## NAME OF THE MEDICINAL PRODUCT
MINIRIN® Injection 4 µg/ml

## QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml MINIRIN® solution for injection contains 4 microgram desmopressin acetate equivalent to 3.56 microgram desmopressin.

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

Full list of excipients: Sodium chloride, hydrochloric acid, water for injection

## PHARMACEUTICAL FORM
Solution for injection.
Clear colourless 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.

Hemophilia A and von Willebrand's disease
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 the 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 II B.

## POSOLOGY AND METHOD OF ADMINISTRATION
### Posology
Central diabetes insipidus
The injection may be used when the intranasal or oral administration is considered unsuitable. Individual dosage is determined after testing of the effect on urine osmolality and diuresis at different dose levels. In the event of signs of water retention/hyponatraemia treatment should be interrupted and the dose should be adjusted.

Normal dosage, intravenous injection:
Adults: 1-4 µg (0.25-1 ml) 1-2 times daily.
Children above the age of 1 year: 0.4-1 µg (0.1-0.25 ml) 1-2 times daily.
Children below the age of 1 year: 0.2-0.4 µg (0.05-0.1 ml) 1-2 times daily.

For patients who have been controlled on intranasal MINIRIN® and who must be switched to the injection form, either because of poor intranasal absorption, or because of the need for surgery, the comparable antidiuretic dose of the injection is about 10% of the intranasal dose.

Renal concentrating capacity test
Normal adult dose by intramuscular or subcutaneous injection is 4 µg (1 ml).
For children above the age of 1 year the dose is 1 to 2 µg (0.25 to 0.5 ml).
For children below the age of 1 year the dose is 0.4 µg (0.1 ml).
For children it is recommended to use primarily the intranasal presentation.

After administration of MINIRIN® injection, any urine collected within 1 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 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 repeated 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.

Haemophilia A and von Willebrand's Disease
MINIRIN® injection is administered as an intravenous infusion at a dose of 0.3 µg/kg bodyweight diluted in sterile physiological saline and infused slowly over 15-30 minutes. In adults and children weighing 10 kg or more, 50 ml of diluent is used; in children weighing 10 kg or less, 10 ml of diluent is used.

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 the desired increase of VIII:C is appraised by the same criterion as in the treatment with factor VIII-concentrate. The VIII:C-concentration must be followed up regularly since in a few cases the effect has been seen to decrease with repeated doses. If the MINIRIN®-infusion does not lead to the desired increase of the VIII:C-concentration in plasma, the treatment may be complemented with a supply of factor VIII-concentrate. The treatment of patients with haemophilia should be conducted in consultation with each patient's coagulation laboratory.

Determination of the coagulation factor 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 standardized 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 cooperation or consultation with a coagulation laboratory.

Posology for special populations
Renal impairment
MINIRIN® injection should be used with caution in patients with moderate and severe renal insufficiency (see section Pharmacokinetic properties).

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.

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

**CONTRAINDICATIONS**
- Hypersensitivity to the active substances or to any of the excipients
- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours)
- A history of unstable angina and/or known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- von Willebrand's disease type IIB

**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 Undesirable effects.

In addition for renal concentration capacity testing:
When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 L 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:
The benefits of desmopressin versus other hemostatic therapies should be carefully assessed in situations where prolonged haemostasis is required including active postoperative bleeding and variceal bleeding in patients with cirrhosis.

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

Special attention must be paid to the risk of fluid retention/hyponatraemia (see section Undesirable effects). 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 130 mmol/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 in thrombocytopenia.

**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 Interaction with other medicinal products and other forms of interaction). 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 Undesirable effects).

Due to post-marketing reports with MINIRIN® injections of deep vein thrombosis, cerebrovascular accident and disorder (stroke), cerebral thrombosis, myocardial infarction, angina pectoris and chest pain, considerations should be taken before using MINIRIN® injection in elderly patients and in patients with risk factors and history of thrombosis, thrombophilia and known cardiovascular disease.

**INTERACTION WITH OTHER MEDICINAL PRODUCTS 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 Special warnings and precautions for use).

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.

**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 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 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 concentration corresponding to recommended dose.

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

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

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
MINIRIN® injection has no or negligible influence on the ability to drive and use machines.

**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, water intoxication, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusion, decreased consciousness, generalized or local oedemas (peripheral, face), and in severe cases brain oedema, hyponatraemic encephalopathy, convulsions, and coma (see section Special warnings and precautions for use).

Rare cases of serious hypersensitivity reactions including anaphylactoid shock and reaction have been reported in association with MINIRIN® injection (see section Special warnings and precautions for use).

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 or in other desmopressin formulations 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 (≥1/10,000 to <1/1,000)** | **Very rare (<1/10,000)** | **Not known[4]** |
|---|---|---|---|---|
| Immune system disorders | | | | Hypersensitivity reactions including anaphylactic reaction and other serious |

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|---|---|---|---|---|
| | | | | allergic conditions |
| Metabolism and nutrition disorders | | | Hyponatraemia | Water intoxication[1]<br>Weight increased[1] |
| Psychiatric disorders | | | | Confusional state[1] |
| Nervous system disorders | Headache[2] | Dizziness[2] | | Coma[1]<br>Loss of consciousness[1,3]<br>Hyponatraemic encephalopathy[1]<br>Brain oedema[1,3]<br>Convulsions[1] |
| Cardiac disorders | Tachycardia | | | Myocardial infarction[3]<br>Angina pectoris[3]<br>Chest pain[3] |
| Vascular disorders | Flushing<br>Hypotension | | | Deep vein thrombosis[3]<br>Cerebrovascular accident and disorder (stroke)[3]<br>Cerebral thrombosis[3]<br>Hypertension[3] |
| Respiratory, thoracic and mediastinal disorders | | | | Dyspnoea<br>Pulmonary embolism[3] |
| Gastrointestinal disorders | Nausea[2]<br>Abdominal pain[1] | | | Vomiting[2] |
| Skin and subcutaneous tissue disorders | | | | Rash maculo-papular<br>Rash erythematous<br>Rash macular<br>Urticaria<br>Erythema<br>Pruritus<br>Rash |
| General disorders and administration site conditions | Fatigue | | | Generalized or local oedemas[2] (peripheral, face)<br>Injection/infusion site reactions including swelling, pain, extravasation, erythema, bruising and nodules<br>Chills[3]<br>Malaise[1] |

[1] Reported with hyponatraemia
[2] Reported with or without hyponatraemia
[3] Reported mainly for the heamatological indications (high dose)
[4] Adverse drug reactions from spontaneous reports (frequency not known). The adverse drug reactions have been derived from post-marketing experience with MINIRIN®/OCTOSTIM® injection 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 categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Description of selected adverse reactions

During post-marketing the most frequently reported adverse reaction with MINIRIN®/OCTOSTIM® injection is hyponatraemia. Hyponatraemia may cause headache, nausea, vomiting, water intoxication, weight increase, malaise, abdominal pain, muscle cramps, dizziness, confusional state, decreased consciousness, generalized or local oedemas (peripheral, face), and in severe

cases brain oedema, hyponatraemic encephalopathy, convulsions, and coma. Nausea, vomiting, 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 Special warnings and precautions for use.

Hyponatraemia is reversible. Treatment should be individualised and rapid overcorrection should be avoided to reduce the risk of further complications (see sections Posology and method of administration and Special warnings and precautions for use).

Post-marketing hypersensitivity reactions including local allergic reactions such as dyspnoea, erythema, generalized or local oedemas (peripheral, face), pruritus, rash, rash macular, rash maculopapular, rash erythematous, skin plaque 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. Allergic reactions usually occur rapidly after drug administration and may occur during first time usage or after repeated exposure of MINIRIN®/OCTOSTIM® injection.

Rare post-marketing cases of deep vein thrombosis, cerebrovascular accident/disorder (stroke), cerebral thrombosis, pulmonary embolism, myocardial infarction, angina pectoris and chest pain have been reported in patients treated with desmopressin. Due to confounding factors and/or missing information, a causal relationship with MINIRIN®/OCTOSTIM® injection has not been established/confirmed.

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 Special warnings and precautions for use).

**OVERDOSE**

Symptoms
Overdose of MINIRIN® injection leads 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.

**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, 0.3 µg/kg body weight intravenously, leads to a two- to fourfold 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.

**PHARMACOKINETIC PROPERTIES**

Absorption

The bioavailability following subcutaneous injection compared with intravenous administration is about 85%. Maximal plasma concentration after 0.3 µg/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%) (12). The half-life for desmopressin after IV dosing is 2.8 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.

**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.

**INCOMPATIBILITIES**
This medicinal products must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling.

**SHELF LIFE**
48 months

**SPECIAL PRECAUTIONS FOR STORAGE**
MINIRIN® injection should be stored at 2-8°C.

**NATURE AND CONTENTS OF CONTAINER**
1 ml colourless, type I glass ampoule.

Pack size: 10 x 1 ml

**SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING**
For intravenous infusion the dose (0.3 µg/kg body weight) should be diluted in 0.9% sodium chloride for injection (physiological saline) and given over 15-30 minutes.

**MANUFACTURER**
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