

Desmopressin-PH&T

Desmopressin tablets 0.1mg and 0.2mg

Presentation

Desmopressin-PH&T 0.1mg tablets are round, white, scored tablets, debossed "0.1" on one side. Each tablet contains 0.1mg of desmopressin acetate equivalent to 0.089 mg desmopressin and typically weighs 200mg.

Desmopressin-PH&T 0.2mg tablets are round, white, scored tablets, debossed "0.2" on one side. Each tablet contains 0.2mg of desmopressin acetate equivalent to 0.178mg desmopressin and typically weighs 200mg.

Uses

Actions

Desmopressin is a synthetic analogue of vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. These structural differences with vasopressin result in a significant increase of the anti-diuretic activity, while the vasopressor activity is reduced considerably. The duration of the anti-diuretic activity is extended considerably. After oral administration, duration of the effect of 6 to 14 hours is to be expected.

Clinical trials with desmopressin tablets in the treatment of nocturia showed the following ($p < 0.001$):

- A reduction of not less than 50% in the mean number of nocturnal voids was obtained in 39% of patients with desmopressin compared with 5% of patients with placebo
- The mean number of voids per night decreased by 44% with desmopressin compared with 15% with placebo
- The mean duration of first undisturbed sleep period increased by 64% with desmopressin compared with 20% with placebo
- The mean duration of first undisturbed sleep period increased by 2 hours with desmopressin compared with 31 minutes with placebo.

Effect of treatment with individual oral dose of desmopressin between 0.1 and 0.4 mg during 3 weeks compared with placebo (pooled data)

Variable	Desmopressin		Placebo		Statistical significance vs placebo
	Mean baseline value	Mean value during 3 weeks of treatment	Mean baseline value	Mean value during 3 weeks of treatment	
Number of nocturnal voids	2.97 (0.84)	1.68 (0.86)	3.03 (1.10)	2.54 (1.05)	P < 0.0001
Nocturnal diuresis rate (mL per min)	1.51 (0.55)	0.87 (0.34)	1.55 (0.57)	1.44 (0.57)	P < 0.0001
Duration of first undisturbed sleep period (min)	152 (51)	270 (95)	147 (54)	178 (70)	P < 0.0001

8% of the patients interrupted in the desmopressin dose titration phase due to adverse effects and 2% in the subsequent double-blind phase (0.63% on desmopressin and 1.45% on placebo)

Pharmacokinetics

The absolute bioavailability of orally administered desmopressin varies between 0.08% and 0.16% with maximum plasma concentration reached within 2 hours. The distribution volume is 0.2-0.3 L/kg. Desmopressin does not cross the blood-brain barrier. The oral terminal half-life varies between 2.0 and 3.21 hours. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. After oral administration of a single dose of 0.4mg desmopressin to healthy subjects, approximately 50% of the subjects had plasma concentrations of desmopressin above 1pg/mL for up to 14 hours post dosing. Concomitant use of food decreases the rate and extent of absorption by 40%.

In *in-vitro* studies in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolised, and thus human liver metabolism *in vivo* is not likely to occur.

Indications

- For the treatment of central diabetes insipidus
- For the treatment of primary nocturnal enuresis in patients (from 5 years of age) with normal ability to concentrate urine.
- For the symptomatic treatment of nocturia in adults, associated with nocturnal polyuria, i.e. nocturnal urine production exceeding bladder capacity.

Dosage and Administration

Central diabetes insipidus

Dosage is individualised in diabetes insipidus but clinical experience indicates that the total daily dose normally lies in the range of 0.2 to 1.2 mg. A suitable starting dose in adults and children is 0.1 mg three times daily. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 0.1 mg to 0.2 mg three times daily. In the event of signs of water retention/hyponatremia, treatment should be interrupted and the dose should be adjusted.

At signs of water retention/hyponatremia, treatment should be interrupted and the dose adjusted.

Primary nocturnal enuresis

The recommended initial dose is 0.2 mg at bedtime. If this dose is not sufficiently effective, the dose may be increased up to 0.4 mg. Fluid restriction should be observed. In the event of signs or symptoms of water retention and/or hyponatremia (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.

The need for continued treatment should be reassessed after 3 months by discontinuing treatment for a period of at least one week.

Nocturia

The recommended initial dose is 0.1 mg at bedtime. If this dose is not effective, the dose may be increased up to 0.2 mg and subsequently 0.4 mg at weekly intervals. Fluid restriction should be observed.

In nocturia patients, a frequency/volume chart should be used to diagnose nocturnal polyuria for at least 2 days before starting treatment. A night-time urine production exceeding the functional bladder capacity or exceeding 1/3 of the 24-hour urine production is regarded as nocturnal polyuria.

Food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin.

The initiation of treatment in the elderly is not recommended. Should physicians decide to initiate desmopressin treatment in these patients, then serum sodium should be measured before beginning the treatment and 3 days after initiation or increase in dosage and at other times during treatment as deemed necessary by the treating physician.

In the event of signs or symptoms of water retention and/or 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.

If adequate clinical effect is not achieved within 4 weeks following appropriate dose titration the medication should be discontinued.

Contraindications

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 mL/kg/24 hours)
- A history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Moderate and severe renal insufficiency (creatinine clearance below 50mL/min)
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion
- Hypersensitivity to desmopressin or to any of the excipients used in the tablets

Warnings and Precautions

When used for primary nocturnal enuresis and nocturia indications, the fluid intake must be limited to a minimum from 1 hour before until the next morning (at least 8 hours) after administration. Treatment without concomitant reduction of fluid intake may lead to water retention and/or hyponatraemia, with or without accompanying warning signs and symptoms (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions).

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

Elderly patients and patients with low serum sodium levels may have an increased risk of hyponatraemia.

Treatment with desmopressin should be interrupted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance e.g. systemic infections, fever, gastroenteritis.

Precautions to avoid hyponatraemia (including careful attention to fluid restriction and more frequent monitoring of serum sodium) must be taken in case of concomitant treatment with medicines, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, cases of concomitant treatment with NSAIDs.

Use during Pregnancy and Lactation

Category B2

Data on a limited number of exposed pregnancies in women with diabetes insipidus, indicate no adverse effects of desmopressin on pregnancy nor on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

While desmopressin can be found in the milk of nursing mothers, results from analyses of milk from nursing mothers receiving high dose desmopressin (300 µg intranasal), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

Effects on ability to drive and use machines

Desmopressin is unlikely to affect the ability to drive or operate machinery.

Adverse Effects

The most serious adverse reaction is hyponatremia which may cause headache, abdominal pain, nausea, vomiting, weight gain, dizziness, confusion, malaise, memory impairment, vertigo, falls and in serious cases, convulsions and coma. Most adults who develop hyponatremia develop low serum sodium after 3 days of dosing. The risk of hyponatremia increases with increasing dose of desmopressin and women are more at risk.

The most common adverse reaction in both adults (12%) and children (1%) is headache. Other common adverse events include hyponatremia, dizziness, confusion, hypertension, oedema, nausea, vomiting, abdominal pain, diarrhoea and constipation. Less common adverse reactions are insomnia, somnolence and asthenia. Psychiatric disorders have been reported less commonly in children – lability affected, aggression, anxiety, mood swings and nightmares. Anaphylactic reactions have not been seen in clinical trials but have been reported.

Interactions

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

NSAIDs may induce water retention/hyponatraemia.

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention/hyponatraemia. Although not investigated, other agents slowing intestinal transport may have the same effect.

It is unlikely that desmopressin will interact with agents affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in *in*

vitro studies with human microsomes. However, formal *in vivo* interaction studies have not been performed.

Concomitant food intake decreases the rate and extent of the absorption of desmopressin tablets by 40%. No significant effect was observed with respect to urine production or osmolality.

Food intake may reduce the intensity and duration of the antidiuretic effect of low oral doses of desmopressin.

Overdosage

Symptoms

Overdose with desmopressin tablets, leads to a prolonged duration of action with an increased risk of water retention and hyponatremia.

Treatment

Although the treatment of hyponatremia should be individualised, the following general recommendations should be followed:

- Discontinue the desmopressin treatment
- Restrict fluid intake
- Treat symptomatically as appropriate.

Pharmaceutical Precautions

Store below 25°C.

Retain desiccant canister in bottle after opening.

Medicines Classification

Prescription Medicine

Package Quantities

Desmopressin-PH&T 100 mcg and 200 mcg tablets are available in HDPE bottles containing 30 or 90 tablets.

Further Information

Tablets also contain maize starch and lactose.

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