patients with PNE. Using a small dosage range (120–360 µg) it is likely that diuresis can be controlled for a period corresponding to a night's sleep (7–11 hours) for many of the PNE patients.

TOXICOLOGY

(i) Acute Toxicity

The i.v. acute toxicity of desmopressin acetate is very low. Mice tolerate i.v. doses of 2 mg/kg (see table below). At doses of 30 µg/kg in rats and 50 µg/kg in rabbits, only transient changes in clinical behaviour were observed. Intravenous doses up to 24 µg/kg in dogs did not produce any cardiovascular changes.

Acute Toxicity of Desmopressin Acetate

Species	Number	LD_{50} Dose	Route
Mice	10, both sexes	2 mg/kg	i.v.
Rats	12, both sexes	30 µg/kg	i.v.
Rabbits	6, both sexes	50 µg/kg	i.v.
Dogs	5, males	24 µg/kg	i.v.

(ii) Subacute Toxicity

Results from 14-day studies show that the drug given intravenously to rats at 18 µg/kg/day and to rabbits at 6 µg/kg/day caused no biologically significant changes in hematological and clinical chemistry parameters. Post-mortem examinations did not reveal any abnormalities.

Rats which received 5 mg/kg/day subcutaneously for 3 weeks did not show any significant changes in weight, blood count, or organ changes.

(iii) Chronic Toxicity

Subcutaneous Administration

Rat Studies

In a controlled 8-week experiment, 20 rats received 2 µg/kg/day desmopressin acetate subcutaneously. No increase in blood glucose or morphological or histological pancreatic changes occurred.

Rats (20 per group) which received doses of 5, 50 and 500 ng/kg/day, for six months did not show any significant changes in weight, blood values, or levels of transaminases. The weight of heart, lungs and kidneys decreased in female animals in the lower dose groups but not in the higher ones. In the male animals a decrease in non-esterified fatty acids was noted.

Dog Studies

Dogs (3 per group) which received subcutaneous doses of 10 and 100 ng/kg/day for 6 months did not show any significant changes in comparison with control groups in blood sugar or transaminases and did not show histological or morphological organ changes.

Oral Administration

Rat Studies

Oral administration of desmopressin to rats (20 male and 20 females per group dosed at 25, 75 and 200 µg/kg/day) did not reveal any clinical findings related to desmopressin. Treated male and female rats were comparable to controls with respect to food consumption, body weight gain and water consumption. There were no drug-induced ocular abnormalities.

A dosage-related reduction was seen in levels of total circulating white blood cells, attributable to reduced neutrophil and lymphocyte counts in treated females, when compared with controls, at the week 13 and 26 investigations. Treated males were not affected.

Reduced plasma Factor VIII levels were seen in treated females at week 14 and treated males at week 25 in comparison with controls.

The terminal studies revealed no morphological or histological changes related to treatment with desmopressin.

Dog Studies

When desmopressin was given orally to dogs (4 males and 4 females per group, at 0, 25, 75 and 200 µg/kg/day) all animals survived the 26-week period and no clinical signs were observed that were related to treatment. There were no adverse effects on body weight, food and water consumption and no ocular abnormalities. Hematological investigations revealed no treatment-related findings.

During weeks 6, 13 and 26 serum total protein concentrations of treated animals were increased due to an increase in the globulin fraction. However, there were no changes from the pre-dose values in males at 200 µg/kg/day after 13 and 26 weeks treatment and males at 75 µg/kg/day after 26 weeks treatment.

No organ morphological or histological changes were seen on autopsy which could be related to treatment with desmopressin.

(iv) Reproduction Studies

Subcutaneous Administration

Rat Studies

In a teratogenicity study in Wistar rats, neither teratologic nor embryotoxic effects were observed in 369 foetuses from 40 females dosed with up to 50 ng/kg/day desmopressin acetate subcutaneously during day 1 to day 20 of gestation.

Rabbit Studies

In a study of 78 Dutch belted rabbits which received subcutaneous doses of desmopressin acetate up to 10 µg/kg/day during the sixth and eighteenth day of pregnancy, neither teratogenic nor embryotoxic effects were observed in 296 fetuses. Weaning was unaffected.

Intravenous Administration

Rat Studies

A teratology study was performed in rats. Groups of 30 pregnant Slc:Wistar rats were treated daily from day 7 to day 17 of gestation by i.v. administration of DDAVP at dosage levels of 9.47, 47.4 and 238 μg desmopressin/kg/day. A control group received the vehicle, physiological saline. Twenty females in each group were killed on day 20 of gestation to allow fetal examinations; the remaining 10 females were allowed to litter to determine any postnatal effects that might be attributable to prenatal treatment. There were no effects of treatment on the dams, and fetal survival, growth and morphology were also unaffected. Postnatal offspring survival, growth, development, behaviour and reproductive performance also showed no effects of prenatal exposure to desmopressin.

REFERENCES

1. Besser, G.M., Cunnah, D. *A Clinical Trial With Peroral Administration Of DDAVP (Desmopressin Acetate) Tablets In The Treatment Of Central Diabetes Insipidus.-A Long Term Study In Outpatients*. Data on File at Ferring Inc., 1986.

2. Burrow, G.N., Wassenaar, W., Robertson, G.L., Sehl, H. *DDAVP Treatment of Diabetes Insipidus During Pregnancy and the Post-Partum Period*. Acta Endocrinologica 1981; 97:

3. Callréus, T., Odeberg, J., Lundin, S., Höglund, P., 1999, *Indirect-Response Modelling of Desmopressin at Different Levels of Hydration.* J. Pharm. Biopharm., 27:513-529

4. Chau, R. *Acute Intravenous Toxicity of DDAVP in Rats*. Data on File at Ferring Inc., 1982.

5. Chau, R. *Acute Intravenous Toxicity of DDAVP in Rabbits*. Data on File at Ferring Inc., 1982.

6. Chau, R. *Fourteen-Day Intravenous Safety Study of DDAVP in Rats*. Data on File at Ferring Inc., 1982.

7. Chau, R. *Fourteen-Day Intravenous Safety Study of DDAVP in Rabbits*. Data on File at Ferring Inc., 1982.

8. Cort, J.H. Acute *Cardiological Toxicity of Ampouled Desmopressin Acetate*. Data on File at Ferring Inc., 1978.

9. Cunnah, D., Ross, G., Besser, G.M. *Management of Cranial Diabetes Insipidus with Oral* Desmopressin (DDAVP). Clin. Endocrinol. 1986; 24: 253-257.

10. Edwards, C.R.W., Kitau, M.J., Chard, T., Besser, G.M. *Vasopressin Analogue DDAVP in Diabetes Insipidus: Clinical and Laboratory Studies*. Br. Med. J. 1973; 3:375-378.

11. *A Pharmacokinetic Study Of Peroral Administration of DDAVP Given As Tablets in Doses from 12.5 to 400 mg*. Ferring data, 14 January 1987.

12. *A Pharmacokinetic Study of Peroral Administration of Desmopressin (DDAVP) Given As Tablets in Doses from 50 to 200 mg*. Ferring data, 14 January 1987.

13. Fjellestad, A., Czernichow, P. *Central Diabetes Insipidus in Children*. Acta Paediatr. Scand., 1986; 75:605-610.

14. Fjellestad, A., Tubiana, N., Harris, A., Czernichow, P. *Central Diabetes Insipidus in Children: Antidiuretic Effect and Pharmacokinetics of Intranasal and Peroral DDAVP*. Acta Endocrinologica (Copenh) 1987, 115:307-312.

15. Green, O.P., Heaps, C.J. *DDAVP Toxicity to Rats by Repeated Oral Administration for 26 Weeks*. Data on File at Ferring Inc., 1986.

16. Hammer, M. *A Clinical Trial Of Peroral Administration Of DDAVP Tablets In The Treatment Of Central Diabetes Insipidus. A Long Term Study (18 Months) In Outpatients*. Data on file at Ferring Inc., 1986.

17. Hammer, M., Vilhardt, H. *Peroral Treatment of Diabetes Insipidus with a Polypeptide Hormone Analog, Desmopressin*. J. Pharm. Exp. Ther., 1987; 234 (3):754.

18. Harling, R.J., Chesterman, H., Spencer-Briggs, D.J., et al. *DDAVP Oral Toxicity Study in Beagle Dogs*. Data on File at Ferring Inc., 1986.

19. Rittig, S., Jensen, A.R., Jensen, K.T., Pedersen, E.B. *Effect of Food Intake on the Pharmacokinetics and Antidiuretic Activity of Oral Desmopressin (DDAVP) in Hydrated Normal Subjects*. Clin. Endocrinol. (Oxf) 1998; 48:235-241.

20. Moses, A.M., Moses, L.K., Nostman, D.D., Springer, J. *Antidiuretic Responses to Injected Desmopressin, Alone and With Indomethacin*. J Clin Endocrinol Metab 1981; 52: 910-913.

21. Nilsson, A., Hedner, P. *A Clinical Trial with Peroral Administration of DDAVP Tablets in the Treatment of Central Diabetes Insipidus in Adults*. Data on File at Ferring Inc., 1986.

22. Pullan, P.T., Burger, H.G., Johnston, C.I. *Pharmacokinetics of DDAVP in Patients with Central Diabetes Insipidus*. Clin. Endocrinol. 1978; 9: 273-278.

23. Rado, J.P., Marosi, J., Fischer, J. *Comparison of the Antidiuretic Effect of Single Intravenous and Intranasal Doses of DDAVP in Diabetes Insipidus*. Pharmacology 1977; 15, 40-45.

24. Robinson, A.G. *DDAVP in the Treatment of Central Diabetes Insipidus*. N. Engl. J. Med. - 511.

25. Sawyer, W.H., Acosta, M., Balaspiri, L., Judd, J., Manning, M. *Structural Changes in the Arginine Vasopressin Molecule That Enhance Antidiuretic Activity and Specificity*. Endocrinology 1974; 94 (4): 1106.

26. Sawyer, W.H., Acosta, M., Manning, M. *Structural Changes in the Arginine Vasopressin Molecule That Prolong Its Antidiuretic Action*. Endocrinology 1974; (1): 140.

27. Seif, S.M., Zenser, T.V., Ciarochi, F.F., Davis, B.B., Robinson, A.G. *DDAVP Treatment of Central Diabetes Insipidus-Mechanism of Prolonged Antidiuresis.* J. Clin. Endocrinol. Metab. 1978; 46: 381-388.

28. Tucker, M.L. *DDAVP - Teratogenicity in the Rabbit*. Data on file at Ferring Inc., 1972.

29. Vavra, L., Machova, A., Cort, J.H. *Official Translation of the Pharmacological and Toxicological Report on DDAVP for the Ministry of Health*. Prague, Czechoslovakia, 1968.

30. Vilhardt, H., Bie, P. *Antidiuretic Effect of Perorally Administered DDAVP in Hydrated Humans.* Acta Endocrin. 1984; 105: 474.

31. Vilhardt, H., Lundin, S. *Biological Effect and Plasma Concentrations of DDAVP after Intranasal and Peroral Administration to Humans.* Gen. Pharmac., 1986; 17: 481-483.

32. Westgren, V., Wittstrom, C., Harris, A.S. *Oral Desmopressin in Central Diabetes Insipidus. Arch Disease in Childhood*, 1986; 61: 247.

33. Williams, T.D.M., Dunger, D.B., Lyon, C.C., Lewis, R.J., Taylor, F., Lightman, S.L. *Antidiuretic Effect and Pharmacokinetics of Oral 1-Desamino-8-D-Arginine Vasopressin. 1. Studies in Adults and Children*. J. Clin. End. Metab. 1986; 63: 129.

34. Wille, S. *A Study of Desmopressin Tablets in the Treatment of Primary Nocturnal Enuresis in Childhood - A Dose Ranging Study*. Arch. Dis. Child., 1987, 62:674-677.

35. Läckgren, G., Lilja, B., Neveus, T., Stenberg, *A. Desmopressin in the Treatment of Severe Nocturnal Enuresis in Adolescents- A 7 -Year Follow-Up Study. British Journal of Urology* (1998), 81. Suppl. 3, 17-23.

36. Fjellestad, A., Wille, S., Harris, A.S. *Comparison of Intranasal and Oral Desmopressin for Nocturnal Enuresis*. Arch. Dis. Child., 1987; 62:674-677.

37. Nørgaard, J.P., Rittig, S., Matthiesen, T. *A Dose Titration and an Open Six-Week Efficacy and Safety Study Of Desmopressin Tablets In The Management Of Nocturnal Enuresis*. J. Urol.,1994 Feb; 151(2):460-3.

38. Norgaard JP, Hansen JH, Nielsen JB et al. *Nocturnal Studies In Enuretics. A Polygraphic Study of Sleep-EEG and Bladder Activity*. Scand J Urol Nephrol Suppl 1989; 125; 73-8.

39. Skoog, S.J. *Oral Desmopressin Acetate (DDAVP) In the Treatment of Primary Nocturnal Enuresis (PNE).* Today's Therapeutic Trends Vol. 16: 275-285.

40. Turner, K.L., Stokes, A. *A Randomized, Double-Blind, Placebo-Controlled, Parallel Study Of DDAVP Tablets In Patients With Primary Nocturnal Enuresis*. Comprehensive Medical Report. 22 January 1997 RG-84063-607.

41. Skoog, S.J., Stokes, A., Turner, K.L. *Oral Desmopressin: A Randomized, Double-Blind, Placebo-Controlled Study of Effectiveness in Children with Primary Nocturnal Enuresis*. J. Urol., 1997; 158: 1035-40.

42. Wolfish, N.M., Barkin, J., Gorodzinsky, F., Schwartz, R. *The Canadian Enuresis Study and Evaluation. Short and Long Term Safety and Efficacy of an Oral Desmopressin Preparation.* Scan. J. Urol. Nephrol., 36: 00-00, 2002.

43. Wolfish, N.M., Barkin, J., Gorodzinsky, F., Schwartz, R. *The Canadian Enuresis Study and Evaluation. Short and Long Term Safety and Efficacy of an Oral Desmopressin Preparation*. Scan. J. Urol. Nephrol., 37:22-27, 2003.

44. FE992026 CS011 Statistical Report. *A Phase I Study Investigating The Anti-Diuretic Effect And Pharmacokinetics of Five Low Doses of Desmopressin And Placebo Administered as a Constant Rate Intravenous Infusion in Over-Hydrated Healthy Non-Smoking Male Volunteers*, Ferring Pharmaceuticals A/S. December 2003.

45. FE992026 CS004, Clinical Trial Report. *Absolute Bioavailability of Three Different Doses Of Desmopressin in an Orodispersible Tablet In Healthy Non-Smoking Male Volunteers*, Ferring Pharmceuticals A/S. 25 June 2002.

46. FE992026 CS020, Clinical Trial Report. *An Open-Label, Randomized, Two Period Cross-Over Study Investigating The Relative Bioavailability of Two Single Doses of The Current Marketed DDAVP Tablet (2×200 µG) And A Single Dose of Desmopressin Administered As A New Orodispersible Tablet (240 µG)*, Ferring Pharmaceuticals A/S. 16 January 2004.

47. FE992026 CS019 *An Open-Label, Replicated, Randomised, Cross-over Study with Four Periods and Two Sequences Investigating the Bioequivalence of a Single Dose of MINIRIN Tablets (2×0.2 mg) and a Single MINIRIN MELT (240 µg) Dose of Desmopressin Administered Sublingually*. Ferring Pharmaceuticals A/S. 11 February 2005.

48. FE992026 CS021 - Clinical Trial Report. *A Three-Period Cross-Over Study Comparing the Exposure of Oral Lyphilisates Containing 60, 120 and 240 µg Desmopressin in 24 Healthy Non-Smoking Subjects.* Ferring Pharmaceuticals A/S. 9 December 2004.

49. FE992026 CS006 – Clinical Trial Report. *Pharmacokinetics And Pharmacodynamics of Desmopressin Administered as a New Orodispersible Tablet in Children With Primary Nocturnal Enuresis* (PNE). Ferring Pharmaceuticals. 02 November 2004.

50. FE992026 CS014- Clinical Trial Report. *A Phase II Study Investigating the Antidiuretic Effect and Pharmacokinetics of Five Low Doses of Desmopressin Administered via Intravenous Infusion at a Constant Rate in Patients with Pituitary Diabetes Insipidus.* Ferring Pharmaceuticals. A/S. 27 August 2003.

PART III: CONSUMER INFORMATION

[Pr]DDAVP® MELT
Desmopressin oral disintegrating tablets

This leaflet is a summary and will not tell you everything about DDAVP MELT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for?
DDAVP MELT is a drug that is prescribed for children 5 years of age and older who wet their bed at night. This condition is called *Primary Nocturnal Enuresis (PNE)*.

What it does:
DDAVP MELT reduces the amount of urine (pee) that your child makes at night. The result is your child's bladder will not fill up as much and your child will be less likely to wet the bed at night.

When it should not be used:
There are people who should not take DDAVP® MELT. Tell your child's doctor or pharmacist if your child has:

- Diarrhea
- Vomiting
- Any heart, liver or kidney problems
- Hyponatremia (low blood sodium levels)
- Bleeding problems such as Type II B or platelet-type (pseudo) von Willebrand's disease
- Constant thirst
- Eating disorders such as bulimia (over-eating followed by purging) or anorexia nervosa (self-starvation)
- Adrenal problems (e.g. Addison's disease)
- An allergy to desmopressin acetate or to any of the ingredients listed under "What the nonmedicinal ingredients are"

What the medicinal ingredient is:
Desmopressin acetate.

What the nonmedicinal ingredients are:
Gelatin, mannitol, citric acid.

What dosage forms it comes in:
DDAVP MELT, 60 µg, is a white, round tablet marked with a drop shaped figure on one side.

DDAVP MELT, 120 µg, is a white, round tablet marked with two drop shaped figures on one side.
DDAVP MELT, 240 µg, is a white, round tablet marked with three drop shaped figures on one side.

DDAVP MELT is supplied in a blister pack. Each blister pack contains 10 tablets in boxes of 10 and 30.

WARNING AND PRECAUTIONS

BEFORE your child uses DDAVP MELT, talk to your child's doctor or pharmacist if your child has:

- hyponatremia (low blood sodium level)
- heart problems
- liver disease
- kidney problems
- bleeding problems
- fever
- cystic fibrosis
- any allergies to desmopressin acetate or any of the ingredients listed in "What the nonmedicinal ingredients are"

It is important to limit the number of drinks of any kind that your child has after supper, especially one hour before bedtime, until the next morning (at least 8 hours) in order to decrease the potential occurrence of water intoxication and hyponatremia.This can become a serious problem and may lead to convulsions.

DDAVP MELT should not be given to dehydrated patients until water balance is adequately restored.

INTERACTIONS WITH THIS MEDICATION

Tell your child's doctor or pharmacist if your child is taking any of the following medications:

- Nonsteroidal anti-inflammatory drugs (NSAIDs such as etodolac or Ultradol®, ibuprofen or Advil® or Motrin®, naproxen or Naprosyn® ; celecoxib or Celebrex®)
- Tricyclic antidepressants (amitriptyline, nortriptyline)
- Serotonin reuptake inhibitors (for example, fluoxetine or Prozac®, paroxetine or Paxil®, sertraline or Zoloft®, fluvoxamine or Luvox®, citalopram or Celexa®)
- Diuretics (water pills)
- Loperamide or Imodium®
- Chlorpromazine
- Carbamazepine
- Clofibrate
- Chlorpropamide

- Demeclocyclin
- Lithium
- Norepinephrine

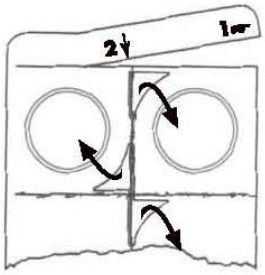
PROPER USE OF THIS MEDICATION

How to Take DDAVP MELT:

DDAVP MELT should be placed under the tongue one hour before bedtime. The tablet quickly disintegrates in the mouth without the need for water.

It is important to limit the number of drinks of any kind that your child has after supper, especially one hour before bedtime, until the next morning (at least 8 hours) after taking the medication.

1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.
2. Remove one blister from the strip by tearing along the perforations.
3. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow.
4. Carefully take a DDAVP MELT out of its blister. Place the DDAVP MELT under the tongue and allow it to dissolve.



How Many DDAVP MELT Should My Child Take:

Take the medication according to the dosing schedule as directed by your child's doctor. The usual recommended initial dose is 120 µg 1 hour before bedtime. If this does not keep your child dry, your doctor may adjust the dose up to either 240 µg or 360 µg.

What should I do if the child is still wetting the bed?

- Make sure the child is taking the correct number of DDAVP MELT tablets each night
- Limit the number of drinks the child has after supper
- If it is still not working, call your doctor

How long should the child take DDAVP MELT:

As children eventually outgrow bedwetting, they should be checked every 3 months to see if they still need the medication.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Symptoms of overdose may include headache, nausea, vomiting, abdominal cramps, facial flushing, and weight gain due to water retention and, in severe cases, convulsions.

You should restrict your child's fluid intake until your child is assessed by his/her doctor.

Missed dose:

Your child should not to take any extra DDAVP MELT. Take the same number of DDAVP MELT as before the child forgot. For example, Mary took 120 µg of DDAVP MELT on Monday but she forgot to take it on Tuesday. On Wednesday, Mary should take 120 µg of DDAVP MELT.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects may be experienced.

With DDAVP MELT, side effects may include:

- headache
- nausea
- mild abdominal cramps
- nasal congestion
- rhinitis
- flushing

These have occurred usually when the medication is being adjusted. Once your child is taking the right amount of medicine for his/her condition, these side effects will usually go away.

Tell your child's doctor about any side effects your child experiences.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	**Convulsions**			✓
	Unusually bad or prolonged headache			✓
	Confusion			✓
	Unexplained weight gain			✓
	Nausea			✓
	Vomiting			✓

This is not a complete list of side effects. For any unexpected effects while taking DDAVP® MELT, contact your doctor or pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

HOW TO STORE IT

DDAVP MELT should be stored in the original package in a dry place at a temperature between 15ºC to 25ºC.

Keep out of reach of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, Ferring Inc., at **1-866-384-1314.**

This leaflet was prepared by Ferring Inc.

Last revised: May 2, 2017.

FERRING
PHARMACEUTICALS

® DDAVP is a registered trade mark of Ferring B.V.

PART III: CONSUMER INFORMATION

PrDDAVP® MELT
Desmopressin oral disintegrating tablets

This leaflet is a summary and will not tell you everything about DDAVP MELT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DDAVP MELT is used to prevent or control the frequent urination, extreme thirst, and loss of water associated with *Diabetes Insipidus (water diabetes),* following head trauma and surgery in the pituitary gland.

What is Diabetes Insipidus (DI):
Diabetes Insipidus is a medical condition in which your kidneys are unable to retain water. This results in the production of large volumes of urine which in turn makes you feel dry and very thirsty.

It is important that you do not try to prevent this by ignoring your thirst and drinking less, or you will disturb the balance of water in your body.

What it does:
DDAVP MELT contains desmopressin, an antidiuretic hormone. DDAVP MELT reduces the amount of urine that you make. The result is that your bladder (where urine is stored) does not fill as quickly, so a person taking this medicine does not need to pass urine as often.

When it should not be used:
There are people who should not take DDAVP® MELT. Tell your doctor or pharmacist if you have:

- Diarrhea
- Vomiting
- Any heart, liver or kidney problems
- Hyponatremia (low blood sodium levels)
- Bleeding problems such as Type II B or platelet-type (pseudo) von Willebrand's disease
- Eating disorders such as bulimia (over-eating followed by purging) or anorexia nervosa (self-starvation)
- Adrenal problems (e.g. Addison's disease)
- An allergy to desmopressin acetate or any of the other ingredients in DDAVP Melt (see What the nonmedicinal ingredients are)

What the medicinal ingredient is:
This medicine contains an active drug called desmopressin acetate.

What the nonmedicinal ingredients are:
The nonmedicinal ingredients are: gelatin, mannitol, citric acid.

What dosage forms it comes in:
DDAVP MELT, 60 µg, is a white, round tablet marked with a drop shaped figure on one side.

DDAVP MELT, 120 µg, is a white, round tablet marked with two drop shaped figures on one side.

DDAVP MELT, 240 µg, is a white, round tablet marked with three drop shaped figures on one side.

DDAVP MELT is supplied in a blister pack. Each blister pack contains 10 tablets in boxes of 10 and 30.

WARNING AND PRECAUTIONS

BEFORE you use DDAVP MELT talk to your doctor or pharmacist if you are:

- Breast-feeding
- Pregnant or think you might be pregnant

And/or if you have:
- hyponatremia (low blood sodium level)
- heart problems
- liver disease
- kidney problems
- bleeding problems
- fever
- cystic fibrosis
- any allergies to desmopressin acetate or any of the ingredients listed in "What the nonmedicinal ingredients are"

Before you commence treatment with this medicine, you should receive appropriate advice concerning fluid intake from your doctor. Excessive fluid intake may lead to a build-up of water in the body resulting in water intoxication and hyponatremia.

DDAVP MELT should not be given to dehydrated patients until water balance is adequately restored.

Talk to your doctor before stopping or interrupting treatment with DDAVP MELT.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with DDAVP MELT include:

- Nonsteroidal anti-inflammatory drugs (NSAIDs such as etodolac or Ultradol®, ibuprofen or Advil® or Motrin®, naproxen or Naprosyn® ; celecoxib or Celebrex®)
- Tricyclic antidepressants (amitriptyline, nortriptyline)
- Serotonin reuptake inhibitors (for example, fluoxetine or Prozac®, paroxetine or Paxil®, sertraline or Zoloft®, fluvoxamine or Luvox®, citalopram or Celexa®)
- Diuretics (water pills)
- Loperamide or Imodium®
- Chlorpromazine
- Carbamazepine
- Clofibrate
- Chlorpropamide
- Demeclocyclin
- Lithium
- Norepinephrine

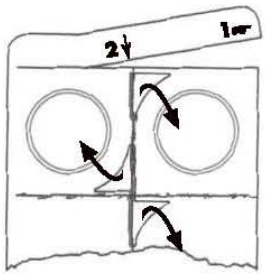
If you are taking any of these drugs, please talk to your doctor or pharmacist before taking DDAVP MELT.

PROPER USE OF THIS MEDICATION

How to Take DDAVP MELT:

DDAVP MELT should be placed under the tongue (*sublingually).* The tablet disintegrates instantaneously in the mouth without the need for water.

1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.
2. Remove one blister from the strip by tearing along the perforations.
3. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow.
4. Carefully take a DDAVP MELT out of its blister. Place the DDAVP MELT under the tongue and allow it to dissolve.



How Many DDAVP MELT Should I Take:

Usual dose:

Follow your doctor's direction on how much medicine you should take. The recommended treatment range for diabetes insipidus is 120-720 µg per day divided equally into 2 or 3 doses a day.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Symptoms of overdose may include headache, nausea, vomiting, abdominal cramps, facial flushing, weight gain due to water retention and, in severe cases, convulsions.

Missed dose:

If you miss a dose of DDAVP MELT, take the missed dose as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects may be experienced.

With DDAVP MELT, side effects may include:

- headache
- nausea
- mild abdominal cramps
- nasal congestion
- rhinitis
- flushing

These have occurred usually when the medication is being adjusted. Once you are taking the right amount of medicine for your condition, these side effects will usually go away.

Tell your doctor about any side effects you experience.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	**In all cases**	
Rare	**Convulsions**			✓
	Unusually bad or prolonged headache			✓
	Confusion			✓
	Unexplained weight gain			✓
	Nausea			✓
	Vomiting			✓

This is not a complete list of side effects. For any unexpected effects while taking DDAVP® MELT, contact your doctor or pharmacist.

HOW TO STORE IT

DDAVP MELT should be stored in the original package in a dry place at a temperature between 15ºC to 25ºC.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, Ferring Inc., at **1-866-384-1314.**
This leaflet was prepared by Ferring Inc.

FERRING
PHARMACEUTICALS

Last revised: May 2, 2017.

® DDAVP is a registered trade mark of Ferring B.V.