MINIRIN 4 microgram/mL solution for injection

Desmopressin acetate

1 PRODUCT NAME

MINIRIN solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml MINIRIN solution for injection contains desmopressin acetate 4 micrograms equivalent to desmopressin 3.56 micrograms.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium-free.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MINIRIN injection is indicated for:

- Treatment of central diabetes insipidus and for establishing renal concentration capacity testing.
- Shortening or normalisation of prolonged bleeding time prior to an invasive therapeutic or diagnostic operation, or for therapeutic control of bleeding in patients with prolonged bleeding time as a consequence of congenital or substance-induced thrombocyte dysfunction, uremia, cirrhosis of the liver or in patients with prolonged bleeding time of unknown aetiology.
- For the therapeutic control of bleeding and bleeding prophylaxis in connection with minor surgical procedures in patients with mild haemophilia A and von Willebrand's disease who respond positively to a test dose. In exceptional cases, even moderate forms of the disease can be treated. MINIRIN must not be used in patients with von Willebrand's disease type IIB.

4.2 Dose and method of administration

Central diabetes insipidus

The injection may be used when the intranasal administration is considered unsuitable. Individual dosage after testing of the effect on urine osmolality and diuresis at different dose levels. In the event of signs of water retention/hyponatremia treatment should be interrupted and the dose should be adjusted.

Adults: 1-4mcg (0.25-1ml) in 1-2 divided doses (maximum 4mcg per day).

Renal function testing

To establish renal concentration capacity the following single doses are recommended (normal dose by intramuscular or subcutaneous injection):

Adults: 4mcg (1ml)

After administration of MINIRIN injection any urine collected within one hour is discarded. During the next 8 hours 2 portions of urine are collected for measurement of osmolality. Fluid restriction should be observed (see section 4.4).

Shortening, normalisation or therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation in patients with prolonged bleeding time

0.3mcg/kg body weight subcutaneously or diluted in physiological saline to 50-100ml and given as an intravenous infusion over 15-30 minutes. If a positive effect is obtained, the initial MINIRIN dose may be repeated 1-2 times with intervals of 12-24 hours. Further repetition of the dose may result in a reduced effect.

In patients with haemophilia A the desired increase of VIII:C is appraised by the same criterion as in the treatment with factor VIII-concentrate. If the MINIRIN infusion does not lead to the desired increase of the concentration of VIII:C in plasma, the treatment may be complemented with administration of factor VIII concentrate. Treatment of haemophilia patients should be conducted in consultation with each patient's coagulation laboratory.

Determination of coagulation factors and bleeding time before MINIRIN treatment. Plasma levels of VIII:C and vWF:Ag increase substantially after desmopressin administration. However, it has not been possible to establish any correlation between the plasma concentration of these factors and the bleeding time, either before or after desmopressin. The effect of desmopressin on the bleeding time should therefore, if possible, be tested in the individual patient.

The bleeding time test should be as standardised as possible, e.g. with the use of Simplate II. Determination of bleeding time and plasma levels of the coagulation factors should be conducted in co-operation or consultation with the Coagulation Laboratories in the country.

Treatment control

The VIII:C concentration must be monitored regularly since in a few cases the effect has been seen to decrease with repeated doses. In connection with administration of MINIRIN solution for injection the patient's blood pressure must be monitored carefully.

Posology for special populations

Renal impairment

MINIRIN injection should be used with caution in patients with moderate and severe renal insufficiency (see section 5.2).

Hepatic impairment

No dose adjustment is needed for patients with hepatic impairment (see section 5.2).

Paediatric population

Treatment of Central Diabetes Insipidus

Children above the age of 1 year: 0.1-1 μg (0.025-0.25 ml) 1-2 times daily.

Children below the age of 1 year: The experience from treatment of children below the age of 1 year is limited. Case reports indicate that 0.05 μg (0.0125 ml) is a suitable initial dose. The dose is then titrated according to the diuresis and electrolyte status of the patient.

Testing renal concentration capacity
For children above the age of 1 year: 1-2 μg (0.25-0.5 ml) as a single dose.
For children below the age of 1 year: 0.4 μg (0.1 ml) as a single dose.
For children it is recommended to use primarily the intranasal formulation for the renal concentration capacity test.
After administration of MINIRIN injection, any urine collected within one hour is discarded. During the next 8 hours two portions of urine are collected for measurement of osmolality. Fluid restriction should be observed, see section 4.4.

Shortening, normalisation or therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation
See adults

Method of administration
The injection is normally administered intravenously but may, if needed, also be given intramuscularly or subcutaneously.

4.3 Contraindications
MINIRIN injection is contraindicated in cases of:

- hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40mL/kg/24hours)
- history of unstable angina pectoris and/or known cardiac insufficiency and other conditions requiring treatment with diuretics
- known hyponatraemia
- syndrome of inappropriate ADH secretion (SIADH)
- von Willebrand's disease type IIB

4.4 Special warnings and precautions for use
Special Warnings

When MINIRIN injection is prescribed, it is recommended to maintain fluid and electrolyte balance. Treatment without concomitant reduction of fluid intake may lead to fluid retention and/or hyponatremia with or without accompanying warning signs and symptoms, see section 4.8.

In addition for renal concentration capacity testing
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. Renal concentration capacity testing in children below the age of 1 year should only be performed in hospital and under careful supervision.

In addition for haemostatic use

Due to risk of development of tachyphylaxis following repeated dosing with desmopressin, alternative haemostatic therapies, other than desmopressin, should be considered in situations where long-term haemostasis is required (active bleeding for more than 2-4 days).

Measures to prevent fluid overload must be taken in patients requiring treatment with diuretic agents.

Special attention must be paid to the risk of water retention/hyponatremia (see section 4.8). The fluid intake should be restricted to the least possible and the body weight should be checked regularly. If there is a gradual increase of the body weight, decrease of serum sodium to below 130mmol/l or plasma osmolality to below 270 mOsm/kg body weight, the fluid intake must be reduced drastically and the administration of MINIRIN interrupted.

MINIRIN injection does not reduce prolonged bleeding time thrombocytopenia.

Due to post-marketing reports of acute myocardial infarction and ischaemic stroke in relation to MINIRIN injections used for the haematological indications, considerations should be taken before using MINIRIN injection in elderly patients and in patients with risk factors for or a history of thrombosis, cardiovascular disease, atherosclerotic cerebrovascular disease or angioplasty.

Precautions:

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment for central diabetes insipidus.

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

Infants, elderly and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia. Treatment with MINIRIN injection should be interrupted or carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis) as well as in excessive bleeding, and the fluid and electrolyte balance should be carefully monitored.

Special attention should be given when desmopressin is co-administered with other drugs affecting water and/or sodium homeostasis (see section 4.5). In patients with chronic therapy with drug(s) affecting water and/or sodium homeostasis, MINIRIN injection should be administered after confirmation of normal baseline sodium.

Precautions must be taken in patients with moderate and severe renal insufficiency *(creatinine clearance below 50 ml/min)*.

MINIRIN injection should not be used in patients with hypersensitivity to desmopressin or to any of the excipients in the product (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Special attention should be given when desmopressin is co-administered with other drugs affecting water and/or sodium homeostasis, e.g. opioids, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs), chlorpromazine, carbamazepine and some antidiabetics of the sulfonylurea group since concurrent use can lead to an increased risk of fluid retention/hyponatraemia (see section 4.4).

It is unlikely that MINIRIN injection will interact with drugs affecting hepatic metabolism, since MINIRIN injection 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 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 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 has shown that there is no transplacental transport of desmopressin when administered at therapeutic concentration corresponding to recommended dose.

Breastfeeding

Results from analyses of milk from nursing mothers receiving high dose 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. Therefore it is not considered necessary to stop breastfeeding.

Fertility

Studies with desmopressin in animals have shown no impairment of fertility in male and female rats.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reaction with MINIRIN injection during post-marketing is hyponatraemia. Hyponatraemia may cause headache, nausea, vomiting, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness, generalized oedemas, and in severe cases brain oedema, convulsions, and coma (see section 4.4).

Rare cases of serious hypersensitivity reactions including anaphylactic/anaphylactoid shock and reaction have been reported in association with MINIRIN injection (see section 4.4).

Tabulated list of adverse reactions

The below table is based on the frequency of adverse drug reactions reported in clinical trials with MINIRIN injection conducted in adults for treatment of central diabetes insipidus and haematological indications (n=53) and OCTOSTIM injections (n=76), combined with the post marketing experience for MINIRIN/OCTOSTIM injections. Reactions only seen in post marketing have been added in the 'Not

known' frequency column. The table below shows the frequencies of adverse reactions reported. Adverse reactions are classified according to frequency and system organ class. Frequency categories are defined according to the following convention: Common (≥1/100 to < 1/10); Uncommon (≥1/1,000 to < 1/100); Rare (≥1/10,000 to < 1/1,000); Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

Table 1. Frequency of adverse drug reactions reported (clinical trials, spontaneous reports including the literature)

MedDRA Organ Class	Common (≥ 1/100 to < 1/10)	Rare (1/1000)	Very rare (< 1/10,000)	Not known[3]
Immune system disorders				Hypersensitivity, Anaphylactic reaction Anaphylactoid reaction
Metabolism and nutrition disorders			Hyponatraemia	
Nervous system disorders	Headache	Dizziness		Ischaemic stroke[1]
Cardiac disorders	Tachycardia[2]			Acute Myocardial infarction[1]
Vascular disorders	Flushing[2] Hypotension[2]			
Gastrointestinal disorders	Nausea Abdominal pain			
General disorders and administration site conditions	Fatigue			

1. Only for the haematological indications (high dose) and only in patients with known history of, or risk factors for, thrombosis, atherosclerotic cardiovascular/cerebrovascular disease, or a history of angioplasty.
2. At high doses, transient fall in blood pressure with a reflex tachycardia and facial flushing at the time of administration.
3. ADRs from spontaneous reports (frequency not known). The ADRs have been derived from post-marketing experience with Minirin/Octostim via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Description of selected adverse reactions

During post-marketing the most frequently reported adverse reaction with MINIRIN/OCTOSTIM is hyponatraemia. Hyponatraemia may cause headache, nausea, vomiting, , weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusional state, decreased consciousness, generalized oedemas , and in severe cases brain oedema, , convulsions, and coma. Nausea, headache and dizziness have been reported without registered hyponatraemia. The hyponatraemia is a result of the antidiuretic effect, arising from increased water reabsorption by the renal tubules and osmotic dilution of plasma. Special attention should be paid to the precautions addressed in section 4.4.

Hyponatraemia is reversible. Treatment should be individualised and rapid overcorrection should be avoided to reduce the risk of further complications (see sections 4.2 and 4.4)

Post-marketing hypersensitivity reactions including local allergic reactions such as dyspnoea, erythema, generalized or local oedemas (peripheral, face), pruritus, rash, and urticaria, have been reported in association with MINIRIN/OCTOSTIM injection. More serious hypersensitivity reactions including anaphylactic shock and reaction, and anaphylactoid shock and reaction have also been reported in association with MINIRIN/OCTOSTIM injection. Hypersensitivity reactions usually occur rapidly after drug administration and may occur during first time usage or after repeated exposure of MINIRIN/OCTOSTIM injection.

Paediatric population
Adverse reaction data from clinical trials in children is very limited.

Other special populations
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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose
Overdose of MINIRIN injectionleads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment
The treatment of hyponatraemia should be individualised and can include discontinuation of MINIRIN treatment, fluid restriction and symptomatic treatment.

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 solution for injection contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the deamination 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.

Desmopressin at high dosage, 0.3mcg/kg body weight intravenously, leads to a two- to four-fold increase in plasma of factor VIII coagulant activity (VIII:C). Also the content of von Willebrand factor-antigen (vWF:Ag) increases, but to a lesser extent. At the same time there is a release of the plasminogen activator (t-PA).

Administration of desmopressin at a high dosage has also been shown to lead to a shortening or normalisation of the bleeding time in patients with prolonged bleeding time as in uremia, liver cirrhosis, congenital or drug-induced thrombocyte dysfunction and in patients with prolonged bleeding time of unknown aetiology.

By administration of desmopressin instead of factor VIII concentrates, the risk of transmission of HIV-infection and hepatitis virus is avoided.

5.2 Pharmacokinetic properties
Absorption

The bioavailability following subcutaneous injection compared with intravenous administration is about 85%. Maximal plasma concentration after 0.3 micrograms/kg given as a subcutaneous injection is achieved after approximately 60 minutes and it amounts to 600 pg/ml in average.

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. In healthy subjects the fraction excreted unchanged was 52% (44-60%). Plasma half life varies between 3 and 4 hours. The duration of the haemostatic effect depends of the half-life for VIII:C which is about 8-12 hours.

Characteristics in specific groups of patients

Renal Impairment:
Precautions must be taken in patients with moderate and severe renal insufficiency.

Hepatic impairment:
No studies have been performed in this population.
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.

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
MINIRIN 4 microgram/ml solution for injection in 1 ml ampoule:
Sodium chloride, hydrochloric acid, water for injection.

6.2 Incompatibilities
This medicinal products must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
4 years.

6.4 Special precautions for storage

MINIRIN solution for injection should be stored at 2°C-8°C.

6.5 Nature and contents of container

Colourless, Type I glass ampoule. One vial of solution for injection contains 1ml (nominal volume).

Pack size: 10 x 1ml.

6.6 Special precautions for disposal and other handling

For intravenous infusion the dose should be diluted 50-100ml 0.9% sodium chloride for injection (physiological saline) and given over 15-30 minutes.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

11 April 1980

10 DATE OF REVISION OF THE TEXT

September 2024

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.2 Posology	For shortening, normalisation or therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation in patients with prolonged bleeding time: Tightening of frequency of repeat dosing to increase safety