

NEW ZEALAND DATA SHEET

MINIRIN 0.1mg/mL Nasal Drops

Desmopressin acetate

1 PRODUCT NAME

MINIRIN 0.1mg/mL nasal drops

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1mL contains 0.1mg desmopressin acetate which corresponds to 0.089mg desmopressin per mL.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal drops are a clear, colourless solution in an amber glass bottle.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

4.2 Dose and method of administration

The 0.025mL mark corresponds to a 2.5 microgram dose, the 0.05mL mark to a 5 microgram dose, the 0.1mL mark to a 10 microgram dose, the 0.15mL mark to a 15 microgram dose, and the 0.2mL mark to a 20 microgram dose.

Central diabetes insipidus

Dosage is individual after testing, but normal dosage for adults is 10-20 micrograms 1-2 times daily. For children 5-10 micrograms 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 40 micrograms administered intranasally. A suitable dose is 20 micrograms intranasally at bedtime. Start at lowest dose. Increase dose progressively and with caution. Fluid restriction should be observed, please see Section 4.4. 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:

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The normal dose for adults is 40 micrograms.

For children over 1 year 20 micrograms.

For children under 1 year 10 micrograms.

After administration of MINIRIN nasal drops 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 Section 4.4.

4.3 Contraindications

MINIRIN nasal drops are contraindicated in cases of:

- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 mL/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 50 mL/min)
- hypersensitivity to the active ingredient or to any of the excipients

4.4 Special warnings and precautions for use

Only use nasal solution in patients where orally administered formulations are not feasible.

When MINIRIN nasal drop solutions are 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 purpose. 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.

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Infants, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia. 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 and carbamazepine, and some antidiabetics of the sulfonylurea group, particularly chlorpropamide, and in case of concomitant treatment with NSAID.

4.5 Interaction with other medicines and other forms of interaction

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.

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.

4.6 Fertility, 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

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Results from analyses of milk from nursing mothers receiving a high dose of desmopressin (300 micrograms intranasally), indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

4.7 Effects on ability to drive and use machines

MINIRIN nasal drops have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable 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.

MedDRA Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to ≤ 1/100)	Not known
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders			Hyponatraemia	Dehydration***
Psychiatric disorders		Insomnia, Affect lability** Nightmare** Nervousness** Aggression**		Confusional state*
Nervous system disorders		Headache*		Convulsions* Coma* Dizziness* Somnolence
Vascular disorders				Hypertension
Respiratory, thoracic and mediastinal disorders	Nasal congestion Rhinitis	Epistaxis Upper respiratory tract infection**		Dyspnoea
Gastrointestinal disorders		Gastroenteritis Nausea* Abdominal pain*	Vomiting*	Diarrhoea
Skin and subcutaneous tissue disorders				Pruritus Rash Urticaria

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Musculoskeletal and connective tissue disorders				Muscle spasms*
General disorders and administration site conditions				Fatigue* Peripheral oedema* Chest pain Chills
Investigations	Body temperature increased**			Weight increased*

* Reported in connection with hyponatraemia

** Reported primarily in children and adolescents

*** Reported in the CDI indication

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 Section 4.4.

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 Section 4.4).

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Overdose of MINIRIN nasal drops solution leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues

ATC code: H01B A02

MINIRIN nasal drops 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.

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5.2 Pharmacokinetic properties

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%).

5.3 Preclinical 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Chlorobutanol hemihydrate

Sodium Chloride

Hydrochloric Acid

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years. After opening, discard after 2 months.

6.4 Special precautions for storage

MINIRIN nasal drops solution should be stored at 2°C-8°C.

6.5 Nature and contents of container

Brown Type I glass vial, fitted with a dropper set + 2 rhinyle tubes (volume marks are indicated on the rhinyle tube from 0.025 to 0.20mL printed in black). Pack size: 2.5mL.

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6.6 Special precautions for disposal and other handling

The preparation is to be administered according to the instructions for use supplied with the package.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL

18 December 1975

10 DATE OF REVISION OF THE TEXT

June 2017

(CCDS 2012/08 Vers 04)

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatted to new SPC format