MINIRIN NASAL SPRAY
Desmopressin acetate

Presentation
MINIRIN 0.1mg/ml nasal spray solution. 1ml nasal spray solution contains 0.1mg desmopressin acetate equivalent to desmopressin 0.089mg. A clear, colourless solution in an amber glass bottle.

Uses

Actions
Pharmacotherapeutic group: vasopressin and analogues. ATC code: H01B A02. MINIRIN nasal spray solution contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

Pharmacokinetics

Absorption
The bioavailability is about 3-5%. Maximum plasma concentration is reached after approximately one hour.

Distribution
The distribution of desmopressin is best described by a two-compartment distribution model with a volume of distribution during the elimination phase of 0.3-0.5 L/kg.

Biotransformation
The in vivo metabolism of desmopressin has not been studied. In vitro human liver microsome metabolism studies of desmopressin have shown that no significant amount is metabolized in the liver by the cytochrome P450 system, and thus human liver metabolism in vivo by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the PK of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolizing system.

Elimination
The total clearance of desmopressin has been calculated to 7.6 L/hr. The terminal half-life of desmopressin is estimated to 2.8 hours. In healthy subjects the fraction excreted unchanged was 52% (44-60%).

Indications
MINIRIN nasal spray solution is indicated for the treatment of central diabetes insipidus and for establishing renal concentration capacity testing.

MINIRIN nasal spray solution is also indicated for the treatment of primary nocturnal enuresis in patients (from 5 years of age) with normal ability to concentrate urine.
**Dosage and Administration**

1 dose of the spray provides 0.1ml, which corresponds to 10µg desmopressin acetate.

**Central diabetes insipidus**
Dosage is individual after testing, but normal dosage for adults is 10-20µg 1-2 times daily. For children 5-10µg 1-2 times daily. In the event of signs of water retention/hyponatremia treatment should be interrupted and the dose should be adjusted.

**Primary nocturnal enuresis**
A clinically effective dose is individual and may vary from 10 to 40µg administered intranasally. A suitable dose is 20µg intranasally at bedtime. Start at lowest dose. Increase progressively and with caution. Fluid restriction should be observed, (see under **Warnings and Precautions**). In the event of signs of water retention/hyponatremia treatment should be interrupted. Assessment of the necessity of continued treatment should be made after three months during one substance-free week.

**Renal function testing**
To establish renal concentration capacity, the following single doses are recommended:

The normal dose for adults is 40µg.
For children over 1 year 20µg.
For children under 1 year 10µg.

After administration of MINIRIN nasal spray solution any urine collected within one hour is discarded. During the next 8 hours 2 portions of urine are collected for osmolality testing. Fluid restriction should be observed, see under **Warnings and Precautions**.

**Contraindications**
MINIRIN nasal spray solution is contraindicated in cases of:

- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40mL/kg/24 hours)
- syndrome of inappropriate ADH secretion (SIADH)
- known hyponatraemia
- 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)
- hypersensitivity to the active substance or to any of the excipients

**Warnings and Precautions**
Only use nasal spray in patients where orally administered formulations are not feasible.

When MINIRIN nasal spray is prescribed it is recommended:

- to start at the lowest dose
- to ensure compliance with fluid restriction instructions
- to increase dose progressively, with caution
to ensure that in children administration is under adult supervision in order to control the dose intake

In addition for primary nocturnal enuresis:
When used for primary nocturnal enuresis, the fluid intake must be limited to a minimum from 1 hour before until 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.

All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.

In addition for renal concentration capacity testing:
Renal concentration capacity testing in children below the age of 1 year should only be performed in hospital and under careful supervision. When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 litres to quench thirst from 1 hour before until 8 hours after administration.

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

Treatment with desmopressin should be interrupted or carefully adjusted during acute intercurrent illness characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Precautions must be taken in patients at risk of increased intracranial pressure.

Desmopressin should be used with caution in patients with conditions characterised by fluid and/or electrolyte imbalance.

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 suspected to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine, and some antidiabetics of the sulfonylurea group, particularly chlorpropamide, and in case of concomitant treatment with NSAID.

Infants, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia.

There is some evidence from post-marketing data of the occurrence of severe hyponatraemia in association with the nasal spray formulation of desmopressin when it is used in the treatment of central diabetes insipidus.

Due to the presence of benzalkonium chloride this product may cause bronchospasm.

**Use in pregnancy and lactation**

**Pregnancy**
Published data on a limited number (n = 53) of exposed pregnancies in women with diabetes insipidus as well as data on exposed pregnancies in women with bleeding
complications (n = 216) indicate no adverse effects of desmopressin on pregnancy or 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.

Animal reproduction studies have shown no clinically relevant effects on parents and offspring. In vitro analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentrations corresponding to the recommended dose.

Breastfeeding
Results from analyses of milk from nursing mothers receiving high dose desmopressin (300µg 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
MINIRIN nasal spray has no or negligible influence on the ability to drive and use machines.

Adverse Effects

Summary of the safety profile
The most serious adverse reaction with desmopressin is hyponatraemia, which may cause headache, nausea, vomiting, decreased serum sodium, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness and in severe cases convulsions and coma.

The majority of other events are reported as non-serious.

The most commonly reported adverse reactions during treatment were nasal congestion (27%), high body temperature (15%), and rhinitis (12%). Other common adverse reactions were headache (9%), upper respiratory tract infection (9%), gastroenteritis (7%), abdominal pain (5%). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Tabulated summary of adverse reactions
The below table is based on the frequency of adverse drug reactions reported in clinical trials with nasal MINIRIN, conducted in children and adults for treatment of CDI, PNE and RCCT (N = 745), combined with the post marketing experience for all indications. Reactions only seen in post marketing or in other desmopressin formulations have been added in the 'Not known' frequency column.

<table>
<thead>
<tr>
<th>MedDRA Organ Class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Not known</th>
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<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hyponatraemia</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<td>Dehydration***</td>
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<td>Psychiatric disorders</td>
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<td>Insomnia, Affect lability**</td>
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<td>Nightmare**</td>
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<td>Nervousness**</td>
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<td>Aggression**</td>
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<td>Nervous system disorders</td>
<td></td>
<td></td>
<td>Headache*</td>
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<td>Convulsions*</td>
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<td></td>
<td></td>
<td>Coma*</td>
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</table>
### Description of selected adverse reactions

The most serious adverse reaction with desmopressin is hyponatraemia, and in severe cases its complications, i.e. convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect.

**Paediatric population**

The hyponatraemia is reversible and in children it is often seen to occur in relation to changes in daily routines affecting fluid intake and/or perspiration. In children special attention should be paid to the precautions addressed in **Warnings and Precautions**.

**Other special populations**

Infants, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of developing hyponatraemia (see **Warnings and Precautions**).

**Interactions**

Substances, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, as well as some antidiabetics of the sulfonylurea group, particularly chlorpropamide, may cause an additive antidiuretic effect leading to an increased risk of water retention/hyponatraemia.

Indomethacin increases the urine concentrating effect of desmopressin without influencing the duration. The effect is probably without any clinical significance.

NSAIDs may induce water retention/hyponatraemia.

It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in **in vitro** studies with human microsomes. However, formal **in vivo** interaction studies have not been performed.
Overdosage
Overdose of MINIRIN nasal spray solution leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Pharmaceutical Precautions

List of excipients
Sodium Chloride, Citric Acid monohydrate, Disodium Phosphate dihydrate, Benzalkonium Chloride, Purified Water.

Incompatibilities
Not applicable.

Shelf-life
MINIRIN nasal spray is stable for three years when stored unopened at room temperature (max 25°C). After opening, discard after 2 months.

Special precautions for storage
MINIRIN nasal spray solution should be stored at room temperature (up to 25°C).

Instructions for use/handling
Before MINIRIN nasal spray solution is used for the first time, prime the pump by pressing downward 4 times or until an even spray is obtained. If the spray has not been used for a week it is necessary to prime the pump again by pressing it downwards once or until an even spray is obtained.

The patient should blow his/her nose before using the spray.

1. Remove the protection cap.
2. Ensure that the end of the tube inside the bottle is submerged in the liquid.
3. Re-prime the pump if the spray has not been used within the last week.
4. Once it has been primed, the pump delivers one dose each time pressure is applied.
5. The head must be tipped back slightly while inserting the applicator straight into the nostril.
6. When a higher dose is needed, spray alternatively into each nostril.
7. Replace cap after use and store the bottle in an upright position.

The spray bottle should always be stored in an upright position.

If there is any doubt concerning the correct intake of the dose, the spray should not be re-administered until the next scheduled dose.

In young children, administration should be under strict adult supervision to ensure the correct dosage.

Medicine Classification
Prescription Medicine.
**Package Quantities**
Brown Type I glass vial. Fill-volume: 5ml, 6ml.

MINIRIN nasal spray is actuated by a manual dose pump without propellant. The spray pump is designed to deliver 100µl solution (= 10µg desmopressin acetate) per dose.

**Further Information**

**Pre-clinical safety data**
Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No studies of the carcinogenic potential have been performed.

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