PRODUCT MONOGRAPH

[Pr]DESMOPRESSIN

(Desmopressin Acetate Trihydrate)

0.1 mg and 0.2 mg Tablets

Antidiuretic

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TABLE OF CONTENTS

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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 *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DESMOPRESSIN Tablets is indicated for:

- treatment of Central Diabetes Insipidus
- treatment of Nocturnal Enuresis

Central Diabetes Insipidus
DESMOPRESSIN Tablets (0.1 and 0.2 mg desmopressin acetate Trihydrate) 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.

Nocturnal Enuresis.

DESMOPRESSIN Tablets (0.1 and 0.2 mg desmopressin acetate Trihydrate) are indicated in the management of nocturnal enuresis in patients 5 years of age and older who have normal ability to

concentrate urine. DESMOPRESSIN Tablets should be used in conjunction with non-medicinal therapy, such as motivational counselling and bladder exercises.

CONTRAINDICATIONS

Hypersensitivity to desmopressin acetate or any of the tablet's constituents. Because of the risk of platelet aggregation and thrombocytopenia, the drug should not be used in patients with type IIB or platelet-type (pseudo) von Willebrand's disease.

Known hyponatremia, severe liver disease, nephrosis or any other condition associated with impaired water excretion, cardiac insufficiency, chronic renal insufficiency, congestive heart failure, habitual or psychogenic polydypsia.

Patients with existing medical conditions, which lead to sodium losing states such as nausea, bulimia, anorexia nervosa, chronic vomiting, diarrhea and adrenocortical insufficiency as well as salt losing nephropathies, should only be prescribed DESMOPRESSIN under close medical supervision and with extreme caution.

WARNINGS AND PRECAUTIONS

General

In general, by adequate treatment with desmopressin, thirst is automatically reduced. However, there is potential risk of water intoxication, if during treatment, excessive liquid is consumed. It is advisable that patients, and especially the parents of child patients, be cautioned about this.

In patients with water and/or electrolyte balance disorder [such as systemic infections, fever, and Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH)], and in patients with high intra-cranial pressure, it is also necessary that extra care be exercised with liquid intake.

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

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 an extreme decrease in plasma osmolality and resulting seizures in young children.

Intranasal formulation of desmopressin acetate at high dosage (40 µg or more) has occasionally produced a slight elevation of blood pressure, which disappeared 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.

Lack of therapeutic response to oral desmopressin may be noted in some patients even at the maximum recommended dosage. These patients should be switched to the intranasal or injectable dosage form of desmopressin.

In the control of diabetes insipidus, 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.

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

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

Children and geriatric patients should be closely observed for possible water retention due to over ingestion of fluids. When fluid intake is not excessive, there is little danger of water intoxication and hyponatremia. Fluid intake should be carefully adjusted to prevent overhydration.

There are reports of changes in response over time, usually when the drug has been administered for periods longer than 6 months. Some patients may show decreased responsiveness, others a shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to local inactivation of the peptide.

Special Populations

Pregnant Women:

Reproductive studies performed in rats and rabbits have revealed no evidence of harm to foetus by desmopressin. The use of desmopressin acetate in pregnant women with no harm to the foetus has been reported.

No controlled studies in pregnant women have been carried out. However, as with all medication used during pregnancy, the physician should weigh possible therapeutic advantages against potential risks in each case.

Nursing Women:

There have been no controlled studies in nursing mothers. A single study on a post-partum woman demonstrated a marked change in maternal plasma desmopressin acetate level following an intranasal dose of 10 μg, but little desmopressin was detectable in breast milk.

Pediatrics Use:

Desmopressin acetate has been used in children with diabetes insipidus. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease of plasma osmolality with resulting convulsions. Dosage in infants younger than 3 months has not been established. Dose should start at 100 µg or less. Use of desmopressin acetate in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication.

Monitoring and Laboratory Tests

Diagnosis of Central Diabetes Insipidus

Central diabetes insipidus may be demonstrated by the inability to produce urine of osmolality above 175 mOsm/kg with dehydration severe enough to cause a loss of greater than 2% of body weight.

Patients are selected for therapy by establishing a diagnosis by means of a water deprivation test, the hypertonic saline infusion test, and/or response to 5 units arginine vasopressin given s.c. after dehydration. Continued response to desmopressin acetate is monitored by urine volume and osmolality. In cases of severe dehydration, plasma osmolality determination may be required.

ADVERSE REACTIONS

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

Clofibrate, chlorpropamide and carbamazapine may potentiate the antidiuretic activity of desmopressin while demeclocycline, lithium and norepinephrine may decrease its activity.

Although the pressor activity of desmopressin acetate is very low compared with the anti-diuretic activity, use of large doses of desmopressin with other pressor agents should be done only with careful patient monitoring.

Concomitant treatment with drugs which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water intoxication.

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors such as Celebrex® may induce water retention and hyponatremia.

Concomitant treatment with 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.

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

Central Diabetes Insipidus

Desmopressin dosage must be determined for each patient and adjusted according to the pattern of response. Response should be estimated by adequate duration of sleep and adequate, not excessive, water turnover and maintenance of urine osmolality at levels of 400 mOsmol/kg or greater.

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. In less severe cases, prior water loading may be desirable to establish a vigorous flow of urine. When the urine osmolality reaches a plateau at the low level (in most cases, less than 100 mOsm/kg), the first oral dose (eg., 100 µg) of desmopressin is administered. A urine sample is obtained after two hours and hourly thereafter; urine volume is measured and urine osmolality determined. When the patient has reached the previous baseline urine osmolality and urine flow, the drug effect has ceased and the next desmopressin dose is administered. The cycle is then repeated until the patient has reached a stable condition.

Dosage must be individualized. A suitable starting dose for adults and children is 100 µg (0.1 mg desmopressin acetate Trihydrate) 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 the usual adult dose 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 (400 µg t.i.d.). Although there is no evidence that potentially serious adverse reactions would occur at daily doses greater than 1.2 mg, a maximum of 1.2 mg is being recommended at the present time since clinical experiences with daily dosages exceeding 1.2 mg is limited. 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 DESMOPRESSIN Tablets must be determined for each individual patient and adjusted according to response. Patients previously on intranasal desmopressin therapy can begin tablet therapy the night following (24 hours after) the last intranasal dose. The recommended initial dose is 0.2 mg 1 hour before bedtime. The dose may be titrated up to 0.6 mg to achieve the desired response using the following dosage plan. 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. As most children sleep between 8 to 12 hours, further restriction is not required. In the event that the child wakes up during the night, liquid intake should be restricted.

OVERDOSAGE

Overdose symptoms include headaches, abdominal cramps, nausea, and facial flushing. There is no known antidote. Dosage and frequency of administration should be reduced, or the drug withdrawn, according to severity of the condition.

Water retention can be controlled by decreasing the dosage of desmopressin; severe water retention caused by overdosage may be treated with a diuretic such as furosemide.

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

ACTION AND CLINICAL PHARMACOLOGY

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.

Although the bioavailability of orally ingested desmopressin is low, reported as being about 1 to 5%, it is sufficient to induce an antidiuresis (urine osmolality greater than 400 mOsm/kg) lasting 7 to 9 hours in healthy subjects and in patients with diabetes insipidus. Recent clinical studies of the pharmacokinetics and pharmacodymamics of desmopressin showed that desmopressin has a longer antidiuretic action than previously reported. Plasma desmopressin concentrations from healthy volunteers were analysed using a new and sensitive bioassay with a low limit of quantification (LLOQ) of 0.8 ng/L. Desmopressin in-vivo potency was found to be 1.64 ng/L based on urine osmolality of 200 mOsm/kg. Given the high variability in absorption, the pharmacological antidiuretic effects of desmopressin can be expected to last from 6 hours up to 14 hours.

Onset of action, as determined by decreased urine volume and increased urine osmolality, is within one hour. In both adults and children, there is a log linear relationship between desmopressin acetate doses and maximal urine osmolality and duration of antidiuresis within the dose range 12.5 to 400 µg. Measurements of plasma desmopressin concentrations after peroral desmopressin acetate administration show a linear relationship between amounts of desmopressin acetate absorbed and dose, but with great interindividual differences.

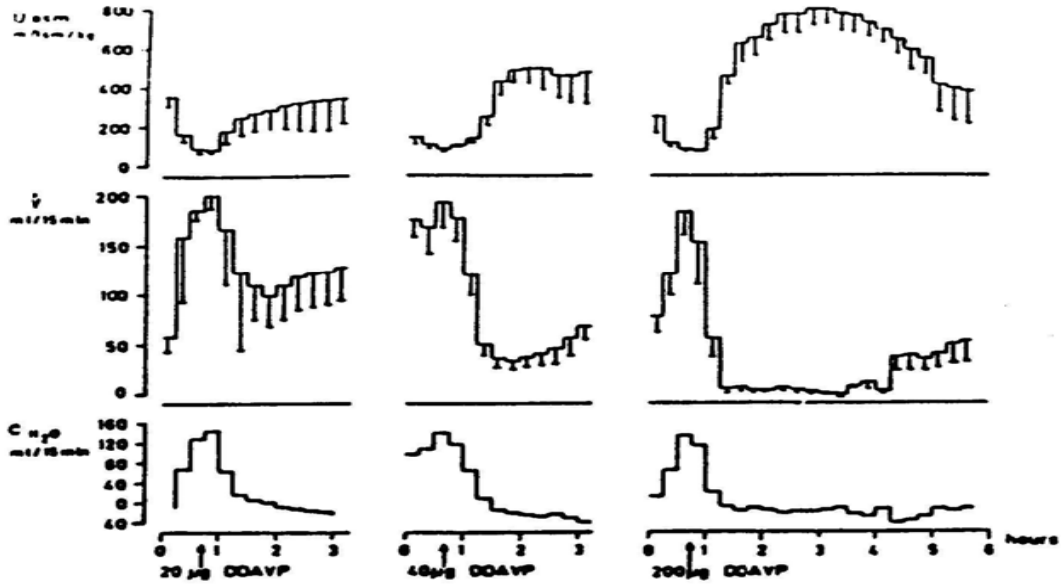
Pharmacodynamics

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

When administered as a solution (20-200 µg per 50 mL water), desmopressin acetate produced a dose dependent effect both on the magnitude and the duration of the antidiuretic response as determined by measurements of urine osmolality, urine volume and free water clearance. Administration of desmopressin acetate through a duodenal tube caused similar antidiuretic effects, indicating that the intact peptide can be absorbed from the gastrointestinal mucosa. Onset of action was approximately 1 hour.

Figure 1

Urine osmolality (top panel), urine volume (mid panel) and free water clearance (lower panel) during 15 minute periods in hydrated human volunteers following peroral administration of 20, 40 and 200 µg of desmopressin acetate. Mean ± SEM, N = 5 for each dose.



The effect of desmopressin acetate tablets was similar to that of the desmopressin solution but with an apparently slightly longer duration of action; each patient required a slightly different daily regimen for satisfactory control of water balance. The average daily PO dose, 300 µg (range of 200 - 350 µg), was 11x that of the mean previous intranasal dose (27 µg, range of 10 to 40 µg), with dosing frequency being more often t.i.d. (in 8/9 patients) rather than the more usual b.i.d. intranasal regimen.

Urine osmolality increased rapidly during the second hour and in a similar manner following either intranasal doses of 10 or 20 µg or peroral doses of 200 or 400 µg desmopressin acetate. The onset of action tends to coincide with the appearance of desmopressin in the plasma (15 min) and plasma levels, which reached maximal values 1-2 hours after 100-200 µg desmopressin acetate was administered orally, remained fairly constant over the six-hour observation period.

There are no differences in terms of magnitude and duration of the response between the two routes of administration, with free water clearance remaining negative for approximately 7 to 8 hours. When the criterion for a good antidiuretic effect was set at a urine osmolality of greater than 400 mOsmol/kg, the mean (± SD) duration of the antidiuretic effect, in hours, was 7.4 ± 3.0 and 9.0 ± 3.2 after 10 and 20 µg IN, respectively, and 7.2 ± 3.3 and 8.8 ± 2.3 after 200 and 400 µg PO, respectively. Large interindividual differences in duration of the antidiuretic effect (i.e., 5-24 hours) following intranasal application of 20 µg desmopressin acetate have also been reported in earlier studies.

The data recorded from urine volume and osmolality measurements showed no statistically significant difference between fasting and non-fasting healthy subjects in response to 100 and 200 µg desmopressin acetate tablets; no effects on blood pressure 1 or 3 hours after desmopressin acetate administration were seen.

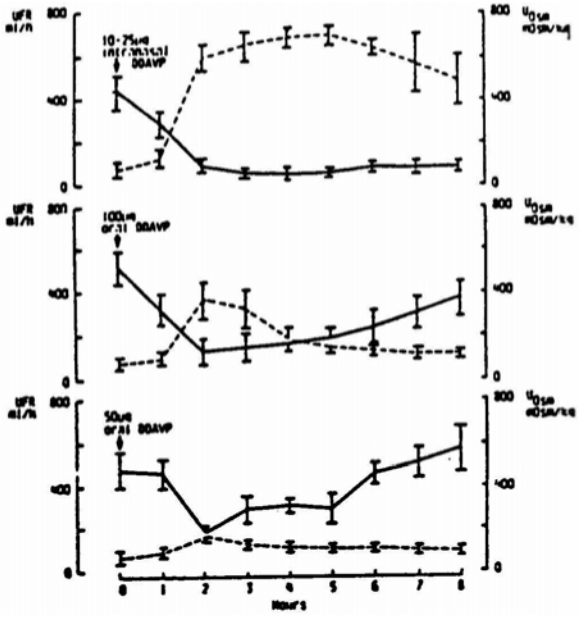
Intranasal desmopressin acetate (10-25 µg) in children had a more marked and prolonged

antidiuretic effect compared to the response obtained with 50 and 100 µg oral doses in the same children. This difference is not surprising in view of the greater peptidase activity in GI secretions.

Desmopressin acetate does not directly affect urinary sodium or potassium excretion, or serum sodium, potassium, or creatinine concentrations. It does not stimulate uterine contractions, adrenocorticotropic hormone release or increase plasma cortisol concentrations.

Figure 2

Mean (±SEM) urine flow rate (solid lines)] and urinary osmolality (dotted lines) in four water-loaded children with CDI after 50 and 100 µg oral desmopressin acetate and 10-25 µg intranasal desmopressin acetate.



Pharmacokinetics

The results of pharmacokinetic studies conducted with oral desmopressin acetate are summarized in Table 1. The most striking feature of the pharmacokinetic data was the large intra- and interindividual differences noted in all of the studies.

Dose-response relationships and pharmacokinetic profile 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.

Table 1: Summary of Pharmacokinetic Parameters in Normal Subjects (NS) and Patients with Central Diabetes Insipidus (CDI). Numbers in brackets indicate the number of subject/patients from which the parameter was derived.

Dose (µg)	AUC (ng/L.hr)(N)				Cmax (ng/L)N)				Tmax (min)(N)				$T_{1/2}$(hour)(N)			
	A	**B**	**C**	**D**	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
50.0 NS	10.2 (2)	-	-	-	1.9 (5)	1.7 (5)	-	-	96 (5)	60	-	-	3.1 (2)	1.4 (5)	-	-
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)	-	-
12.5 CDI	-	-	-	-	-	-	3.5 (3)	-	-	-	53 (3)	-	-	-	-	
25 CDI	-	-	15.1 (5)	-	-	-	5.3 (5)	-	-	-	96 (5)	-	-	-	2.3 (5)	-
50 CDI	-	-	11.4 (2)	-	-	-	7.3 (3)	-	-	-	84 (3)	-	-	-	2.3 (2)	-
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)

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. In contrast, the elimination of desmopressin after IV injection is biexponential with rapid first phase and slower second phase half-lives of 7.8 minutes and 75.5-103 minutes, respectively. Because of the great inter-individual differences, the dose-response curves of the different patients show different slopes.

Linear regression analysis suµgests that the lowest dose of peroral desmopressin acetate having a biological effect is approximately 10 µg and that a significant antidiuretic effect (i.e., urine volume less than 2 mL/min) would be obtained with a peroral desmopressin acetate dose of 40 µg; doubling this dose would increase the duration of the antidiuresis approximately 4.5 hours. These results are in accordance with those reported by Moses *et al*. following SC administration of desmopressin acetate.

A graded renal response to desmopressin acetate seems to take place between plasma concentrations of 1 to 5 ng/L with maximal effect of desmopressin acetate on the water permeability of the collecting ducts being reached at plasma concentrations of 4-5 ng/L. To obtain an effective plasma concentration, an oral dose of at least 100 µg will be needed in most cases.

Both the intranasal and oral routes of administration exhibited first order kinetics and the plasma half-life was not different after oral or intranasal dosing. The pharmacokinetic data obtained in a recent study in children are presented in Table 2.

Table 2: Pharmacokinetics of Typical Therapeutic Doses of Oral and Intranasal Desmopressin in CDI Patients

Test	Unit	10 µg IN	20 µg IN	200 µg PO	400 µg PO
AUC (0-infinity)	ng/L/h	135± 116	226± 187	148± 152	246± 367
C_{max}	ng/L	41.4± 31.6	75.6± 70.3	33.2± 30.7	103.9± 176.4
T_{max}	min	41± 23	39± 14	48± 21	49± 19
$t_{1/2}$	hours	2.52± 1.39	4.19± 2.84	2.96± 2.04	2.47± 2.92
K_{el}	h^{-1}	0.35± 0.16	0.23± 0.11	0.34± 0.22	0.47± 0.27
Max osm	mOsm/kg	756± 201	828± 198	733± 156	809 ± 77
time to max osm	min	253± 111	373± 126	315± 127	345 ± 77

The distribution of desmopressin has not been fully characterized. It is not known if desmopressin crosses the placenta. The drug may be distributed into milk. The metabolic fate of desmopressin is unknown. Unlike vasopressin, desmopressin apparently is not degraded by aminopeptidases or other peptidases that cleave oxytocin and endogenous vasopressin in the plasma during late pregnancy.

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.

Comparisons of Routes of Administration

Peroral desmopressin acetate offers an effective alternative to intranasal administration in the treatment of central diabetes insipidus and nocturnal enuresis. In one study, five out of six patients with CDI of varying etiology who were effectively treated with intranasal desmopressin acetate therapy (mean daily dose = 37 µg, range: 15-75 µg) were well-controlled with mean daily doses of 345 µg desmopressin acetate PO (range: 75-900 µg). The ratio of PO/IN dose was therefore approximately 10 in this study. As with intranasal application, patient dosage requirements varied and a dose range rather than a standard dose is usually necessary to control diabetes insipidus in a given patient population. However, a significant ($p<0.01$) correlation between the previous intranasal dose and the effective oral daily dose can generally be established both in adults (Fig. 3) and children (Fig. 4).

Other long term studies of 6 to 18 months duration have variously reported IN/PO dose ratios as being 1:14, 1:15, 1:20, and 1:40. In CDI patients, the intranasal dose was 25x greater than an equipotent intravenous dose and the peroral dose is approximately 10 to 20x the previous intranasal dose. Thus, the ratio between equipotent doses of IV, IN and PO administered desmopressin acetate seems to be, in general, 1:25:300.

Figure 3

Relationship between intranasal and oral dosing were seen with any of the desmopressin doses administered.

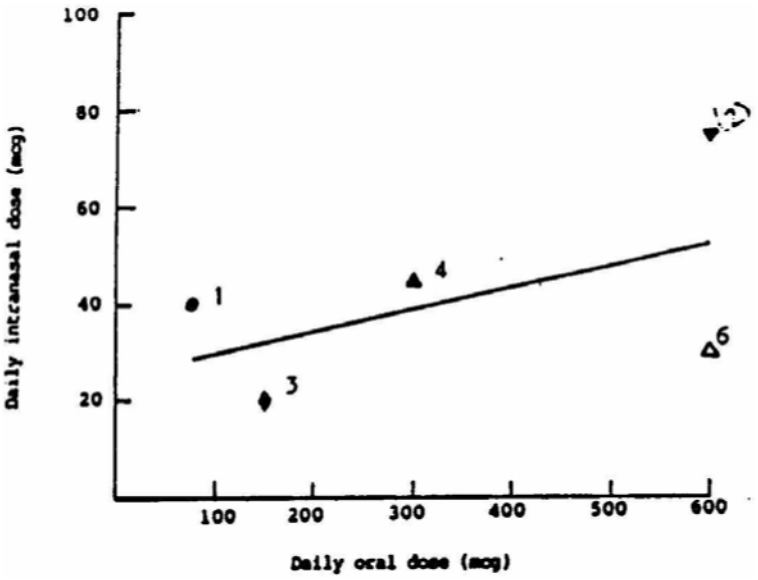
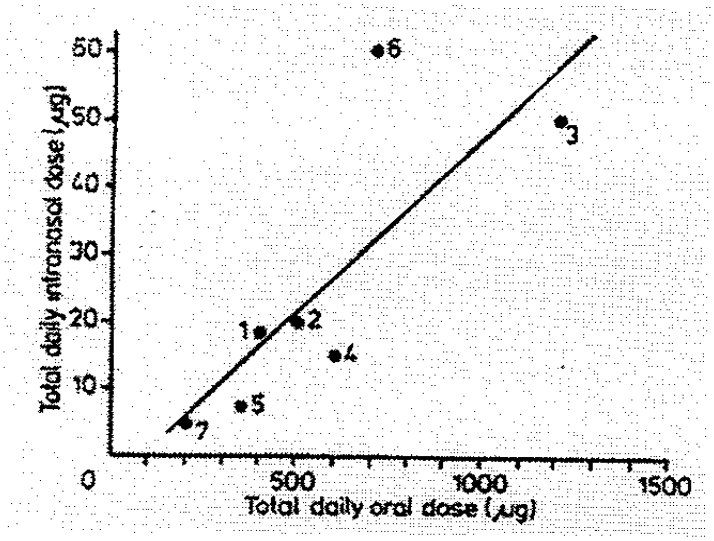


Figure 4

Correlation between intranasal and oral doses of demopressin acetate in seven pediatric cases. Coefficient of correlation r = 0.79 ($p < 0.01$).



In a recently conducted study, healthy subjects were water loaded to suppress endogenous vasopressin levels. The aim of the study was to investigate the antidiuretic effectiveness of five low doses of desmopressin and placebo. Due to wide inter- and intra-individual variations seen with the oral route, an intravenous infusion study was designed to minimize the variations. The study provided information about the pharmacokinetic and pharmacodynamic (PK/PD) relationship of low doses of desmopressin levels and their duration of anti-diuretic action. Combining this new insight into the correlation between plasma desmopressin levels and anti-diuretic effects of desmopressin with plasma concentration-time profiles after oral administration of desmopressin, showed that desmopressin is a potent compound with EC_{50} value of 1.6 ng/L. Thus desmopressin can be expected to have a continued effect even at a very low plasma level of 1 ng/L. After oral administration, an effect lasting from 6 to 14 hours can be expected.

Seventy two over-hydrated non smoking male subjects participated in a phase I study investigating the antidiuretic effect and pharmacokinetics of 30, 60, 125, 250 and 500 ng desmopressin and placebo infused intravenously at a constant rate for two hours. A clear positive dose-response slope was seen between duration of anti-diuretic action (primary endpoint) and dose of desmopressin (placebo included as zero), independent of the cut-off level (either 200 mOsm/kg or 400 mOsm/kg. No placebo response was seen, and very limited response was seen with 30 ng desmopressin. An increase in duration of antidiuretic action (DOA) with increasing dose of desmopressin was statistically significant for most pairwise comparisons. In the 250 ng and 500 ng desmopressin groups the median duration of anti-diuretic action was 5.36 hours (range: 0.75-10.64 hours) and 8.00 hours (range: 4.45-11.66 hours), respectively, when using 200 mOsm/kg as cut-off, while it was 3.94 hours (range: 0-7.56 hours) and 6.27 hours (range: 4.35-8.28 hours), respectively, when using 400 mOsm/kg as cut-off. The dose-response curve for the DOA did not flatten out within the dose range of 0-500 ng desmopressin for either cut-off (200 or 400 mOsm/kg), i.e. the plateau of the curve was not observed. This indicates that further increase in dosage (>500 ng) may increase duration of anti-diuretic action. Linear relationship between DOA and log (dose) among the dose range of 30-500 ng desmopressin was observed independent of cut-off level (either 200mOsm/kg or 400mOsm/kg).

No serious adverse events were seen with any of the desmopressin doses administered.

The analysis of other pharmacodynamic endpoints (maximum osmolality, AUC 0-6 hour for osmolality, AUC 0-6 hour for absolute change from dosing in osmolality) showed a clear positive dose-response relationship. The median maximum osmolality in the placebo group was 80 mOsm/kg (range: 55-183 mOsm/kg), while median maximum osmolality was 830 mOsm/kg (range: 762-1052 mOsm/kg) in the 500 ng desmopressin group.

Twenty-eight non-smoking healthy (n=14 male and n=14 female) subjects took part in a single-centre, open-labelled, randomised, study investigating the antidiuretic effect and pharmacokinetics of a 400 µg dose of desmopressin, taken as two of the currently marketed 200 µg tablets. Blood samples for plasma concentrations of desmopressin were collected according to the following schedule: pre-dose (i.e. 0-30 minutes pre-dosing), 15, 30 min 1, 1.5, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13 and 14 hours after dosing. The concentration of desmopressin in plasma was determined by a validated RIA method. The lower limit of quantification (LLOQ) of the assay was 0.8 ng/L. After administration of DESMOPRESSIN tablets, the geometric mean t_{max} was

observed at 1.0 hour after dosing, the geometric mean value for C_{max} was 20.8 (CV =60%) ng/L, the geometric mean value for AUC_t was 71.8 (CV=57%) (hr.ng/L), and the geometric value for AUC was 77.2 (CV=55%) (hr.ng/L).

Sixty four percent (64%) of the subjects had plasma desmopressin concentration above 1 ng/L at 12 hours post dose. No safety concerns were observed.

Pediatric Considerations:
As was the case with adults, peroral desmopressin acetate proved to be as effective as the intranasal administration of desmopressin acetate and was preferred by the patients. The pharmacodynamic activity is also similar. Doses as small as 12.5 µg have an effect on diuresis and urine osmolality but therapeutic doses start at above 100 µg; 200 µg peroral desmopressin acetate produces antidiuresis varying from 8 to 12.5 hr. As with adults, more frequent oral administration (t.i.d. vs. b.i.d.) often resulted in a better clinical response.

Bioavailability
Any cleavage of peptide bonds or reduction of the disulfide bridge of desmopressin leads to biological inactivation. The antidiuretic effect observed after peroral administration indicates that the desmopressin molecule is absorbed into the systemic circulation in intact chemical form.

Transmucosal absorption of the peptide takes place over a considerable period of time. Using a value of 2.2 mL/min/kg body weight for the metabolic clearance of desmopressin obtained during infusion of desmopressin acetate in humans, it was calculated that the bioavailability of desmopressin acetate during the first 6 hours after administration of the drug was 11.3% for the intranasal route as compared to 1.0 and 0.7% for the oral route at doses of 100 and 200 µg respectively. This value is lower than that calculated for children in which the relative bioavailability of the oral route of administration compared to the intranasal route was found to be approximately 5%.

STORAGE AND STABILITY

Store between 15°C and 30°C. Avoid humidity and light exposure.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

DESMOPRESSIN 0.1 mg Tablets are supplied as white, oval-shaped tablet with “0.1” debossed on one side and scored on the other side.

DESMOPRESSIN 0.2 mg Tablets are supplied as white, round tablet with “0.2” debossed on one side and scored on the other side.

DESMOPRESSIN Tablets are packaged in HDPE bottles of 100 tablets.

Composition

DESMOPRESSIN 0.1 and 0.2 mg Tablets contains 0.1 and 0.2 mg desmopressin acetate Trihydrate respectively. The tablets also contain the following non-medical ingredients (alphabetically): lactose anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

Product Monograph available upon request.

Meliapharm Inc.
Montréal, Québec H4P 2T4

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Desmopressin Acetate

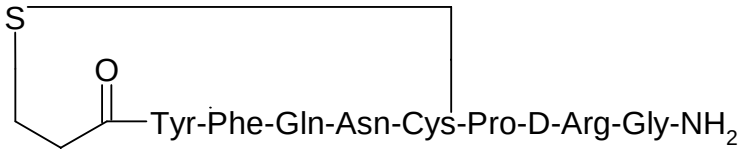
Chemical Name: 1-Desamino-8-D-arginine vasopressin acetate trihydrate

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

Molecular formula: $C_{48}H_{74}N_{14}O_{17}S_2$ (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 Trihydrate 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

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 adverse reactions were reported. 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.

No adverse reactions were reported that could be related to desmopressin acetate therapy. One patient was withdrawn at 6 months after tests revealed recovery from diabetes insipidus. Four patients showed elevated serum SGOT levels at 6 months which, however, were normal on repeated testing at 9 month follow-up. Two patients experienced elevated alkaline phosphatase values. One of these patients had elevated levels at baseline. Elevated alkaline phosphatase levels are quite normal during growth and the 2 patients showing elevated baseline levels were 5 and 15 years old. 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.

Two trials investigated the long-term efficacy and safety of desmopressin 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).

Comparative Bioavailability Studies

A randomized two-way crossover, blinded, single-dose comparative bioavailability study was performed in normal healthy male volunteers (n=33) under fasting conditions on Desmopressin tablets using Meliapharm Inc. DESMOPRESSIN 0.2 mg tablets (Lot # P-1365, manufactured on December 2004) versus the reference product, DDAVP® 0.2 mg Tablets (Lot # GC8858D, expiring on March 2007), by Ferring Inc. Canada. The pharmacokinetic data calculated for the DESMOPRESSIN 0.2 mg tablets and DDAVP® 0.2 mg tablets formulation are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Desmopressin (__4_ x __0.2_ mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90 % Confidence Interval#
AUC_T (pg·h/mL)	176.44 210.14 (65.88)	185.02 216.50 (63.16)	95.36 %	83.88 %-108.42 %
AUC_I (pg·h/mL)	204.92 238.18 (61.46)	216.97 249.41 (62.11)	94.44 %	83.23 %-107.17 %
C_{max} (pg/mL)	56.95 64.74 (58.54)	60.92 69.66 (66.46)	93.49 %	81.76 %-106.90 %
T_{max}§ (h)	1.00 (0.5-2.5)	1.00 (0.5-2.5)		
$T_{½}$▯ (h)	3.57 (44.38)	3.50 (39.49)		

* DESMOPRESSIN 0.2 mg Tablets (Pharmascience, Inc.)
† DDAVP® 0.2 mg Tablets (Ferring, Inc., Canada) were purchased in Canada.
§ Expressed as the median (range) only
▯ Expressed as the arithmetic mean (CV%) only

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.

Table 3: 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.

Reproduction 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.

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.

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PART III: CONSUMER INFORMATION

[Pr]DESMOPRESSIN Tablets

This leaflet is part III of a three-part "Product Monograph" published when DESMOPRESSIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DESMOPRESSIN. Contact your physician or pharmacist if you have any questions about the drug.

Pharmacist: Please dispense this insert with product.

ABOUT THIS MEDICATION

Bedwetting Background
Over 200,000 Canadian children between the ages of 5-19 years wet the bed at night. The children do not have control over this problem. **It is not their fault.**

Children may wet the bed because their bodies do not make enough of a chemical called vasopressin at night. This chemical helps to limit the amount of urine (pee) a person makes at night.

When children do not produce enough of this chemical, their bladder (the place in the body where urine is stored) gets too full. When it can't hold all the pee, children will wet the bed.

How many 3 year olds wet the bed at night?
- About 40 out of 100

How many 4 year olds…?
- About 20 out of 100

How many 5 year olds…?
- About 15 out 100

How many 12 year olds…?
- About 3 out of 100

How many 15 year olds…?
- About 1 out of 100

As children get older, many grow out of the problem and stop wetting the bed at night. Older children who still wet the bed feel a lot more stress than younger children who wet the bed. But the facts are the same: it's not the child's fault.

Did you know ?
- If one parent was a night bed wetter, there is a 5 out of 10 chance that their children will wet the bed.
- If both parents wet the bed as children, the chance of their children wetting the bed goes up to 8 out of 10.

Almost twice as many boys as girls wet the bed.

How Do DESMOPRESSIN Tablets (desmopressin) work?

DESMOPRESSIN Tablets reduce 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.

Getting ready to use DESMOPRESSIN Tablets

1. Reduce the number of drinks the child has after supper.
2. If your child was on [Pr]DDAVP® Spray and is now switching to DESMOPRESSIN Tablets, he/she can start taking the Tablets 24 hours after the last time the Spray was used.

What the medicinal ingredient is:
Desmopressin acetate Trihydrate

What the nonmedicinal ingredients are:
Lactose anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

What dosage forms it comes in:
Tablets: 0.1 mg and 0.2 mg, supplied in bottles of 100 tablets.

WARNINGS AND PRECAUTIONS

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.
Please contact your physician should your child experience any side effects. For DESMOPRESSIN to work at its best, it is very important to limit the number of drinks the child has after supper, especially 1 hour before bedtime. As most children sleep between 8 to 12 hours, further fluid restriction is not required. In the event the child wakes up during the night, liquid intake should be restricted.

INTERACTIONS WITH THIS MEDICATION

Tell your child's doctor or pharmacist in the unlikely event your child is taking any of the following medications (they are adult medications known to cause water retention and should be avoided when taking DESMOPRESSIN; clofibrate, chlorpromazine, carbamazapine, tricyclic antidepressants (such as amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs 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®, naprosen or Naprosyn®), celecoxib or Celebrex®) and loperamide or Imodium®.

PROPER USE OF THIS MEDICATION

How many DESMOPRESSIN Tablets should be used?

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptom / effect	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Common	Headache		√	
	Nausea, mild abdominal cramps		√	
	Nasal congestion, rhinitis,		√	
	Flushing of the face		√	
Uncommon	Dizziness			√
	Chills, edema of face and hands			√
	Wheezing			√
	Rash			√

	Nausea, constipation, loss of appetite, increased appetite			√
	After taste in mouth			√
	Eye infection			√
	Water retention, water intoxication			√

HOW TO STORE IT

Store in a dry place between 15°C and 30°C. Avoid humidity and light exposure.

MORE INFORMATION

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 0701C
    Ottawa, ON 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.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Meliapharm Inc., at 1-888-550-6060.

This leaflet was prepared by Meliapharm Inc.

Last revised: March 16, 2010

PART III: CONSUMER INFORMATION

[Pr]DESMOPRESSIN Tablets

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Pharmacist: Please dispense this insert with product.

ABOUT THIS MEDICATION

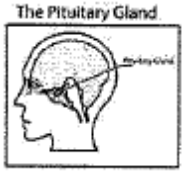
What is the medication used for?

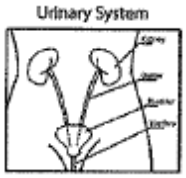
What are DESMOPRESSIN Tablets?
DESMOPRESSIN tablets are used to prevent or control the frequent urination, increased thirst, and loss of water associated with Diabetes Insipidus (*water diabetes*).

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.

It is important to point out that DI is **not** related to the type of diabetes most people have heard of, Diabetes Mellitus (sugar diabetes).

In DI, there is no problem with the sugar in the blood or urine. The problem either concerns the lack of water-retaining hormone in the blood (called vasopressin or Anti-Diuretic Hormone –ADH) or is sometimes due to an abnormality in the kidneys which prevents them from responding to this hormone. The hormone itself is normally secreted by the pituitary gland, which is located at the base of the brain, just behind the bridge of the nose.





What causes DI?

Most DI is caused by inadequate secretion of vasopressin by the pituitary gland. This can happen in varying degrees. Sometimes it occurs on its own, but in many cases it is accompanied by loss of other hormones made by the pituitary. In this event, it is most likely to be caused either by abnormalities of the pituitary gland or as a result of treatment to remove an enlarged pituitary gland.

If you experience DI following pituitary surgery, this may be temporary, in which case it will only last a week or two, but in some cases it may be permanent.

DI can occur at any age, but is mostly found in adults, as pituitary enlargement is most common between the ages of 20 and 50. It is a rare disorder, affecting only about 1 in 25, 000 people.

The other form of DI occurs when the kidneys cannot respond to vasopressin secreted by the pituitary gland. It is caused by an inherited abnormality in the mechanism which recognizes vasopressin in the kidney, or by a number of diseases of the kidney itself.

What does it feel like to have DI?
If you suffer from DI, you may find you feel generally unwell for no obvious reason. The main symptoms, however, are that you will feel extremely thirsty much of the time, no matter how much you drink, and you will find you need to pass urine very frequently, even during the night. You may excrete as much as 2.5-3 gallons of urine a day. 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.

How is it diagnosed?

What tests are carried out?

The method of diagnosis is simply to deprive you of fluid for 6-8 hours and see if there is a reduction in the volume of urine. You can expect to feel quite thirsty during this part of the test. The next stage is to give you a small quantity of vasopressin, usually as an injection. You will then make less urine. Once you are allowed to drink again, you will feel better. If you need other hormone treatments, you will need to continue taking them during the test. This can be performed in an outpatient clinic, but it does require attendance for a whole day.

How id DI treated?
If your DI is diagnosed as being caused by a lack of vasopressin production from the pituitary gland, it needs to be treated with a substance like vasopressin, which acts specifically on the kidneys. This substance is called desmopressin, but you will normally hear it referred to as DESMOPRESSIN.

You will gradually feel better once you are taking desmopressin. Overall, the treatment of DI is very straightforward and you need not worry about handling this aspect of your illness.

It is possible that your condition will require long term monitoring. If you do not take enough desmopressin, your original symptoms of thirst and passing a lot or urine will return. If you take more desmopressin than you need, your body may become overloaded with fluid, which could result in headaches, dizziness and abnormal weight gain. In turn this may result in low amounts of sodium in your blood, which is called hyponatremia. It is important that you contact your doctor if you experience any of these symptoms. Your doctor will help you to find the right dose of desmopressin and will advise you on the amount of fluid you should take.

How Do DESMOPRESSIN Tablets work?
DESMOPRESSIN 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.

Who should not take DESMOPRESSIN Tablets?
There are people who should not take DESMOPRESSIN Tablets. Tell your doctor or pharmacist if you have:

- Hyponatremia (low blood sodium levels)
- Diarrhea
- Any heart, liver or kidney problems
- Bleeding problems
- Bulimia or anorexia nervosa
- Type II B or platelet-type (pseudo) von Willebrand's disease.
- Adrenal problems (e.g. Addison's disease)
- An allergy to desmopressin acetate or to any of the ingredients listed.

What do DESMOPRESSIN Tablets contain?

What the medicinal ingredient is:
The medicine contains an active drug called desmopressin acetate. If you have a known allergy or sensitivity to desmopressin acetate, call your doctor before using this medicine.

What the important non-medicinal ingredients are:
lactose anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate

What dosage form it comes in:
DESMOPRESSIN Tablets are supplied in bottles of 100 tablets.

WARNINGS AND PRECAUTIONS

BEFORE you use DESMOPRESSIN Tablets, talk to your doctor or pharmacist if you are:

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

And/or if you have:

- Heart problems
- Liver disease
- Kidney problems
- Bleeding problems
- Fever
- Any allergies to desmopressin acetate or any of the ingredients listed in "What the important non-medicinal ingredients are".

Infrequently, high doses of desmopressin have produced temporary headache and nausea, and mild abdominal cramps have been reported. Symptoms disappeared with reduction in dosage. Please contact your doctor if you experience any side effects.

If you are taking any of the drugs that are known to cause water retention listed in "Interactions with this medication", it may be necessary to monitor the amount of sodium in your blood. Use of both drugs together could increase the chances of getting low amounts of sodium in your blood. Contact your

doctor if you experience worsening of the symptoms such as headache, nausea and vomiting. This may indicate possible changes in the amount of sodium in your blood and your doctor may need to do a blood test.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with DESMOPRESSIN Tablets include: clofibrate, chlorpromazine, carbamazapine, tricyclic antidepressants (such as amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (SSRIs 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®, naprosen or Naprosyn®), celecoxib or Celebrex®) and loperamide or Imodium®.

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

PROPER USE OF THIS MEDICATION

How many DESMOPRESSIN Tablets Should I Take?

Take the medication only as directed by your doctor. Do not use more of it and do not use it more often than your doctor ordered. To do so may increase the chance of side effects.

When using DESMOPRESSIN tablets, it is important that you get the right amount of medicine for your condition. The dose of desmopressin will be different for different patients. Your doctor will determine the right amount of DESMOPRESSIN Tablets for you.

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.

What if I forget to take DESMOPRESSIN Tablets?
If you miss a dose of DESMOPRESSIN Tablets, take the missed dose as soon as possible. Then go back to your regular dosing schedule. 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

What are the possible side effects of DESMOPRESSIN Tablets?
As with all medicines, side effects may be experience. With DESMOPRESSIN Tablets, these may include headache, dizziness, rash, and mild abdominal cramps. These have occurred usually when the medication is being adjusted. Once you are taking the right amount of medicine of your condition, these side effects will usually go away. Tell you doctor about any side effects you experience.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

	Symptom / effect	Talk with your physician or pharmacist		Stop taking drug and call your physician or pharmacist
		Only if severe	In all cases	
Common	Headache		√	
	Nausea, mild abdominal cramps		√	
	Nasal congestion, rhinitis,		√	
	Flushing of the face		√	
Uncommon	Dizziness			√
	Chills, edema of face and hands			√
	Wheezing			√
	Rash			√
	Nausea, constipation, loss of appetite, increased appetite			√
	After taste in mouth			√
	Eye infection			√
	Water retention, water intoxication			√

HOW TO STORE IT

Where do I keep DESMOPRESSIN Tablets?

Store in a dry place between 15°C and 30°C. Avoid humidity and light exposure.

MORE INFORMATION

REPORTING 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 0701C
    Ottawa, ON 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.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting Meliapharm Inc., at 1-888-550-6060.

This leaflet was prepared by Meliapharm Inc.

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