1. NAME OF THE MEDICINAL PRODUCT

Minirin 2.5 microgram/dose nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 25 microgram desmopressin acetate corresponding to 22.3 microgram desmopressin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Central diabetes insipidus.
Polyuria polydipsia syndrome after removal of the pituitary.
Diagnostic use: Testing of the kidney's capability to concentrate urine.

4.2 Posology and method of administration

Posology

One dose of spray provides 0.1 ml which corresponds to 2.5 microgram desmopressin acetate.
Also refer to section 6.5.

Central diabetes insipidus and polyuria polydipsia syndrome after hypophysectomy:

The dosage is individual in accordance with urine volume and osmolality. Start with a low dose.
Normal dosage:
Adults: 10-20 microgram 1-2 times a day.
Paediatric population: 5-10 microgram 1-2 times a day.

Fluid restriction must be enforced. In the event of signs or symptoms of fluid retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in serious cases convulsions) the treatment should be interrupted until the patient has recovered completely. When treatment is resumed, strict fluid restriction is necessary (see section 4.4).

Diagnostic use for testing of the kidney's capability to concentrate urine:

The following single doses are recommended:
Adults: 40 microgram given as 20 microgram in each nostril.
Paediatric population:
Children over 1 year: 20 microgram.
Children under 1 year: 10 microgram.

After administration of Minirin any urine collected from 0 to 1 hour is discarded. During the next eight hours two portions of urine is collected for osmolality determination. Fluid restriction must be enforced (see section 4.4).

Method of administration

For instructions concerning administration of this medicinal product, see section 6.6.
An instruction for use is also included in the leaflet.

4.3 Contraindications

- Habitual or psychogenic polydipsia (24 hour urine production exceeding 40 ml/kg);
- Known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics;
- Moderate to severe renal insufficiency (creatinine clearance under 50 ml/min);
- Syndrome of inappropriate ADH secretion (SIADH);
- Known hyponatraemia;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and special precautions for use

Minirin nasal spray should only be used by patients in which administration of oral forms is not feasible.

Severe bladder dysfunctions and outlet obstructions should be considered before starting treatment.

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

When used for diagnostic purposes, fluid intake must be limited to 0.5 liter to quench thirst from one hour before to eight hours after administration.

Treatment without concomitant reduction in fluid intake may lead to fluid retention and/or hyponatraemia with or without warning signals and symptoms (headache, nausea/vomiting, weight gain and in serious cases convulsions).

Elderly patients and patients with serum sodium levels in the lower range of normal may have an increased risk of hyponatraemia.

The treatment with desmopressin should be carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalances (such as systemic infections, fever, gastroenteritis).

Desmopressin should be used with caution in patients with conditions characterised by fluid and/or electrolyte imbalance.

Precautions to avoid hyponatraemia, including fluid restriction and frequent monitoring of serum sodium, must be taken in case of:
- concomitant treatment with drugs which are known to induce syndrome of inappropriate ADH secretion (SIADH), e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine;
- concomitant treatment with NSAIDs.

Post-marketing data indicate risk of severe hyponatraemia when patients with central diabetes insipidus are treated with nasal desmopressin formulations.

Paediatric population

When prescribing Minirin nasal spray it is recommended to ensure that children are under adult supervision so that the correct dose is taken.

Small children may have an increased risk for hyponatraemia.

Renal concentration testing of children below 1 year should be performed in hospitals and under careful supervision.

4.5 Interaction with other medicinal products and other forms of interaction

Substances that are known to induce syndrome of inappropriate ADH secretion (SIADH), e.g. tricyclic antidepressant substances, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine may cause an additive antidiuretic effect with an increased risk of fluid retention/hyponatraemia (see section 4.4).

NSAIDs can induce fluid retention/hyponatraemia (see section 4.4).

It is unlikely that desmopressin will interact with medication affecting hepatic metabolism, since desmopressin has not been shown to undergo any significant liver metabolism in *in vitro* studies with human microsomes. However, no formal interaction studies *in vivo* have been carried out.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from use in a limited number (n = 53) of pregnant women with diabetes insipidus as well as data from pregnant 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.

Lactation

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

Desmopressin enters milk from nursing mothers, but any risk for the child is judged to be unlikely at therapeutic doses.

Fertility

Human fertility studies have not been performed. Desmopressin did not impair fertility in male or female rats. *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.

4.7 Effects on ability to drive and use machines

Minirin nasal spray has 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 (3%). Anaphylactic reactions have not been seen in clinical trials, but spontaneous reports have been received.

Tabulated summary of adverse reactions

The data is based on the frequency of adverse drug reactions reported in clinical trials with nasal Minirin formulations given to children and adults for treatment of central diabetes insipidus, primary nocturnal enuresis and renal concentration capacity testing (n=745) combined with the post marketing experience for all indications. Reactions only seen post marketing or with the use of other Minirin formulations have been added in the 'Not known' frequency column.

MedDRA organ class	**Very common (≥1/10)**	**Common (≥1/100 til <1/10)**	**Uncommon (≥1/1000 til <1/100)**	**Not known**
Immune system disprders				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
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 central diabetes insipidus 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 hyponatraemia (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions. This should be done via report form available at the internet page of the Norwegian Medicines Agency: www.legemiddelverket.no/meldeskjema.

4.9 Overdose

In case of overdose, the Norwegian Poison Control (phone: +47 22 59 13 00) should be contacted.

Overdose leads to prolonged duration of action with increased risk of fluid retention and hyponatraemia.

Treatment of hyponatraemia must be individualised, but the following general recommendations may be given:
Hyponatraemia is treated by interrupting the desmopressin treatment and initiate fluid restriction and symptomatic treatment if necessary. If the patient has symptoms, an infusion of isotonic or hypertonic sodium chloride may be given. When the fluid retention is severe (convulsions and loss of consciousness) furosemide treatment should be given.

Toxicity: Even normal doses may in combination with considerable fluid intake cause intoxication. Doses from 0.3 microgram/kg intravenously and 24 microgram/kg intranasally have caused hyponatraemia and convulsions in children and adults. On the other hand, 40 microgram intranasally administered to a five-month-old baby or 80 microgram intranasally administered to a five-year-old gave no symptoms. Four microgram administered parenterally to a newborn caused oliguria and weight gain.

Symptoms: Headache, nausea, fluid retention, hyponatraemia, oliguria, convulsions, lung oedema.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Posterior pituitary lobe hormones (vasopressin and analogues), ATC code: H01B A02

Minirin contains desmopressin, a synthetic structural analogue of the natural posterior pituitary hormone arginine vasopressin. Desmopressin differs from the natural hormone in that the amino group in cysteine has been removed and L-arginine has been substituted by D-arginine. These structural changes result in a considerably longer duration of action and a complete lack of pressor effect at clinically used dosages.

5.2 Pharmacokinetic properties

Absorption

An intranasal dose of 10-20 μg provides antidiuretic effect for 8-12 hours.
Bioavilability is approximately 5-6%. Maximal plasma concentration is reached within 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 pharmacikinetics 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. After intravenous injection 52% (44-60%) of desmopressin can be found in the urine within 24 hours.

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

Sodium chloride
Hydrochloric acid (for pH adjustment)
Chlorobutanol hemihydrate

Water, purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

The product can be stored for up to three weeks below 25°C. Thereafter the product must be discarded.

Opened bottle must be used within two months.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

The spray bottle should always be stored in an upright position.

6.5 Nature and contents of container

Brown glass bottle (type I glass) of 5 ml.

Minirin nasal spray is operated by a manual pump without propellant. The spray pump is designed to deliver 100 microliter solution (= 2.5 microgram desmopressin acetate) per spray dose.

6.6 Special precautions for disposal and other handling

Instructions concerning use

Prior to first time use, the pump must be filled by pressing four times or until an even flow is obtained. If the spray has not been used for the last week, the pump must be filled again by pressing once or until an even spray is obtained.

Instructions for use:

1. Blow the nose before using the spray.
2. Remove the protective cap.
3. Ensure that the lower end of the pump tube is submerged in the liquid.
4. Fill the pump if the spray has not been used within the last week.
5. When filled, the pump delivers one dose each time it is pressed.
6. Tip the head slightly backwards and insert the tip straight into the nostril.
7. If a higher dose is needed, the spraying is repeated in the other nostril. For further doses, alternate between the nostrils.
8. Replace the protective cap after use, and store the spray bottle in an upright position.

If there is any doubt about how large a dose has been taken, one should wait until the time for the next dose before taking further doses.

In small children the administration should be performed under adult supervision in order to ensure that the correct dose has been taken.

7. MARKETING AUTHORISATION HOLDER

Ferring Legemidler AS
Postboks 4445 Nydalen
0403 Oslo
Norway

8. MARKETING AUTHORISATION NUMBER(S)

7672

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 02-Sep-1991
Date of latest renewal: 02-Sep-2006

10. DATE OF REVISION OF THE TEXT

20-Mar-2017