MINIRIN 4 mcg/mL solution for injection
Desmopressin acetate

1 PRODUCT NAME
MINIRIN solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1ml solution for injection contains desmopressin acetate 4mcg equivalent to desmopressin 3.56mcg
For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
A clear, colourless solution in a glass ampoule with two brown rings and a blue cut point

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
MINIRIN solution for injection is indicated as follows:
- 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 etiology.
- 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).
Children above the age of 1 year: 0.1-1mcg (0.025-0.25ml) 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 0.05mcg (0.0125ml), is a suitable initial dose. The dose is then titrated according to the diuresis and electrolyte status of the patient.
The injection is normally administered intravenously but may, if needed, also be given intramuscularly or subcutaneously.

Renal function testing
To establish renal concentration capacity the following single doses are recommended (normal dose by intramuscular or subcutaneous injection):
Adults: 4mcg (1ml)
For children above the age of 1 year: 1-2mcg (0.25-0.5ml).
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For children below the age of 1 year: 0.4mcg (0.1ml).

For children it is recommended to use primarily the intranasal presentation for the renal concentration capacity test.

After administration of MINIRIN solution for 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 under 4.4 Special Warnings and Precautions).

**Therapeutic control of bleeding or bleeding prophylaxis prior to an invasive operation**

0.3mcg/kg body weight 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 6-12 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.

### 4.3 Contraindications

MINIRIN solution for injection is contraindicated in cases of:

In general:
- 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
- von Willebrand’s disease type IIB
4.4 Special warnings and precautions for use
For all indications MINIRIN solution for injection should be used with caution in:
- very young and elderly patients
- conditions characterised by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure

*In addition for renal concentration capacity testing*
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*
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. The fluid intake should be restricted to the least possible and the body weight should be checked regularly. Should there be 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 does not reduce prolonged bleeding time thrombocytopenia.

*Precautions:*
Moderate and severe renal insufficiency (creatinine clearance below 50mL/min).

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 drugs, which are suspected to induce SIADH, e.g; tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine and in case of concomitant treatment with NSAIDs.

Treatment with desmopressin should be reassessed during acute illnesses and the fluid and electrolyte balance should be carefully monitored, especially in situations with excessive bleeding.

4.5 Interaction with other medicines and other forms of interaction
Substances which are expected 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 fluid retention/hyponatremia (see 4.4 Special warnings and precautions for use).

NSAIDs may induce fluid retention/hyponatraemia (see 4.4 Special warnings and precautions for use).

4.6 Fertility, pregnancy and lactation

*Pregnancy*
Published data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus 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.

**Breastfeeding**
Results from analyses of milk from nursing mothers receiving high dose desmopressin (300mcg 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**
None.

4.8 **Undesirable effects**
A few per cent of treated patients can be expected to experience side effects such as fatigue, headache, nausea and stomach pain.

**Common (>1/100)**
- **General:** Headache. At high doses: Fatigue.
- **Circulation:** At high doses: Transient fall in blood pressure with a reflex tachycardia and facial flushing at the time of administration.
- **Gastrointestinal:** Abdominal pain, nausea.

**Rare (<1/1000)**
- **General:** At high doses: Dizziness.

**Very rare (<1/10,000)**
- **Metabolism:** Hyponatraemia

Treatment without concomitant reduction of fluid intake may lead to fluid retention/hyponatremia with or without accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain, and in serious cases, convulsions).

**Post marketing experience:**
Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported.

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 solution for injection can lead to water retention and hyponatremia.

Treatment
Although the treatment of hyponatremia should be individualised, the following general recommendations can be given. Discontinue the desmopressin treatment, restrict fluid intake and treat symptoms if needed.

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 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.
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 etiology.
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
The duration of the antidiuretic effect is about 8-12 hours.
Maximal plasma concentration following a dose of 0.3mcg/kg body weight, is reached after approximately 60 minutes and it amounts to 600pg/mL on average. Plasma half-life ranges between 3 and 4 hours. The duration of the haemostatic effect is dependent of the half-life for VIII:C which is about 8-12 hours.

5.3 Preclinical safety data
There were no unusual findings during the examination of the safety profile of desmopressin.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride, hydrochloric acid, water for Injection.

6.2 Incompatibilities
Not applicable.

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 <and special equipment for use, administration or implantation>
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>
The injection is administered by intramuscular or subcutaneous injection or intravenous infusion. 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
Pharmaco (NZ) Ltd
4 Fisher Crescent
Mt Wellington
Auckland 1060
Telephone: 09 377 3336

9 DATE OF FIRST APPROVAL
11 April 1980

10 DATE OF REVISION OF THE TEXT
May 2017

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