MINIRIN®

Nasal spray 10 microg/dose (0.1 mg/ml)

FERRING PHARMACEUTICALS

QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 0.1 mg desmopressin acetate equivalent to 89 µg desmopressin, and 0.1 mg benzalkonium chloride.
Excipients: Benzalkonium chloride (solution), sodium chloride, citric acid monohydrate (E 330), disodium phosphate dihydrate, and purified water.

PHARMACEUTICAL FORM

Nasal spray, solution.

THERAPEUTIC INDICATIONS

Central diabetes insipidus
The use of MINIRIN® in patients with an established diagnosis will result in a reduction in urinary output with concomitant increase in urine osmolality and decrease in plasma osmolality. This will result in decreased urinary frequency and decreased nocturia.

Renal concentrating capacity test
MINIRIN® can be used to test the capacity of the kidneys to concentrate urine; as a diagnostic aid in the examination of the kidney function. This is especially useful in the differential diagnosis between level of urinary tract infections. Cystitis will opposite to pyelonephritis not cause a subnormal ability to concentrate urine.

POSOLOGY AND METHOD OF ADMINISTRATION

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

MINIRIN® nasal formulations should be used only when treatment with oral formulations is inappropriate and always start at the lowest dose (see section Special warnings and precautions for use).

Fluid restriction should be observed (see indication specific instructions in section Special warnings and precautions for use).

If signs of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions) develop, treatment should be discontinued until the patient has recovered completely. Fluid intake should be strictly limited when treatment is reinstated (see section Special warnings and precautions for use).

Indication specific
Central diabetes insipidus:
Dosage is individual but clinical experience has shown that the normal daily dose for adults is 10-20 µg 1-2 times daily and for children 5-10 µg 1-2 times daily.

Renal concentrating capacity test:
Normal adult dose is 40 µg. For children over 12 months the dose is 20 µg. For children under 12 months the dose is 10 µg. After administration of MINIRIN® any urine collected within 1 hour is discarded. During the next 8 hours 2 portions of urine are collected for osmolality testing. Fluid restriction should be observed, see also under Special warnings and precautions for use.

The reference level for normal urine osmolality after MINIRIN® administration is 800 mOsm/kg for most patients. With values under this level, the test should be repeated. A similar low result indicates an impaired ability to concentrate urine and the patient should be referred for further examination into the underlying cause of the malfunction.

Special populations
Elderly: see section Special warnings and precautions for use.
Renal Impairment: see section Contraindications.
Hepatic Impairment: see section Interaction with other medicinal products and other forms of interaction.
Paediatric Population: MINIRIN® is indicated in children with central diabetes insipidus and for testing of renal concentration capacity, see section Special warnings and precautions for use and Undesirable effects.

CONTRAINDICATIONS

MINIRIN® must NOT be used in:
- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40ml/kg/24 hours)
- syndrome of inappropriate ADH secretion (SIADH)
- known hyponatraemia
- 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 substances or to any of the excipients

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

MINIRIN® nasal formulations should be used only when treatment with oral formulations is inappropriate.

When MINIRIN® is prescribed it is recommended to:
- start with the lowest dose
- ensure compliance with fluid restriction instructions
- increase dose progressively, with caution
- ensure that children administration is under adult supervision in order to control the dose intake

MINIRIN® should be used with caution to prevent fluid overload in:
- the treatment of small children and elderly patients
- patients with fluid and/or electrolyte imbalance
- patients with risk of increased intracranial pressure

Without simultaneous reduction in fluid intake, treatment can lead to water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions).

Elderly patients, patients with low plasma sodium levels and patients with high 24-hour urine volumes (above 2.8 to 3 litres) have an increased risk of developing hyponatraemia.

In patients with urgency/urge incontinence, organic causes for increased micturition frequency or nocturia (e.g. benign prostatic hyperplasia, urinary tract infection, bladder stones/tumours), polydipsia or poorly controlled diabetes mellitus, the specific cause of the symptoms should be dealt with primarily.

To prevent hyponatraemia, caution must be exercised and particular attention should be paid to fluid retention and frequent checks made of sodium plasma levels in the following circumstances;
- concomitant treatment with drugs that are known to induce inappropriate ADH secretion syndrome (SIADH), e.g. tricyclic antidepressants, SSRIs, chloropromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group such as chlorpropamide.
- concomitant treatment with NSAID preparations.

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

Experience from clinical use indicates a risk of severe hyponatraemia in association with the nasal formulation of desmopressin, when it is used in the treatment of central diabetes insipidus.

MINIRIN® 0.1mg/ml nasal spray may cause bronchospasm due to the presence of benzalkonium chloride in this product.

At testing of renal concentration capacity
When used diagnostically, fluid intake should be restricted to a maximum of 0.5 L to satisfy thirst for 1 hour before administration until 8 hours after administration. Renal concentration capacity testing in children below 1 year of age should only be performed in hospital and under careful supervision.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Substances that are known to induce inappropriate ADH secretion, e.g. tricyclic antidepressants, SSRIs, chloropromazine and carbamazepine as well as some antidiabetics of the sulfonylurea group such as chlorpropamide may cause an additive antidiuretic effect with an increased risk of fluid retention, see section Special warnings and precautions for use.

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

NSAID preparations may induce water retention/hyponatraemia, see section Special warnings and precautions for use.

It is unlikely that desmopressin interacts with pharmaceuticals affecting hepatic metabolism, since desmopressin has not been shown to undergo any significant liver metabolism in *in vitro* studies with human microsomes. However, formal interaction studies *in vivo* have not been performed.

PREGNANCY AND LACTATION

Fertility
Fertility studies have not been carried out.

Pregnancy
In vitro analysis of human cotyledon models have shown that there is no transplacental transport of desmopressin when administered at therapeutic concentrations corresponding to recommended doses.

Published data on a limited number of exposed pregnancies in women with diabetes insipidus (n = 53) 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, embryonic/foetal development, parturition or postnatal development.

Caution should be exercised when administering MINIRIN® to pregnant women.

Lactation
Results from analyses of milk from nursing mothers receiving high doses of desmopressin (300 µg intranasally), indicate that desmopressin is transferred to the breast milk but that the amount of desmopressin that may be transferred to the child is low and probably less than the amounts required to influence diuresis.

Whether desmopressin will accumulate in breast milk upon repeated doses has not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MINIRIN® has no or negligible influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS

Summary of the safety profile
The most serious adverse reaction with desmopressin is hyponatraemia, see below under “Description of selected adverse reactions”.

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 central diabetes insipidus, primary nocturnal enuresis and at testing of renal concentration capacity (N=745) combined with the post marketing experience for all indications. Reactions only reported post-marketing or for other desmopressin formulations have been added in the “Not known” frequency column.

MedDRA Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Not known (cannot be estimated from available data)
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders			Hyponatraemia	Dehydration***
Psychiatric disorders		Insomnia, Affect lability**, Nightmare**, Anxiety**, Aggression**		Confusional state*
Nervous system disorders		Headache*		Convulsions*, Coma *, Dizziness*, Somnolence
Vascular disorders				Hypertension
Respiratory, thoracic and mediastinal disorders	Nasal congestion, Rhinitis,	Nosebleed, Upper respiratory tract infection**		Dyspnoea
Gastrointestinal disorders		Gastroenteritis, Nausea*, Abdominal pain*	Vomiting*	Diarrhoea
Skin and subcutaneous tissue disorders				Pruritus, Rash, Urticaria
Musculoskeletal and connective tissue disorders				Muscle spasms*
General disorders and administration site conditions				Fatigue*, Peripheral oedema*, Chest pain, Chills
Investigations				Weight increased*

*Reported in connection with hyponatraemia.
** Above all reported in children and adolescents.
*** Reported for central diabetes insipidus indication.

Description of selected adverse reactions
The most serious adverse reaction with desmopressin is hyponatraemia, which may give symptoms like headache, nausea, vomiting, weight increase, malaise, abdominal pain, muscle spasms, dizziness, confusion, decreased consciousness and in serious cases convulsions and coma. The cause of the potential hyponatraemia is the anticipated antidiuretic effect.

Paediatric population
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.
Special precautions should be observed in children, see section Special warnings and precautions for use.

Special populations
Elderly patients and patients with low serum sodium levels may have an increased risk of developing hyponatraemia (see section Special warnings and precautions for use).

OVERDOSE
Toxicity
Overdosage leads to prolonged duration of action with an increased risk of fluid retention and hyponatraemia. Even normal doses may cause water intoxication in association with a high fluid intake. Doses exceeding 0.3 µg/kg i.v. and 2.4 µg/kg intranasally have together with fluid intake caused hyponatraemia and convulsions in children and adults.

Symptoms
The same symptoms as for water intoxication. Headache, nausea. Fluid retention, hyponatraemia, hypoosmolality, oliguria, CNS depression, convulsions, pulmonary oedema. See also section Undesirable effects.

Treatment
The treatment of hyponatraemia must be tailored to the individual, but the following general recommendations may be given.

Hyponatraemia is treated by discontinuing the desmopressin treatment and restricting fluids. If the patient has symptoms, an infusion of isotonic or hypertonic sodium chloride may be given. When the fluid retention is serious (convulsions and loss of consciousness), treat with furosemide.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: vasopressin and analogues.
ATC code: H01B A02.

MINIRIN® contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in that the amino group in cysteine has been removed and L-arginine has been substituted by D-arginine. This results in a considerably longer duration of action with intranasal administration and a complete lack of pressor effect in the dosages used clinically.

PHARMACOKINETIC PROPERTIES
Absorption: Bioavailability is approx. 3-5%. The maximum plasma concentration is reached after approx. one hour and does not increase in proportion to the administered dose. One intranasal dose of 10-20 µg produces an antidiuretic effect for 8-12 hours.

Distribution: The distribution volume during the elimination phase is 38 L. Desmopressin does not cross the blood-brain barrier.

Metabolism: In vitro studies with human liver microsomes have shown that an insignificant amount of desmopressin is metabolised in the liver microsomes. It is therefore unlikely that desmopressin is metabolised in the liver in humans. Desmopressin does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 *in vitro* and thus should desmopressin not affect the pharmacokinetics of other drugs metabolized by CYP enzymes.

Elimination: The total clearance of desmopressin has been calculated to 7.6 L/h. The half-life for desmopressin in the elimination phase is 2.8 hours in average. In healthy subjects the fraction excreted unchanged in urine is 52%.

INCOMPATIBILITIES
Not applicable.

SHELF LIFE
3 years.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 25°C at room temperature.

NATURE AND CONTENTS OF CONTAINER
MINIRIN® nasal spray is propelled by a manual dose pump without propellant gas. The spray pump is constructed to administer 100 µl solution (= 10 µg desmopressin acetate) per spray dose.

Pack size: 1 x 2.5 ml; 1 x 5 ml; 10 x 2.5 ml; 10 x 5 ml
Not all pack sizes may be marketed.

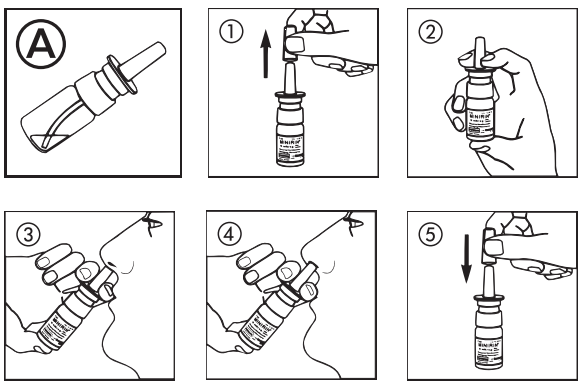
LEGAL CATEGORY
Prescription only medicine

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING
Before MINIRIN® nasal spray is used for the first time, the pump should be primed by pressing it downwards 4 times, or until an even spray is obtained. If the spray has not been used during the previous week, the pump must be primed again by pressing once or until an even spray is obtained.

IMPORTANT! The lower end of the tube must always be submerged in the liquid when you use the spray (see figure A).

At the least hesitation whether correct dose is administered, no further spray dose should be given until the next time for administration. In small children the administration should be monitored by an adult to ensure correct dosing.

Instructions for use:
1. Remove the protective cap.
2. Hold the bottle according to the figure.
3. Tilt your head slightly backwards. Insert the nasal applicator into one nostril according as shown in figure 3. Hold your breath and spray once.
4. If you are prescribed more than one dose, repeat the administration in the other nostril. For every further dose, change nostrils and repeat according to instructions.
5. Replace the protective cap. Always store the bottle upright.



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