PRODUCT MONOGRAPH

PrMINIRIN® TABLETS

(Desmopressin Acetate)

0.1 mg and 0.2 mg Tablets

Antidiuretic

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MINIRIN® TABLETS

Desmopressin Acetate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

Minirin® Tablets is indicated for:

- Treatment of Nocturia in adults

CONTRAINDICATIONS

Hypersensitivity to desmopressin acetate or any of the tablet's constituents. Known hyponatraemia, 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. Existing medical conditions, which lead to sodium losing states such as nausea, bulimia, anorexia nervosa, chronic vomiting, diarrhoea and adrenocortical insufficiency as well as salt losing nephropathies, are contraindicated for the use of desmopressin acetate. 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.

WARNINGS AND PRECAUTIONS

General

Desmopressin acetate is not effective in controlling polyuria caused by renal disease, nephrogenic diabetes insipidus, diabetes mellitus, psychogenic polydypsia, hypokalaemia or hypercalcaemia.

Fluid intake should be adjusted to reduce the possibility of water intoxication and hyponatraemia especially in very elderly patients (see Special Patient Populations).

Precautions to avoid hyponatraemia must be taken in:

- conditions characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, and SIADH (Syndrome of Inappropriate ADH secretion) and in patients with high intra-cranial pressure.

- conditions requiring concomitant treatment with diuretic agents,

- cases of concomitant treatment with drugs which are known to induce SIADH, e.g. tricyclic antidepressants (amitriptyline, nortriptyline), selective serotonine reuptake inhibitor antidepressants (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram), chlorpromazine and carbamazepine,

- cases of concomitant treatment with NSAIDs.

In general, both hyponatraemia and SIADH respond to fluid intake limitation and restriction in the range of 1000 to 1200 mL per day. Physicians should not use hypertonic saline infusion for rapid correction of severe hyponatraemia as this may lead to severe sequelae.

Genitourinary

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

Sensitivity /Resistance

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 the fetus by desmopressin. The use of desmopressin acetate in pregnant women with no harm to the fetus has been reported.

No controlled studies in pregnant women have been carried out. However, as with all medications 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.

Geriatrics (≥ 65 years of age)

Elderly patients (≥ 65 years) and patients with low serum sodium levels may have an increased risk of hyponatraemia. For this reason, additional safety monitoring is recommended. These recommendations include serum sodium evaluations before beginning treatment, 3 days after the start of therapy or 3 days following a change of dose. If the serum sodium level is below normal limits, or has significantly decreased from baseline, a repeat serum sodium should be obtained within 3 to 4 days. If Minirin® Tablets (desmopressin acetate) are being used long-term, a further sodium test at one month should be taken. If Minirin® Tablets are being used long term and the patient shows a tendency to hyponatraemia, the sodium should be measured every month. If there is no tendency to hyponatraemia, then measuring the sodium every 2 to 3 months is appropriate. In the event serum sodium levels are not within normal limits, or have not stabilized, the patient should be discontinued from further treatment.

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

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 hyponatraemia. Fluid intake should be carefully adjusted to prevent over-hydration.

Monitoring and Laboratory Test

In nocturia patients, a frequency/ volume chart should be used to diagnose nocturnal polyuria for at least two days before starting treatment. A night-time urine production exceeding the functional bladder capacity or exceeding 20% in the young, 27% in the middle age and 33 % in the elderly of the 24 hour urine production is regarded as nocturnal polyuria.

Serum sodium should be measured before beginning the treatment, 3 days after initiation of therapy or increase in dosage and at other times during treatment as deemed necessary by the treating physician.

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 monitoring.

Special Conditions/Diseases

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

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

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.

Two clinical studies in patients with Nocturia were conducted. The two clinical trials (male and female studies) were identical in design. They were randomized, double blind, placebo-controlled, parallel group, multicentre investigations in adult males or females aged ≥ 18 years. The patients had an average of ≥ 2 nocturnal voids. Exclusion criteria were adopted to ensure that the presence of Nocturia was not due to other well-defined causes of increased urinary frequency as multiple sclerosis, urge incontinence, diabetes insipidus or polydipsia. Patients with cardiac insufficiency, those requiring diuretic therapy and those with any other medical condition characterized by a fluid or electrolyte imbalance, were also excluded. Patients receiving diuretics, tricyclic antidepressants, indomethacin, carbamazepine, or chlorpromamide were excluded. Anti-hypertensives were permitted providing that no dose adjustments occurred in the previous 3 months and patients were receiving long-term treatment.

The studies commenced with a 1-week screening period to establish baseline. In week 1, patients received daily one 0.1 mg Minirin® Tablet at bedtime for seven days. If necessary, medication was increased in week 2 to one 0.2 mg tablet daily for seven days and again in week 3 to two 0.2 mg tablets (i.e., 0.4 mg) daily for an additional seven days. If patient obtained zero nocturnal voids during the dose-titration week, this dose was chosen as the optimal dose for the double-blind treatment period and the patient would not proceed to the next dose level. In patients not achieving zero nocturnal voids with any of the doses, the tolerated dose giving the lowest nocturnal diuresis was selected. The double-blind period commenced after the seven-day wash-out period. Patients were randomly assigned to their optimal dose of Minirin® tablets or placebo. The treatment period was five weeks, giving a total of 6-8 weeks depending on the length of the titration period.

Table 1 summarizes the incidence of related adverse events with an occurrence rate of at least 1% in both the male and female study. The majority of adverse events were seen in the dose titration phase (Table 2).

Apart from hyponatraemia, there were no differences between Minirin® tablets and placebo with respect to number of abnormal laboratory values, or changes in vital sign measurements from baseline to study end. The most commonly used concomitant medication was anti-thrombotic agents.

Clinical Trial Adverse Drug Reactions (Frequency ≥ 1%)

Table 1: Incidence of related adverse events with occurrence rate of at least 1% in the male and female studies.

	Male Study*			Female Study*		
	Titration	Double-Blind		Titration	Double-Blind	
	desmopressin (N=224)	desmopressin (N=86)	Placebo (N=65)	desmopressin (N=224)	desmopressin (N=72)	Placebo (N=72)
	%	%	%	%	%	%
Body As A Whole						
Headache	12	2	2	22	10	7
Abdominal Pain	3			4		
Fatigue	2	1		3		
Back Pain						1
Nervous System						
Dizziness	4			3		
Insomnia	<1			2		
Somnolence	1					
Gastrointestinal						
Nausea	4			8		1
Dry Mouth	3	1		4		
Diarrhoea	4			1		
Dyspepsia	1		2	<1		
Flatulence				2		
Vomiting	<1	1		1		
Constipation		1		1		
Cardiovascular						
Hypertension	1			2		
Arrhythmia		1				
Urogenital						
Micturation Frequency	1			4		
Urinary Incontinence					1	
Metabolic						
Oedema Peripheral	1	1	3	3		
Musculoskeletal						
Cramp Legs				2		
Blood Disorders						
Thrombocytopenia			2			
Laboratory Changes						
Hyponatraemia	4			6		
SGPT Incr.			2	<1		
Creatine Phosphokinase Incr.	<1	1			1	

*In both the male and female studies there was an open dose titration arm, where the optimal dose was determined. The double blind period commenced after a 7 day wash out period. Patients were assigned to their optimal dose, as determined in the titration phase of desmopressin or to a placebo in a randomized fashion. Most AEs were reported during the dose titration phase.

Male Study

A total of 237 adverse events in 107 (48%) patients occurred during the dose titration and wash out periods. Treatment related events were reported in 60 (27%) patients during the dose-titration period. In the double-blind period: 12 patients experienced at least one related event; six (7%) patients on desmopressin and six (9%) patients on the placebo.

Female Study

Three hundred ninety eight (398) adverse events were reported in158 (71%) patients in the dose titration and wash out periods. Two hundred thirty one (231) related adverse events occurred in 109 (49%) patients during the dose-titration period. In the double-blind period, fifteen patients experienced at least one related adverse event; 9 (13%) patients on desmopressin and 6 (8%) on placebo.

A summary of the most frequently reported (>3%) related adverse events during the dose titration phase is listed below (Table 2).

Table 2: Summary of Treatment Related Adverse Events >3 % during the dose titration phase

	Male Study		*Female Study*	
	N (%)	*E*	*N (%)*	*E*
Patient Exposed	*224 (100)*		*224 (100)*	
Total Adverse Events	*107 (48)*	*237*	*158 (71)*	*398*
Adverse Events Related to Study Medication	*60 (27)*	*139*	*109 (49)*	*231*
Body As a Whole				
Headache	*26 (12)*	*32*	*50 (22)*	*63*
Abdominal Pain			*9 (4)*	*10*
Fatigue			*7(3)*	*8*
Nervous System				
Dizziness	*9 (4)*	*10*	*7(3)*	*7*
Gastrointestinal				
Diarrhoea	*9 (4)*	*10*		
Nausea	*10 (4)*	*11*	*17 (8)*	*18*
Dry mouth			*9 (4)*	*9*
Urogenital				
Micturation frequency			*8 (4)*	*9*
Metabolic				
Peripheral Edema			*7(3)*	*9*
Laboratory Changes				
Hyponatraemia	*8 (4)*	8	*14 (6)*	*15*

N = Number of patients with event
% = Proportion of patients with event
E = Number of events

Frequency of Adverse Events

Male Study

The most frequently reported adverse events during the dose titration period were headache (12%), followed by diarrhea, nausea, dizziness, and hyponatraemia (all 4%). The adverse event with the highest frequency during the double blind period was headache: 4% (2% of desmopressin treated group and 2% of placebo treated group).

Female Study

The most frequently reported adverse events during the dose titration were headache (22%), followed by nausea (8%), hyponatraemia (6%), abdominal pain, dry mouth, and micturation frequency (all 4%), and fatigue, dizziness and peripheral edema (all 3%). In the double blind period, the most frequent adverse event related to desmopressin was headache which was reported in 10% of desmopressin treated patients and 7% of placebo treated patients.

DRUG INTERACTIONS

Overview

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

Substances which are known to induce Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH), e.g. tricyclic antidepressants (amitriptyline, nortriptyline), selective serotonin reuptake inhibitor antidepressants (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram), chlorpromazine and carbamazepine may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia.

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 Inhibitors such as Celebrex® may induce water retention/hyponatraemia.

Patients treated with diuretics for fluid retention should not be treated with antidiuretics.

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 gastrointestinal motility, or disease characterized by impaired gastrointestinal motility (e.g. diabetic gastroparesis), may increase exposure to desmopressin.

Clinically significant inhibition of desmopressin metabolism by other drugs is unlikely. Desmopressin is a peptide analogue of vasopressin and its *in vivo* inactivation occurs via disulfide reductases, aminopeptidases, and serine proteases, similar to the inactivation of vasopressin. However, the structural modifications to the molecule render desmopressin less susceptible to inactivation by these enzymes compared with vasopressin. Furthermore,

incubation of desmopressin with human liver microsomes revealed no significant oxidative metabolism. The relative resistance to usual peptide inactivation pathways and the lack of oxidative metabolism are supported by the observation that desmopressin is excreted largely unchanged in the urine. Thus, the likelihood of desmopressin exposure being affected by drugs known to inhibit common oxidative metabolic pathways (e.g. CYP450) is low. Thus, metabolic drug-drug interactions that would result in increased exposures to desmopressin are not likely to occur.

The precise relationship between increased exposure to desmopressin, prolongation of effect, and the development of hyponatraemia, has not been determined. However, clinical data suggest the approach to treating Nocturia with desmopressin is to initiate therapy at a low dose and titrate upward according to tolerability and response.

Drug-Food Interactions

Intake of a standardized meal with oral desmopressin resulted in a significant decrease in bioavailability compared to the fasting condition. This is hypothesized to be due to reduced absorption from the gastrointestinal tract. However no effect on dynamics was observed.

The clinical impact of decreased exposure to desmopressin when administered with a meal, or following a meal, is likely to be inconsequential because pharmacodynamic response to desmopressin is similar in either feeding regimen. Furthermore, the intended bedtime administration of desmopressin is not typically the time of a meal.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of Minirin7 tablets (desmopressin acetate) must be determined for each individual patient and adjusted according to response. Response should be measured by reduction of nocturnal voids and an increase mean duration of first undisturbed sleep by two hours. The treatment with Minirin® tablets begins with a 3 week period of titration to establish the optimal dose. In this period Minirin® Tablets are taken orally once daily at bedtime. In the first week patient takes one 0.1 mg tablet daily for seven days and if necessary increasing in week 2 to one 0.2 mg tablet daily for seven days, and again in week 3 to two 0.2 mg tablets (0.4) daily for seven days. If the patient obtains zero nocturnal voids during a dose-titration week, this dose is chosen as the optimal dose. If a patient is not achieving zero nocturnal voids on any of the doses, the tolerated dose giving the lowest nocturnal diuresis is selected. After the 3 week period of titration, the patient continues treatment with the established dosage.

In patients 65 years or older, serum sodium should be measured before beginning the treatment and three days after initiation or increase in dosage and at other times during treatment as deemed necessary by the treating physician. (see Warnings and Precautions).

In the event of signs and symptoms of water retention and hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions) treatment should be

interrupted until the patient has fully recovered. When restarting treatment strict fluid restriction should be enforced.

Recommended Dose and Dosage Adjustment

The recommended initial dose is 0.1 mg at bedtime. The dose may be titrated up to 0.4 mg to achieve the desired response using the following dosage plan:

If the initial dose of 0.1 mg does not sufficiently achieve the desired response (see Warnings and Precautions), the dose may be increased up to 0.2 mg and subsequently to 0.4 mg by weekly dose increases. The maximum recommended dose is 0.4 mg per day.

Missed Dose

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

Administration

Restricted fluid intake is recommended a few hours before administration, especially one hour before, and until the next morning (at least 8 hours) after administration. As well, during the evening, the amount of alcohol and caffeine intake should be limited.

OVERDOSAGE

Overdosage of desmopressin acetate may lead to an increased duration of action. This will increase the risk of fluid retention and symptoms which 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.

If hyponatraemia 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], a slow normalization of serum sodium is required to avoid additional complications. Intensive fluid intake regulation may be required in these cases.

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

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 bioavailability of orally ingested desmopressin has been found to be approximately 0.08%, sufficient to induce 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 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. Mean maximum plasma concentrations in the range 6.57-16.6 pg/mL (0.2 mg dose) to 31.4-51.6 pg/mL (0.4 mg dose) are reached within 2 hours (t_{max} 0.75-1.9 hours). The oral mean terminal half-life varies between 2.0 and 3.2 hours. Intra- and inter-individual variability of about 30% in absorption of desmopressin is apparent. However, the plasma levels obtained are well above the amount required for a maximal antidiuretic effect, even for a prolonged period.

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 inter-individual differences.

Pharmacodynamics

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

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.

Currently available information indicates that although absorption of desmopressin is low after oral administration, sufficient quantities are available to be clinically effective. 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.

To explore the pharmacology of desmopressin, two Phase II dose ranging studies have been conducted with oral desmopressin tablets. The target populations were women with Nocturia and elderly subjects with nocturnal polyuria. The efficacy criteria for both studies included change in nocturnal micturition episodes.

In one of the phase II studies a dose-titration phase was used before randomization to either desmopressin or placebo. The population was considered to likely benefit from desmopressin treatment, i.e. elderly subjects with Nocturia with a polyuric component (defined as urine production $\geq$ 0.9 ml/min) and without daytime urinary symptoms. The study showed that desmopressin decreased nocturnal diuresis as well as the frequency of nocturnal voidings in patients included in the study, in a statistically significant manner compared with placebo treatment (Tables 1 and 2) . A decrease in diuresis compared with baseline could be seen at the 0.1 mg dose. Most patients (10 of 17) experienced the best effect on diuresis at 0.2 mg, while 0.4 mg provided the best reduction in only three patients. There was no significant difference between treatments in 24h diuresis (Table 3).

Table 1. Nocturnal diuresis measured after 2 weeks of treatment

Population	Mean		Mean difference[H]	p-values from ANOVA		
	Desmopressin	Placebo	(95% CI)	Treatment	Sequence	Period
APT	1	1.6	-0.59 (-0.85 to -0.33)	0.0002*	0.5463	0.5862
PP	0.9	1.4	-0.48 (-0.76 to -0.19)	0.0033*	0.6314	0.6719

* Statistically significant effect (p<0.05) [H]Least square means from ANOVA
PP= per protocol
APT= all patients treated

Table 2. Nocturnal voids during second week of treatment

Population	Mean		Mean difference[H]	p-values from ANOVA		
	Desmopressin	Placebo	(95% CI)	Treatment	Sequence	Period
APT	1.1	1.7	-0.59 (-0.85 to -0.32)	0.0003*	0.8219	0.921
PP	0.9	1.5	-0.54 (-0.84 to -0.24)	0.0022*	0.4612	0.8974

* Statistically significant effect (p<0.05) [H]Least square means from the ANOVA
PP= per protocol
APT= all patients treated

The number of nocturnal voiding episodes was reduced in parallel with the reduction in nocturnal diuresis (Table 3). Secondary to the decrease in nocturnal micturition episodes, the maximum duration of sleep between nocturnal voidings was significantly longer for desmopressin compared with placebo (5.4h versus 4.0h; mean difference 1.31 (95% CI 0.7-1.9).

Table 3. 24h diuresis measured after 2 weeks of treatment

Population	Mean		Mean difference[H]	p-values from ANOVA		
	Desmopressin	Placebo	(95% CI)	Treatment	Sequence	Period
APT	1.3	1.4	-0.12 (-0.33 to 0.09)	0.2220	0.4144	0.3869
PP	1.2	1.2	-0.11 (-0.34 to 0.13)	0.7977	0.8431	0.5839

[H]Least square means from the ANOVA
PP= per protocol
APT= all patients treated

A third Phase II study was an exploratory epidemiological survey of Nocturia in three parts, during which subjects with Nocturia aged 65 years and over were treated with 0.2 mg oral desmopressin.

The aim was to mimic clinical practice, namely, treatment of elderly subjects with Nocturia on an unselected basis.

Part A: A questionnaire was sent to all inhabitants aged 65 years in a defined area (Tierp) in Sweden. A response was obtained from 2866 subjects.

Part B: A frequency B volume chart was sent to all consenting nocturics and non-nocturics from part A; a response was obtained from 159 nocturics and 131 non-nocturics.

Part C: A short therapeutic trial where all patients received 0.2 mg desmopressin for three consecutive nights; 72 subjects were included.

One hundred percent of the nocturic subjects (Nocturia defined as ≥2 voids/night) had a Nocturia index >1, i.e. a urine production exceeding bladder capacity. The need to void at night could be explained, at least partly, by a polyuric component to their condition. When treated with desmopressin, 78% of subjects showed a response in terms of decreased nocturnal urine production (≥ 20% decrease from baseline). The mean number of nocturnal voids was 1.6 during treatment compared to 2.6 at baseline and the mean change in nocturnal urine output was 286 ml (95% CI 336 to 237 ml). The mean time from bedtime to the first void increased from 2.8 hours at baseline to 4.6 hours during treatment.

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

Desmopressin did not show any effect on any of the nine Cytochrome P450 subtypes. *In vivo* drug-drug interactions based on activation or inhibition of Cytochrome P450 are therefore very unlikely.

Pharmacokinetics

Human pharmacokinetic studies have been conducted on desmopressin using the oral and intravenous formulations. Three studies enrolled healthy volunteers. Two additional studies were conducted in elderly male subjects, considered to represent an element of the population for Nocturia. The studies are summarised below (Table 4). The pharmacokinetic profile of oral desmopressin is summarized in Table 5.

Table 4. Summary of Pharmacokinetic Data

Duration	Dose/dosage form	Exposure	Tmax (h)	Cmax (pg/ml)	AUC (pgxh/ml)	t 2 (h)	t $2\lambda_2$ (h)	Vss (L)	Cl (L/h)
Desmopressin was administered both orally and intravenously, both during the day and in the night, yielding 4 different sessions: Day p.o. Day i.v. Night p.o. Night i.v. During each session, volunteers were hospitalized for 12 hours. Between each session, there was a washout period of at least 2 days. All four sessions were performed within one month.	0.2mg tablet per oral desmopressin 2□g i.v. desmopressin	night p.o. day p.o. night i.v. day i.v.	1.9 1.4 -- --	6.21 6.57 18.1 20.4	22.9 21.3 2.84 2.69	 0.25 0.22	 3.09 2.77	 25.6 24.1	 6.6 7.2
3 single doses with at least 7 days washout between doses.	2x 0.2 mg tablet	Period 1 2 3	 1.0 - 1.0	 27.6 29.8 34.4	 79.6 90.3 99.5	 0.34 0.34 0.35	 B	 -	-
Erythromycin - 4 times daily (7, 13 and 18 and at bed time) with the first dose in the morning 3 days before the study day and the last one 1 hour before intake of desmopressin. Loperamide at 24, 12 and 1 hour before intake of desmopressin	2 x 0.2 mg tablet	*A* *B* *C*	*1.3* *2.0* *0.9*	*25.4* *58.4* *19.2*	*90.4** *280.0** *70.4** *75.6*** *239.0*** *58.7***	*2.4* *2.5* *2.4*	*0.3H* *0.2H* *0.2H*	-	-
A single oral dose of 0.4 mg (2 tablets of 0.2mg) will be used at PK day 2. Oral dose of 0.4mg (2 tablets at 0.2mg each) at bedtime during the placebo controlled effect evaluation period of 2 x 3 days.	0.4 mg (2 x 0.2 mg) tablet	*N/A*	-	*15.91*	*76.62**** *61.24*□	-	*3.11*	-	-
Single Dose	0.4 mg (2 x 0.2 mg) tablet	with food 1.5 h after food without food	2.4 2.1 2.3	11.8 13.4 24.8	45.2 47.5 80.0	1.5 1.5 1.5	0.5l 0.5l 0.5l	- - -	- - -

* AUC (pg.h/ml)
** AUCt (pg.h/ml)
l t_{lag} (h)
H These T values refer to T lag
A: Desmopressin alone
B: Loperamide/desmopressin
C: Erythromycin/desmopressin
***AUC_{inf}
□ AUC_{o-t}

Table 5: Pharmacokinetic Profile of Oral Desmopressin

Parameter	0.2 mg dose	0.4 mg dose
Average absolute bioavailability (%)	0.08	0.16
C_{max} range (pg/mL)	6.57 - 16.6	31.4 - 51.6
T_{max} mean (h)	2	
T_{max} range (h)	0.75 - 1.9	

Food Effects

Parameter	Desmopressin acetate 400 mcg po		Desmopressin acetate and concomitant meal	
	Estimate	CV%	Estimate	CV%
AUC $_{inf}$ (pg•h/mL)	80.0 (68.6 - 93.1)	49	45.2 (38.8 - 52.6)	22
AUC $_{last}$ (pg•h/mL)	63.1 (53.5 - 74.6)	51	33.1 (28.0 - 39.1)	26
C_{max} (pg/mL)	24.8 (19.9 - 31.0)	67	11.8 (9.5 - 11.8)	28
T_{2} (h)	2.3 (2.1 - 2.5)	21	2.4 (2.2 -2.7)	21
T_{max} (h)	1.0 (0.05 - 3.0)	52	1.5 (0.8-2.5)	38

Absorption:

Orally administered desmopressin is poorly absorbed (Table 5). The oral mean terminal half-life varies between 2.0 and 3.2 hours. Intra- and inter-individual variability of about 30% in absorption of desmopressin is apparent, probably due to the low absorption after oral administration. However, the plasma levels obtained are well above the amount required for a maximal antidiuretic effect even for a prolonged period.

Intake of a standardized meal with oral desmopressin resulted in a significant decrease in bioavailability compared to the fasting condition (Table 5). The pharmacodynamic action of desmopressin appears to be unaffected by food as assessed by urine volume and urine

osmolality for at least 4 hours post-dose. The degree of antidiuresis was similar in the absence of food and when the drug was taken with or 1.5 hours after food.
After daytime administration of desmopressin, the mean urine volume gradually decreased from about 130 mL/h to a level of approximately 70 mL/h during the first collection period (Figure 1). A minimum level of approximately 50 mL/h was achieved during the second collection period. During the subsequent collection periods the urine production returned to pre-dose levels. When desmopressin was given perorally in the evening, the mean urine production decreased from about 115 mL/h to approximately 50 mL/h during the night (Figure 2). There was a slight increase in the morning values to a level of about 60 mL/h.

Urine osmolality increased after daytime administration from a mean value of about 610 mOsm/L to a maximum level of 780 mOsm/L, which was achieved during the second collection period. During the subsequent collection periods the urine osmolality decreased to below pre-dose levels. During the night, urine osmolality increased from a mean per-dose value of 540 mOsm/L to about 700 mOsm/L during the night. This osmolality level was also seen in the urine produced the subsequent morning.

Figure 1. Mean (± SD) day-time diuresis in each collection period before and after day administration (desmopressin given at 11.00 h)

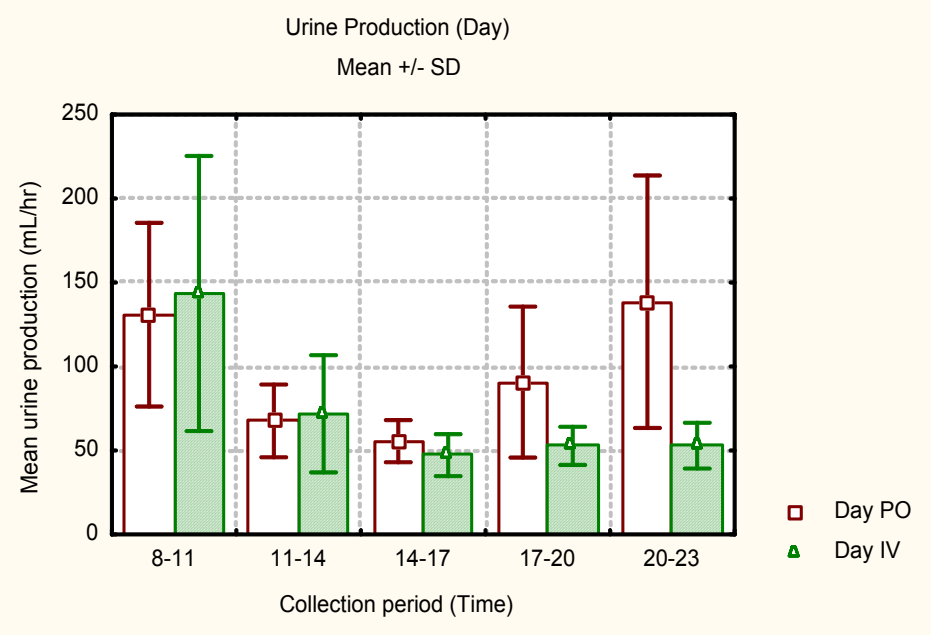
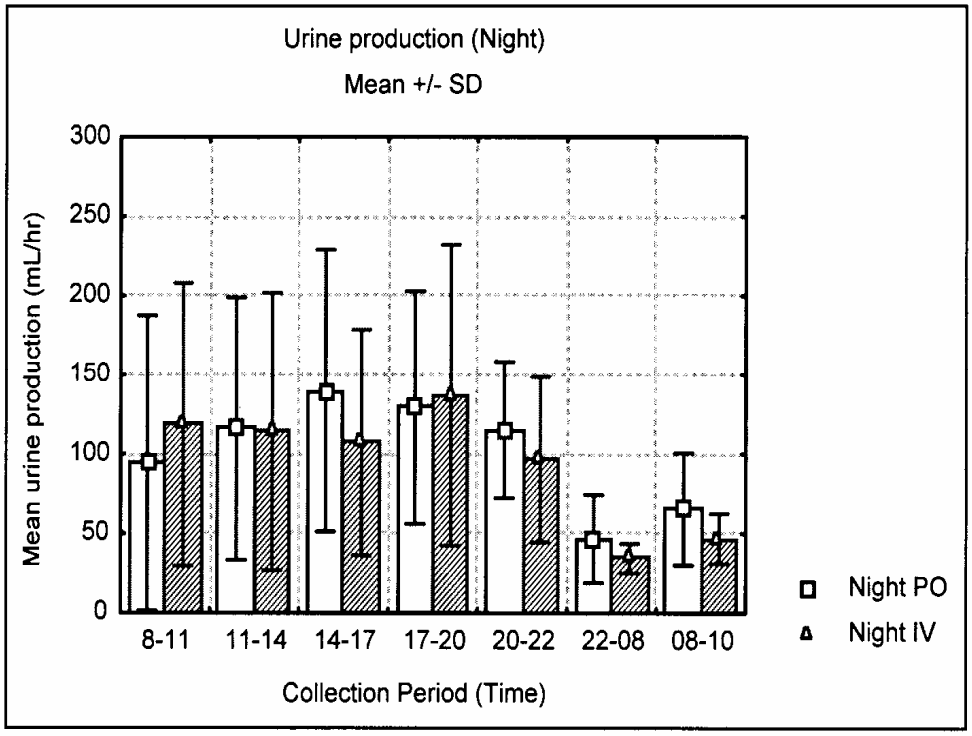


Figure 2. Mean (± SD) night-time diuresis in each collection period before and after day administration (desmopressin given at 22.00 h)



oral = white bars; intravenous = grey bars

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 of1.6 pg/mL.

Thus desmopressin can be expected to have a continued effect even at a very low plasma level of 1 pg/mL. 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 pair-wise comparisons. In the 250 ng and 500 ng desmopressin groups the median DOA 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 with the statistically significant slope, 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 desmopressin 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 two doses of the currently marketed desmopressin tablet (2x200 µg). 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 pg/mL. After administration of DDAVP 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%) pg/mL, the geometric mean value for AUC_t was 71.8 (CV=57%) (hrxpg/mL), and the geometric value for AUC was 77.2 (CV=55%) (hrxpg/ml).

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

Distribution:

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 pregnancy.

Metabolism:

In vitro human liver microsome metabolism of desmopressin has shown that no significant amount is metabolised in the liver, and thus human liver metabolism *in vivo* is not likely to occur. Furthermore, no *in vitro* inhibition of human Cytochrome P450 enzymes could be demonstrated. Desmopressin did not show any effect on any of the nine Cytochrome P450 subtypes. *In vivo* drug-drug interactions based on activation or inhibition of Cytochrome P450 are therefore very unlikely.

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 reported for vasopressin.

Special Populations and Conditions

The pharmacokenitics of desmopressin acetate in the nocturia population do not differ from those in healthy subjects. A pooled data analysis demonstrated no significant correlation between age and pharmacokinetics, and no gender-related difference in AUC_{inf} could be found. In very elderly patients, a decrease in the renal elimination of desmopressin could be expected. A study of pharmacokinetics of desmopressin in patients with decreased renal function showed no effect of elevated creatinine.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

Minirin® Tablets (desmopressin acetate) are available as white uncoated tablets containing 0.1 mg or 0.2 mg of desmopressin acetate, supplied in bottles of 7, 30 or 100 tablets.

STORAGE AND STABILITY

Store between 15ºC and 25ºC in a dry place.

Keep the container tightly closed.

Keep in a safe place out of reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

No special requirement

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

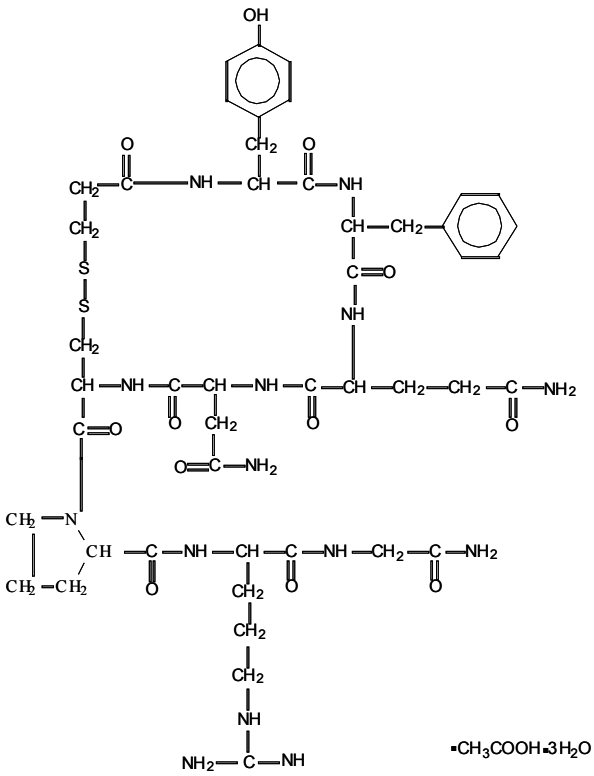
DRUG SUBSTANCE

Proprietary Name: Desmopressin Acetate

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

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

Structural Formula:



Molecular Formula and Molecular Mass: $C_{48}H_{74}N_{14}O_{17}S_2$
(acetate trihydrate)
MW = 1183.2

$C_{46}H_{64}N_{14}O_{12}S_2$ (free base)
MW = 1069.2

Physiochemical Properties:

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

CLINICAL TRIALS

Study demographics and trial design

Summary of patient demographics for clinical trials in the treatment of Nocturia

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (range)	Gender
Male Study	Randomised, Double-blind, Placebo-Controlled, Parallel Group study	Desmopressin acetate, 0.1, 0.2 or 0.4 mg, placebo, oral. Dose-titration 1-3 weeks Double-blind phase 3 weeks	224	66 (24-88 yrs)	Male
Female Study	Randomised, Double-blind, Placebo-Controlled, Parallel Group study	Desmopressin acetate, 0.1, 0.2 or 0.4 mg, placebo, oral. Dose-titration 1-3 weeks Double-blind phase 3 weeks.	224	57 (21-89 yrs)	Female

Two Phase three pivotal studies have been conducted to investigate desmopressin acetate in the treatment of Nocturia, in comparison with placebo, in all-male and all-female populations of Nocturia sufferers. The studies were designed to identify the most effective dose regimen, as well as establishing criteria for selecting those patients most likely to respond safely to the treatment.

The studies took into consideration the known polyuric nature of Nocturia and the current standard of Good Clinical Practice. Patients were titrated to their optimal dose based on their nocturnal diuresis response.

The primary efficacy endpoint was clinical response, defined as a reduction in the number of nocturnal voids by at least 50%. Thirty-four percent (34%) of male and 46% of female desmopressin-treated patients showed a response compared with placebo 3% and 7%, respectively (Tables 1 and 2). The majority of patients (93% and 88%) showing a response in the double-blind period also showed a response in the dose-titration phase.

Study results

Table 1 Clinical Response (ITT Population- Male Study)

	Response		No Response		ITT Population
	N	(%)	N	(%)	
Treatment group					
Placebo	*2*	*(3)*	*61*	*(97)*	*63*
Desmopressin	*28*	*(34)*	*55*	*(66)*	*83*
Analysis results	*Common OR*		*95% CI*		*P-Value*
CMH test	*20.5*		*(4.0; 105.2)*		*< .0001*
Homogeneity test, asympt.	*-*		*-*		*0.8993*
Homogeneity test, exact	*-*		*-*		*1.0000*

Response = at least 50% reduction from baseline in number of nocturnal voids per night.

OR = Odds ratio
CI = Confidence interval
CMH = Cochran-Mantel-Haenszel test controlling for 5 countries

Table 2 Clinical Response (ITT Population- Female Study)

	Response		*No Response*		*ITT Population*
	N	*(%)*	*N*	*(%)*	
Treatment group					
Placebo	*5*	*(7)*	*65*	*(93)*	*70*
Desmopressin	*33*	*(46)*	*39*	*(54)*	*72*
Analysis results	*Common OR*		*95% CI*		*P-Value*
CMH test	*13.4*		*(4.6;39.2)*		*< .0001*
Homogeneity test, asympt.	*-*		*-*		*0.7999*
Homogeneity test, exact	*-*		*-*		*0.6174*

Response = at least 50% reduction from baseline in number of nocturnal voids per night.
OR = Odds ratio
CI = Confidence interval
CMH = Cochran-Mantel-Haenszel test controlling for 5 countries

Desmopressin treatment was associated with an increase in first sleep duration of 108 minutes compared to 25 minutes for placebo in the male study group and 130 minutes compared to 37 minutes in the female study group (Table 3). In the male study 29 of the 83 (35%) desmopressin patients experienced more than 5 hours of sleep before waking to void, compared to two of the 63 (2%) placebo patients. In the female study, the comparable numbers were 24 of the 72 (33%) desmopressin patients and 70 (6%) placebo patients.

Table 3: Analysis of duration of first sleep period (min)

	Male study		*Female study*	
	Desmopressin	*Placebo*	*Desmopressin*	*Placebo*
ITT population	*83*	*63*	*72*	*70*
Screening *N* *Mean (SD)*	 *83* *161 (51)*	 *63* *149 (54)*	 *72* *142 (49)*	 *70* *144 (53)*
Double Blind *N* *Mean (SD)*	 *83* *269 (89)*	 *63* *175 (64)*	 *72* *272 (103)*	 *70* *181 (75)*
Change (absolute)	*108 (88)*	*25 (61)*	*130 (102)*	*37 (74)*

Analysis of Change Male study- Desmopressin-Placebo Mean: 82.73 P- value (< 0.0001)
Analysis of Change Female study- Desmopressin-Placebo Mean: 93.73 P- value (< 0.0001)

TOXICOLOGY

(i) Acute Toxicity

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

Acute Toxicity of Desmopressin Acetate

Species	**Number**	**LD_{50} Dose**	**Route**
Mice	10, both sexes	2 mg/kg	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 haematological and clinical chemistry parameters. Post-mortem examinations did not reveal any abnormalities.

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

(iii) Chronic Toxicity

Subcutaneous Administration - Rat Studies

In a controlled 8-week experiment, 20 rats received 2 μg/kg/day desmopressin acetate subcutaneously. No increase in blood glucose nor morphological or histological pancreatic changes occurred.

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

Dog Studies

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

Oral Administration

Rat Studies

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

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

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

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

Dog Studies

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

Subcutaneous Administration- Rat Studies

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

Rabbit Studies

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

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PART III: CONSUMER INFORMATION

Minirin® Tablets

(desmopressin acetate)

Information for the Patient: Please read this information carefully.

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

Pharmacist: Dispense with enclosed package insert.

ABOUT THIS MEDICATION

What the medication is used for?

What is Minirin® Tablets?

Minirin® Tablets is a drug that is prescribed for people who have to wake and get up in the night to urinate (pee). This condition is called *Nocturia*.

Minirin® Tablets (pills) help to reduce the amount of urine that the body makes at night. The bladder (where urine is stored in the body) does not fill as quickly, so a person taking Minirin® does not need to get up so often.

Who gets Nocturia?

You are not alone. *Nocturia* is a common medical condition that affects both men and women. A person may have *Nocturia* at any age, but older people tend to have it more often.

People with *Nocturia* may wake up one or more times in a night to urinate (pee). *Nocturia* may wake a person every night or only a few times a week.

What causes Nocturia?

People get *Nocturia* because their bodies do not produce enough of a natural chemical called *vasopressin*. Or they may produce enough *vasopressin* but their bodies do not react to it.

What it does:

How does Minirin® Tablets Work?

Minirin® Tablets replaces or adds to the naturally occurring chemical that your body needs to regulate the amount of urine it produces at night.

When it should not be used:

Who Should Not Take Minirin® Tablets?

There are people who should not take Minirin® tablets. Tell your doctor or pharmacist if you have:

- Hyponatraemia (low blood sodium levels)
- Diarrhoea
- Any heart, liver or kidney problems
- Bleeding problems
- Constant thirst
- 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 does Minirin® Tablets contain?

What the medicinal ingredient is:

This medicine contains an active drug called desmopressin acetate. If you know you have an allergy or sensitivity to desmopressin acetate, call your doctor before using this medicine.

What the important nonmedicinal ingredients are:

Minirin® Tablets also contains some other ingredients called lactose, potato starch, povidone and magnesium stearate. If you know you have an allergy or sensitivity to any of these ingredients, call your doctor before using this medicine.

What dosage forms it comes in:

MInirin® Tablets, 0.1 mg tablets are white oval tablets that are marked with "0.1" on one side. Minirin® Tablets, 0.2 mg tablets are also white round tablets that are marked with "0.2" on one side.

WARNING AND PRECAUTIONS

BEFORE you use Minirin® 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
- constant thirst
- fever
- any allergies to desmopressin acetate or any of the ingredients listed in "What the important nonmedicinal ingredients are."

Infrequently, high doses of desmopressin have produced temporary headache and nausea. Nasal congestion, flushing and mild abdominal cramps have been reported. These symptoms disappeared with reduction in dosage. Please contact your doctor if you experience any side effects. For Minirin® Tablets to work best it is important to limit the number of drinks of any kind that you have after supper especially one hour before bedtime, until the next morning (at least 8 hours) after taking the medication. It is also important to reduce alcohol and caffeine intake (coffee, tea, caffeinated pop).

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 can 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 you doctor may have to do a blood test.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Minirin® Tablets include:

- 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®)
- Chlorpromazine
- Carbamazepine
- Diuretics (water pills)
- Loperamide or Imodium®
- Clofibrate
- Chlorpropamide
- Demeclocyclin
- Lithium
- Norepinephrine

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

PROPER USE OF THIS MEDICATION

How Many Minirin® Tablets Should I Take?

Usual dose:

Use the chart below or one that has been recommended by your doctor.

	Recommended Amount of Minirin®	What can you expect?
Step 1 To Start For the first 7 nights	Take **1** Minirin® Tablets, **0.1 mg** tablet at bedtime (0.1 mg is lowest dose tablet)	Cut down on alcohol and caffeine after supper. If you **do not** wake up to go to the bathroom, continue to take the same amount of Minirin® Tablets, each night (0.1 mg). You **do not** need to increase the dose. • If you wake up to go to the bathroom during any of these 7 nights, then you should move to **Step 2**.
Step 2 Second Week Nights 8 – 14	Take **1** Minirin® Tablets, **0.2 mg** tablet at bedtime (0.2 mg is higher dose tablet)	• If you **do not** wake up to go to the bathroom continue to take the same amount of Minirin® Tablets each night (0.2 mg). You **do not** need to increase the dose. • If you wake up to go to the bathroom during these 7 nights, then you should move to **Step 3**.
Step 3 Third Week Nights 15-21	Take **2** Minirin® Tablets, **0.2 mg** Tablets at bedtime	• If you still wake up to go to the bathroom, then: Make sure you are taking the right tablet and the right numbers of tablets each night before you go to bed. Cut down on the number of drinks of any kind after supper

Please note:

Minirin® 0.1 mg tablets are white oval tablets that are marked with "0.1" on one side.

Minirin® 0.2 mg tablets are white round tablets that are marked with "0.2" on one side.

The maximum recommended dose is 0.4 mg per day.

What Can I do to Help the Medicine Work?

1. Cut down on the number of drinks, of any kind, that you have after supper.

2. Cut down on alcohol and caffeine (coffee, tea, caffeinated pop) after supper.

If you are still waking to go to the bathroom after taking 2 Minirin® Tablets, 0.2 mg tablets for 1 week, tell your doctor.

How Long Should I Take My Minirin® Tablets?
Take your Minirin® Tablets for as long as you and your doctor have decided is best for you.

Overdose

If you take too much?

If you take too much of your medication, you should immediately contact your doctor. Symptoms of overdose may include headache, nausea, vomiting, abdominal cramps, facial flushing, weight gain due to water retention and, in severe cases, convulsions.

Missed dose:

What if I Forget to Take My Tablets?

Do not take any extra pills. Take the same number of tablets as before you forgot. For example, Mary took 1 tablet of 0.2 mg on Monday but she forgot to take a tablet on Tuesday. On Wednesday, Mary should take 1 tablet of 0.2 mg.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

What are the Possible Side Effects of Minirin® Tablets?

As with all medicines, side effects maybe experienced. With Minirin® Tablets, these may include headache, nausea, vomiting, dizziness, dry mouth, diarrhoea, feeling tired, abdominal pain, high blood pressure (headache, blurred vision, dizziness and nausea), insomnia, constipation, swelling in the ankles and joints, and leg 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 any side effects you experience.

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

HOW TO STORE IT

Where should I keep Minirin ® Tablets?

Store your Minirin® Tablets in a dry place between 15 and 25ºC. Keep the container tightly closed. Keep out of the reach of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax: 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, Address Locator: 0701C
Ottawa, Ontario K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

FOR MORE INFORMATION

For more information or help, call a Registered Nurse at **1-800-970-4224** or visit our Website at www.bedwetting.ferring.ca

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