PRODUCT MONOGRAPH

PrDDAVP® TABLETS

Desmopressin Acetate

0.1 mg and 0.2 mg Tablets

Antidiuretic

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

Date of Revision:
December 17, 2015.

Control Number: 187744

Table of Contents

DDAVP®TABLETS

Desmopressin Acetate Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 0.1 mg , 0.2 mg	Lactose monohydrate, Potato Starch, Povidone, Magnesium Stearate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DDAVP Tablets is indicated for:

- treatment of Central Diabetes Insipidus
- treatment of Nocturnal Enuresis

Central Diabetes Insipidus

DDAVP Tablets (0.1 and 0.2 mg desmopressin acetate) are 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 Tablets (0.1 and 0.2 mg desmopressin acetate) are indicated in the management of nocturnal enuresis in patients 5 years of age and older who have normal ability to concentrate urine. DDAVP Tablets 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
  Diarrhea
  Bulimia
  Anorexia nervosa
  Adrenocortical insufficiency
  Salt losing nephropathies,

- Lactose intolerance/allergies

WARNINGS AND PRECAUTIONS

General

In general, by adequate treatment with DDAVP Tablets, 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.

The product contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

Pediatric:

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.

Infrequently, high doses of desmopressin have produced transient headache and nausea. Nasal congestion, rhinitis, flushing, and mild abdominal cramps have been reported. These symptoms disappeared with reduction in dosage.

Side effects reported from controlled clinical trials involving 638 subjects included headache (2%), and rhinitis (1%), nasal discomfort (1%), epistaxis (1%) and abdominal pain (1%). Other effects, reported at a frequency of less than 1% included dizziness, chills, wheezing, rash, edema of face and hands, nausea, constipation, anorexia, increased appetite, conjunctivitis and after taste in the mouth. These symptoms disappeared with reduction of dosage or withdrawal of drug. Adverse effects rarely necessitate discontinuance of the drug.

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.

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 Interaction

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 which are 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.
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

Intake of a standardised meal with oral desmopressin resulted in significant decreased bioavailability compared to fasting. This is hypothesised to be due to reduced absorption from the gastrointestinal tract. However no effect on dynamics (urine production or osmolality) was observed.

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

A suitable starting dose for adults and children is 0.1 mg desmopressin acetate three times daily. This dosage regimen should then be adjusted in accordance with the patient's response in order to ensure an optimum dose.

For patients who have been controlled on intranasal desmopressin and who are to be switched to the oral form, the oral dose producing comparable antidiuresis is about 10-20 times greater than the established intranasal dose.

Geriatric patients may be more sensitive to the antidiuretic effect of desmopressin acetate.

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.

The maximum recommended dosage for both adults and children is 1.2 mg per day (0.4 mg three times a day).

The lowest effective dosage should be given. Rarely, during long term use, patients may develop tolerance to the drug and require cautious increase in dosage to achieve adequate therapeutic response.

Primary Nocturnal Enuresis

The dosage of DDAVP Tablets must be determined for each individual patient and adjusted according to response.

Patients previously on intranasal DDAVP therapy can begin tablet therapy the night following (24 hours after) the last intranasal dose. The oral dose producing comparable antidiuresis is about 10-20 times greater than the established intranasal dose.

The recommended initial dose is 0.2 mg 1 hour before bedtime.

If the patient experiences a wet night after three days on an initial dose of 0.2 mg (1 x 0.2 mg tablet), increase the dose by 0.2 mg. The dose may be increased by 0.2 mg increments, in the manner described (every 3 days), to a maximal dose of 0.6 mg.

The physician should be consulted if enuresis persists at the maximal dose. 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.

The need for continued treatment should be reassessed every 3 months by means of a period of at least one week without DDAVP. If the patient is still wetting the bed, then reintroduce DDAVP 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 acetate 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 peroral administration of desmopressin acetate is active in eliciting an antidiuretic effects 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

Absorption:

Dose-response relationships and pharmacokinetic profiles of orally administered desmopressin acetate were similar in normal subjects and in adults and children with CDI. In all studies, both the magnitude of the plasma peak concentration and the AUC were dose dependent. Time to peak plasma concentration and the plasma half-life were not affected by the size of the dose.

Plasma desmopressin levels increased in a dose-dependent fashion and its disappearance from plasma followed an exponential time course, with half-life of 86 to 142 minutes.

Pharmacokinetics of Oral Desmopressin in Normal Subjects and CDI Patients. Numbers in brackets indicate the number of subject/patients from which the parameter was derived.

Dose (µg)	AUC (ng/L.hr)(N)				C_{max} (ng/L)N)				T_{max} (min)(N)				$T_{1/2}$ (hour)(N)			
Study	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
100 NS	14.4 (5)	-	-	-	3.6 (5)	3.2 (5)	-	-	96 (5)	60	-	-	1.9 (5)	1.9 (5)	-	-
200 NS	39.8 (3)	-	-	-	7.1 (4)	7.0 (4)	-	-	90 (4)	120	-	-	2.0 (3)	2.4 (4)	-	-
100 CDI	-	-	25.9 (4)	-	-	-	9.2 (4)	-	-	-	53 (4)	-	-	-	1.8 (4)	-
200 CDI	27.1 (5)	-	129 (5)	148 (7)	7.8 (6)	7 (7)	34 (4)	33 (7)	70 (6)	60	54 (5)	48 (7)	2.5 (5)	2.1 (7)	2.6 (5)	3 (7)
400 CDI	-	-	162 (4)	246 (7)	-	-	56 (4)	104 (7)	-	-	50 (4)	49 (7)	-	-	1.9 (4)	2.5 (7)

Pharmacokinetics of Typical Therapeutic Doses of Oral Desmopressin in Pediatric CDI Patients

	Unit	200 µg	400 µg
AUC (0-infinity)	ng/L/h	148 ± 152	246 ± 367
C_{max}	ng/L	33.2 ± 30.7	103.9 ± 176.4
T_{max}	min	48 ± 21	49 ± 19
$t_{1/2}$	hours	2.96 ± 2.04	2.47 ± 2.92
K_{el}	h^{-1}	0.34 ± 0.22	0.47 ± 0.27
Max osm	mOsm/kg	733 ± 156	809 ± 77
time to max osm	min	315 ± 127	345 ± 77

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 in-vitro metabolism of desmopressin has not been studied. In vitro human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolized 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 PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolizing system.

In healthy subjects the fraction excreted unchanged was 52% (44% - 60%).

Excretion:

Urinary clearance in 6 hydrated volunteers 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. Urinary clearance for desmopressin is thus smaller than that reported for vasopressin.

STORAGE AND STABILITY

DDAVP Tablets should be stored between 15◦C -25◦C in a dry place.

DDAVP Tablets are stable for 36 months.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

DDAVP Tablets are available as white uncoated tablets containing 0.1 mg or 0.2 mg of desmopressin acetate.

Composition

Medicinal ingredients: 0.1mg and 0.2mg desmopressin

Non medicinal ingredients: Lactose monohydrate, magnesium stearate, potato starch. povidone,

Packaging

Bottles of 30 or 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Desmopressin Acetate

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

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

Molecular formula and molecular mass:

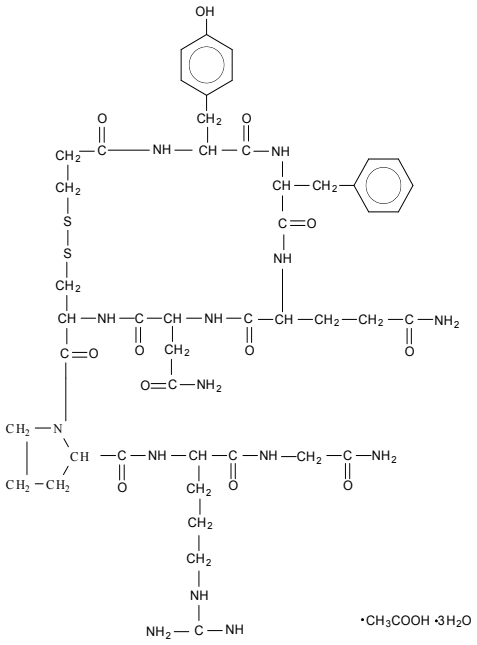
$C_{48}H_{74}N_{14}0_{17}S_2$ (acetate trihydrate)

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 soluable in chloroform and ethyl acetate. An aqueous solution of 1 mg/mL at 24°C has a pH of 4.8.

CLINICAL TRIALS

Central Diabetes Insipidus

Six patients aged 23 to 65 years took part in an open dose-ranging study of desmopressin acetate tablets followed by a four week open study on an out-patient basis. All patients completed the dose range study in hospital and were discharged on a dosage regimen ranging from 25 to 200 µg t.i.d.

A dose-dependent effect was seen at doses of 12.5, 25, 50, 100 and 200 µg desmopressin acetate both for duration and magnitude of antidiuretic activity. All doses elicited an antidiuretic response although doses of 100 to 200 µg induced a more optimum duration of antidiuretic activity. Although there were large interindividual differences, most patients were stabilized on a mean daily dose of 345 µg desmopressin acetate (range 75 to 900 µg). One patient dropped out of the study due to inadequate response to oral therapy, despite being treated with 400 µg t.i.d. This patient had been previously well controlled with a dosage of 10 µg t.i.d., intranasally. The individual response varied greatly between patients in both magnitude and duration but was found to be of the same order of magnitude as for intranasal desmopressin acetate which had previously been administered in daily doses of 15 to 75 µg in these patients.

No significant deviations from normal laboratory values for hematology, blood chemistry including liver function, serum electrolytes or urinalysis were noted, and there were no clinically important changes in body weight or blood pressure. Two patients who received cortisone had lower baseline diuresis than other patients and required a lower desmopressin acetate dose to control adequate water turnover. However, neither cortisone nor thyroxine interfered with desmopressin acetate efficacy.

Six patients aged 21 to 59 years completed 18 months of oral desmopressin acetate therapy and 4 patients had completed 6 to 12 months of therapy. These patients were well controlled with satisfactory water turnover at doses within the range of 100-200 µg t.i.d., with no development of tolerance to desmopressin acetate.

None of the minor changes noted in serum total protein, electrolytes (Na, K, C1) or glucose or in the plasma osmolality were considered to be of any clinical significance. There were no clinically significant changes in blood pressure or body weight.

Primary Nocturnal Enuresis

Two trials investigated the long-term efficacy and safety of DDAVP tablets for primary nocturnal enuresis. The first study continued for six months. One hundred and twenty-five (of the 232 enrolled) completed the trial; 92 were male, 33 were female. Patients were 6-17 years of age with a mean age of 9.34. All patients were assigned to a dose of 200 µg for two weeks. The dose was increased in increments of 200 µg every two weeks until the patient was completely dry (over a 14-day period) or had reached a maximum dose of 600 µg. The data obtained in this trial indicate that desmopressin 200 µg reduces the mean number of wet nights within two weeks and sustains this effect over a six-month treatment period. The safety profile was unremarkable. The number of patients who reported one or more adverse events was: 200 µg dose - 57 (25%); 400 µg dose - 54 (24%), and 600 µg dose - 44 (47%). Headache, pharyngitis, rhinitis and infection were the most commonly reported adverse events.

The second (Canadian) trial investigated the long-term safety of oral desmopressin treatment for up to one year, in children with nocturnal enuresis. Two hundred and fifty-six patients were treated with desmopressin; 80% of these patients were male with a mean age of 9.6 years (range 6-18 years). Of the 80 children completing the trial, 27 became dry (at most one wet night) for at least 28 days. Of the 24 adverse events evaluated as possibly/probably related to treatment, 16 were evaluated as mild, seven were moderate [nausea (1), headache (3), mood swings (2), bacterial infection (1)], and one was severe (vomiting).

In summary, a total of 117/236 children who completed the titration period (49.6%; 95% confidence interval 40–57%) responded (>50% reduction over baseline). Throughout the study their response rate remained constant at ~74%. Continuous treatment reduced the median number of wet nights during the observation period from 5.75 to 1.00 per week. A total of 12.4% of children received the 0.2 mg dose and 87.6% the 0.4 mg dose. The proportion of full responses increased over the course of the study from 5.8% to 37.5%. DDAVP was well tolerated: the majority of reported adverse events were mild, although two adverse events leading to withdrawal were reported. [40, 41]

TOXICOLOGY

(i) Acute Toxicity

The IV acute toxicity of desmopressin acetate is very low. Mice tolerate IV doses of 2 mg/kg (Table 3). 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	IV
Rats	12, both sexes	30 µg/kg	IV
Rabbits	6, both sexes	50 µg/kg	IV
Dogs	5, males	24 µg/kg	IV

(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 SC for 3 weeks did not show any significant changes in weight, blood count, or organ changes.

(iii) Chronic Toxicity

Subcutaneous Administration

Rat Studies
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 SC 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 fetuses from 40 females dosed with up to 50 ng/kg/day desmopressin acetate SC during day 1 to day 20 of gestation.
Rabbit Studies

In a study of 78 Dutch belted rabbits which received SC 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.

REFERENCES

1. Besser GM, 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 of File at Ferring Inc.,1986.

2. Burrow GN, Wassenaar W, Robertson GL, Sehl H. DDAVP treatment of Diabetes Insipidus during pregnancy and the post-partum period. Acta Endocrinologica 1981; 97: 23.

3. Chau R. Acute intravenous toxicity of DDAVP in rats. Data on File at Fering Inc., 1982

4. Chau R. Acute intravenous toxicity of DDAVP in rabbits. Data on File at Fering Inc., 1982

5. Chau R. Fourteen-day intravenous safety study of DDAVP in rats. Data on File at Fering Inc., 1982

6. Chau R. Fourteen-day intravenous safety study of DDAVP in rabbits. Data on File at Fering Inc., 1982

7. Cort JH. Acute cardiological toxicity of ampouled desmopressin acetate. Data on File at Fering Inc., 1978.

8. Cunnah D. Ross G, Besser GM. Management of cranial diabetes insipidus with oral desmopressin (DDAVP). Clin Endocrinol 1986; 24: 253-257.

9. Edwards CRW, Kitau MJ, Chard T, Besser GM. Vasopressin analogue DDAVP in diabetes insipidus: Clinical and laboratory studies. Brit Med J 1973; 2: 375-378.

10. A pharmacokinetic study of peroral administration of DDAVP given as tablets in doses from 12.5 to 400 µg. Ferring data, 14 January 1987.

11. A pharmacokinetic study of peroral administration of desmopressin (DDAVP) given as tablets in doses from 50 to 200 µg. Ferring data, 14 January 1987.

12. Fjellestad A, Czernichow P. Central diabetes insipidus in children. Acta Paediatr Scand 1986; 75: 605-610.

13. 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.

14. Green OP, Heaps CJ. DDAVP toxicity to rats by repeated oral administration for 26 weeks. Data on File at Ferring Inc., 1986.

15. 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.

16. Hammer M, Vilhardt H. Peroral treatment of diabetes insipidus with a polypeptide hormone analog, desmopressin. J. Pharm Exp Ther 1987; 234 (3):754.

17. Harling RJ, Chesterman H, Spencer-Briggs DJ, et al. DDAVP oral toxicity study in beagle dogs. Data on File at ferring Inc., 1986.

18. Rittig S, Jensen AR, Jensen KT, Pedersen EB. Effect of food intake on the pharmacokinetics and antidiuretic activity of oral desmopressin (DDAVP) in hydrated normal subjects. Clin Endocrinol (Oxf) 1998 Feb, Vol: 48 (2) 235-41.

19. Moses AM, Moses LK, Nostman DD, Springer J. Antidiuretic responses to injected desmopressin, alone and with indomethacin. J Clin Endocrinol Metab 1981; 52: 910-913.

20. 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.

21. Pullan PT, Burger HG, Johnston CI. Pharmacokinetics of DDAVP in patients with central diabetes insipidus. Clin Endocrinol 1978; 9: 273-278.

22. Rado JP, 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.

23. Robinson AG. DDAVP in the treatment of central diabetes insipidus. N Engl J Med 1976; 294, 507-511.

24. Sawyer WH, 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.

25. Sawyer WH, Acosta M, Manning M. Structural changes in the arginine vasopressin molecule that prolong its antidiuretic action. Endocrinology 1974;(1): 140.

26. Seif SM, Zenser TV, Ciarochi FF, Davis BB, Robinson AG. DDAVP treatment of central diabetes insipidus-mechanism of prolonged antidiuresis. J Clin Endocrinol Metab 1978; 46: 381-388.

27. Tucker ML. DDAVP - Teratogenicity in the rabbit.Data on file at Ferring Inc., 1972.

28. Vavra L, Machova A, Cort JH. Official translation of the pharmacological and Toxicological Report on DDAVP for the Ministry of Health. Prague, Czechoslovakia, 1968.

29. Vilhardt H, Bie P. Antidiuretic effect of perorally administered DDAVP in hydrated humans. Acta Endocrin. 1984; 105: 474.

30. Vilhardt H, Lundin S. Biological effect and plasma concentrations of DDAVP after intranasal and peroral administration to humans. Gen Pharmac 1986; 17: 481-483.

31. Westgren V, Wittstrom C, Harris AS. Oral desmopressin in central diabetes insipidus. Arch Disease in Childhood 1986; 61: 247.

32. Williams TDM, Dunger DB, Lyon CC, Lewis RJ, Taylor F, Lightman SL. 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.

33. 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.

34. 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.

35. Fjellestad A, Wille S, Harris AS. Comparison of intranasal and oral desmopressin for nocturnal enuresis. Arch.Dis.Child. 1987;62:674-677.

36. Nørgaard JP, 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

37. Skoog SJ. Oral Desmopressin Acetate (DDAVP) in the treatment of primary nocturnal enuresis (PNE) Today's Therapeutic Trends Vol 16: 275-285.

38. Turner KL, 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.

39. Skoog SJ, Stokes A, Turner KL. Oral desmopressin: a randomised, double blind, placebo controlled study of effectiveness in children with primary nocturnal enuresis. J Urol 1997; 158: 1035-40.

40. Wolfish NM, 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.

41. Wolfish NM, 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.

PART III: CONSUMER INFORMATION

Pr DDAVP® Tablets
desmopressin

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

ABOUT THIS MEDICATION

What the medication is used for:
DDAVP Tablets 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 Tablets 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 Tablets. 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"
- Lactose intolerance

What the medicinal ingredient is:
Desmopressin Acetate

What the important nonmedicinal ingredients are:
Lactose monohydrate, Magnesium Stearate
Potato Starch, Povidone,

What dosage forms it comes in:
DDAVP Tablets are available as white uncoated tablets containing 0.1 mg or 0.2 mg of desmopressin acetate. DDAVP Tablets are supplied in bottles of 30 or 100 tablets.

WARNINGS AND PRECAUTIONS

BEFORE your child uses DDAVP, 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 should not be given to dehydrated patients until water balance is adequately restored.6

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

Usual dose:

Take the medication at the dose prescribed by your physician 1 hour before bedtime. Use the following dosage plan or one that has been recommended by your physician.

Step 1 For the first 3 nights.

Take 1 tablet (1 X 0.2 mg) 1 hour before bedtime.

If the child is dry for 3 nights taking 1 tablet each night, continue this way. Do NOT increase the dose.

If the child is NOT dry for these 3 nights, move to Step 2.

Step 2 Nights 4, 5 & 6.

Take 2 tablets (2 X 0.2 mg) 1 hour before bedtime. If the child is dry for 3 nights taking 2 tablets each night, continue this way. Do NOT increase the dose.

If the child is NOT dry for these 3 nights, move to Step 3.

Step 3 Nights 7, 8 & 9.

Take 3 tablets (3 X 0.2 mg) 1 hour before bedtime. If the child is dry for 3 nights taking 3 tablets each night, continue this way. Do NOT increase the dose.

If your child is not dry every night after taking 3 tablets each night for 3 nights, see the **"What should I do if...?"** section below or visit your doctor to find out why the medicine has not worked.

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

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

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.

Missed Dose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, side effects may be experienced. With DDAVP Tablets, these may include:

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

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 Tablets, contact your doctor or pharmacist.

HOW TO STORE IT

DDAVP Tablets should be stored in the original package between 15ºC -25ºC in a dry place.

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 0701D
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.

Last revised: **December 2015.**

FERRING
PHARMACEUTICALS

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

Ferring Inc., Toronto, Ontario

PART III: CONSUMER INFORMATION

[Pr]DDAVP® Tablets
desmopressin

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

ABOUT THIS MEDICATION

What is the medication used for?
DDAVP Tablets are used to prevent or control the frequent urination, increased thirst, and loss of water associated with *Diabetes Insipidus (water diabetes).*

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.

What it does:

DDAVP Tablets reduce 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 so often.

When it should not be used:
There are people who should not take DDAVP Tablets. 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 Tablet (see What the nonmedicinal ingredients are)
- Lactose intolerance

What the medicinal ingredient is:
Desmopressin acetate

What the important nonmedicinal ingredients are:
Lactose monohydrate, magnesium stearate
potato starch, povidone,

What dosage forms it comes in:

DDAVP Tablets are available as white uncoated tablets containing 0.1 mg or 0.2 mg of desmopressin acetate. DDAVP Tablets are supplied in bottles of 30 or 100 tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use DDAVP Tablets, 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 important 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 tablets should not be given to dehydrated patients until water balance is adequately restored.

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with DDAVP Tablets 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®)
- Nonsteroidal anti-inflammatory drugs (NSAIDs such as etodolac or Ultradol®, ibuprofen or Advil® or Motrin®, naproxen or Naprosyn® ; celecoxib or Celebrex®)
- 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 Tablets.

PROPER USE OF THIS MEDICATION

How Many DDAVP Tablets 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 0.2 mg to 1.2 mg 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.

Missed Dose:
If you miss a dose of DDAVP Tablets, 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 Tablets, these may include:

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

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 Tablets, contact your doctor or pharmacist.

HOW TO STORE IT

DDAVP Tablets should be stored in the original package between 15ºC -25ºC in a dry place.

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 0701D
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.

Last revised: **December 17, 2015**

® DDAVP is a Registered Trademark of Ferring B.V.

FERRING
PHARMACEUTICALS