SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Minirin/DDAVP 50mcg/ml nasal spray, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 0.05 mg of desmopressin acetate equivalent to 44.5 mcg desmopressin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal spray, solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Therapeutic use

Pituitary, idiopathic or symptomatic diabetes insipidus; post-surgery polyuria and polydipsia, reversible or permanent.

N.B. Renal diabetes insidipus is not treatable with Minirin/DDAVP.

Diagnostic use

Differential diagnosis of diabetes insipidus.

Testing renal functionality.

4.2 Posology and method of administration

Posology

1 dose of Minirin/DDAVP nasal spray, solution provides 5 mcg of desmopressin acetate hydrate.

The dosage must be individualized case by case.

In post-surgery polyuria and polydipsia, dosage must be adapted in relation to variations of urine osmolality.

Method of administration

Only use Minirin/DDAVP nasal spray, solution in patients where oral formulations are not feasible and always start at the lowest dose (see section 4.4).

Strict fluid restriction must be enforced (see section 4.4).

In the event of signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain, and, in severe cases, convulsions), treatment should be interrupted until the patient has fully recovered. When restarting treatment, strict fluid restriction should be enforced (see section 4.4).

Indication specific
Therapeutic use:
Diabetes insipidus, post-surgery polyuria and polydipsia
Adults
1-2 sprays into each nostril (10-20 mcg) one – two times daily.
Children
From 1 spray in one nostril (5 mcg) one – two times daily to 1 spray in each nostril (10 mcg) one – two times daily.

Diagnostic use:
Differential diagnosis of diabetes insipidus
The diagnostic dose in adults and children is 2 sprays into each nostril (20 mcg).
Inability to elaborate concentrated urine after water deprivation, followed by ability to elaborate concentrated urine after administration of Minirin/DDAVP, confirm a diagnosis of pitituary diabetes insipidus. Inability to concentrate urine after administration of Minirin/DDAVP suggests nefrogen diabetes insipidus.

Test of renal functionality
The following doses are recommended:
Infants (up to 1 year of age)
1 spray into each nostril (10 mcg)
Children (from 1 to 15 years)
2 sprays into each nostril (20 mcg)
Adults
4 sprays into each nostril (40 mcg)
It is recommended to consecutively administer 2 sprays per nostril (20 mcg) and after about 5 minutes the remaining 2 sprays per nostril (20 mcg).
Urine collected within one hour of administering Minirin/DDAVP must be discarded. During the next 8 hours, two portions of urine should be collected for osmolality testing.

In normal infants in the 5 hours after the administration of Minirin/DDAVP a urinary concentration of 600 mOsm/Kg must be obtained.
In children and adults with normal renal function in the 5-9 hours after the administration of Minirin/DDAVP solution for injection, urinary concentration exceeding 700 mOsm/Kg can be expected.
Voiding bladder immediately before administration is recommended.

Special populations
Elderly: see section 4.4
Renal impairment: see section 4.3.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours).

Established or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents.
Syndrome of inappropriate ADH secretion (SIADH).
Known hyponatraemia.
Moderate or severe renal insufficiency (creatinine clearance below 50ml/min).

4.4 Special warnings and precautions for use

Special warnings

Minirin/DDVAP nasal spray, solution should only be used in patients where orally administered formulations are not feasible.

When Minirin/DDVAP nasal spray, solution is prescribed, it is recommended to ensure that administration to children is under adult supervision in order to control the dose intake.

Treatment without concomitant reduction of fluid intake may lead to water retention and/or hyponatraemia with or without accompanying warning signs and symptoms of alarm (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.

For renal function testing:
In case of disgnostic use of Minirin/DDAVP, the fluid intake must be limited and mustn't exceed 0.5 l from 1 hour before until 8 hours after administration.
In infants fluid intake with two meals after administration of Minirin/DDAVP should be decrease of 50% compared to normal intake, to avoid liquid overload.
Renal concentration capacity testing in children below the age of 1 year should only be performed in hospital and under careful supervision.

Precautions

Severe bladder dysfunction and outlet obstruction should be considered before starting treatment.

Infants, elderly and patients with low serum sodium levels may have an increased risk of hyponatraemia. Treatment with desmopressin, should be carefully adjusted during acute intercurrent illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis).

Any alterations of the nasal mucosa caused by scars, edema or other diseases, could give rise to an irregular, unstable absorption of the drug; in this case, the use of the product is not recommended.

The product should be administered with caution to patients suffering from asthma, epilepsy, migraine, heart failure, arterial hypertension, conditions that could worsen due to water retention.

Precautions must be taken in patients suffering of cystic fibrosis and in patients at risk for increased intracranial pressure.

Precautions to avoid hyponatraemia, including restriction in fluid intake and more frequent monitoring of serum sodium, must be taken in case of concomitant treatment with drugs, which are suspected known to induce SIADH, e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine, and carbamazepine, and some antidiabetics of the sulfonylurea group particularly chlorpropamide, and in case of concomitant treatment with NSAIDs.

Some cases of severe hyponatremia associated with the nasal spray formulation of desmopressin when used in the treatment of central diabetes insipidus emerge from post-marketing data.

4.5 Interactions with other medicinal products and other forms of interaction

Indometacin can increase entity but not the duration of the response to desmopressin.
Substances, which are known to induce SIADH, e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine and carbamazepine, clofibrate, 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 (see section 4.4). NSAIDs may induce water retention/hyponatraemia (see section 4.4).
Glibenclamide reduces the antidiuretic effect of desmopressin.
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 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 or 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 excerised when prescribing to pregnant women.

Data on women regarding the transplacental transfer of desmopressin are missing. 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.

Lactation

Results from analyses of milk from nursing mothers receiving a high dose of 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.

Fertility
Fertility studies conducted on animals have not shown clinically relevant effects on parents and offspring.

4.7 Effects on ability to drive and use machines

Minirin/DDAVP nasal spray, solution has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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.
The below table is based on the frequency of adverse drug reactions reported in clinical trials with nasal Minirin/DDAVP, 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 system organ class database	**Very common (≥ 1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥ 1/1.000, <1/100)**	**Not known (cannot be estimated from the available data)**
Immune system disorders				Allergic reaction
Metabolism and Nutrition disorders			Hyponatraemia	Dehydration***
Psychiatric disorders		Insomnia, affect lability**, nightmare**, nervousness**, aggression**		Confusional state
Nervous system		Headache*		Convulsions*,

disorders				coma*, dizziness*, somnolence
Reproductive system and breast disorders			Menstrual uterine spasms	
Cardiac disorders			Cardiac ischemia	
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			Redness of the face	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 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 of suspected adverse reactions.

Reporting suspected adverse reactions after authorization 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 via the national reporting system at the link www.agenziafarmaco.gov.it/it/responsabili.

4.9 Overdose

Overdose of desmopressin leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment:

Although the treatment should be individualized, the following general recommendations can be given:

- Asymptomatic hyponatraemia is treated by discontinuing the desmopressin treatment and fluid restriction.
- Infusion of isotonic or hypertonic sodium chloride may be added in cases of symptomatic hyponatraemia.
- When the fluid retention is severe (convulsions and unconsciousness) treatment with furosemide should be added.

No specific antidote to Minirin/DDAVP is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Vasopressin and analogues, ATC code: H01BA02

Minirin/DDAVP nasal spray, solution contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desaminiation of cysteine[1] and substitution of L-arginine[8] by D-arginine[8].
This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages clinically used.

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 have shown that no significant amount is metabolised in the liver by the cytochrome P450 system, and thus human liver metabolism *in vivo* is unlikely to occur. The effect of desmopressin on the

pharmacokinetic of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450.

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

Sodium chloride, Chlorobutanol, Hydrochloric acid 1M, Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After opening: 2 months.

6.4 Special precautions for storage

Minirin/DDAVP nasal spray, solution must be stored in the refrigerator (+2° and +8°C) in an upright position with a protective cap applied to the nasal dispenser. (between +2° and +8°C).
The product can be stored 4 weeks below 25°C but have to be discarded immediately after.
Minirin/DDAVP nasal spray, solution must always be kept in a dry place, away from heat sources.
The protective cap must always be applied to the nasal dispenser after use.

6.5 Nature and contents of container

Minirin/DDAVP 50 µg/ml nasal spray, solution is packaged in neutral yellow glass bottles, closed with constant automatic dosing pumps. The pumps are equipped with a nasal dispenser, with protective cap.
The 2.5 ml nebulizer bottle delivers 25 self-dosed 5mcg sprays of desmopressin acetate hydrate.

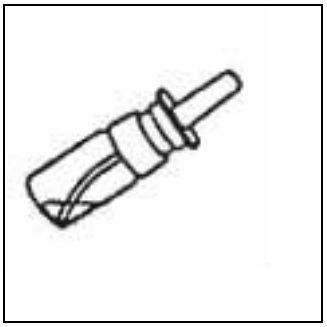
6.6 Special precautions for disposal and other handling

ISTRUCTIONS FOR USE

Before using Minirin/DDAVP nasal spray, solution please read these instructions carefully.

When Minirin/DDAVP nasal spray, solution is used for the first time, to prime the dosing pump it is necessary to deliver 4 sprays to the air, holding the bottle as shown in figure A.
If Minirin/DDAVP nasal spray solution has not been used in the last 7 days, the priming operation must be repeated by holding the bottle as shown in figure A and delivering one or more sprays to the air until the nebulised spray becomes visible.

Figure A



For the use of Minirin/DDAVP nasal spray, solution it is necessary to keep the bottle tilted, so that the end of the tube inside the bottle is below the surface of the solution.

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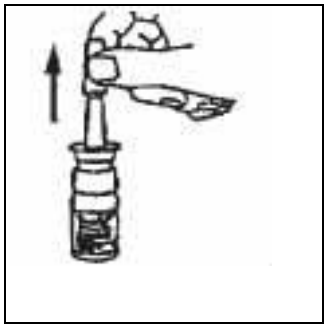
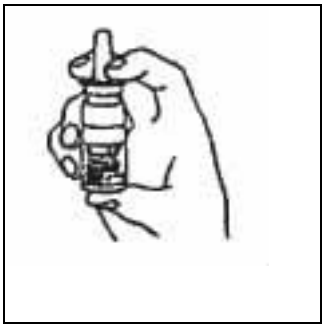
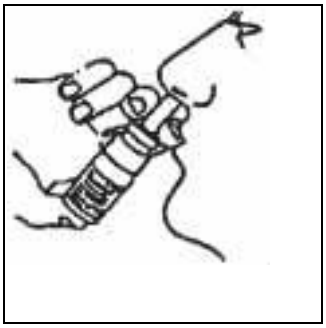


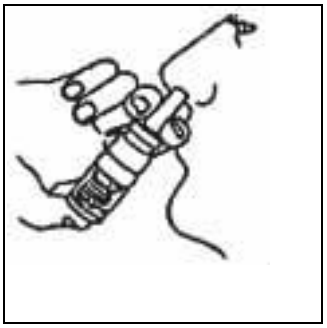
1. Remove the protection cap.



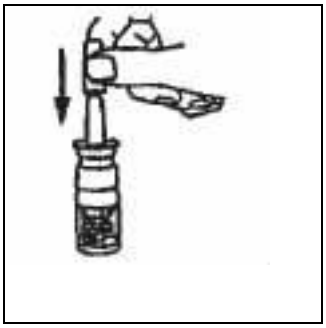
2. Keep the bottle as shown in the figure.



3. The head must be tipped back slightly while inserting the applicator straight into the nostril, as shown in the figure. During administration, hold your breath.



4. In case it is necessary to proceed to more than one dose, spray alternatively into each nostril as indicated indetail in the chapter “dose, method and time of administration”.



5. After use, reapply the protective cap on the nasal dispenser. Always store the bottle of Minirin/DDAVP nasal spray, solutin in an upright position.

If there is any doubt concerning the correct intake of the dose, the spray should not be readministered until the next scheduled dose.
In young children, administration should be under strict adult supervision to ensure the correct dosage.

7. MARKETING AUTHORISATION HOLDER

Ferring S.p.A. - via C. Imbonati, 18 - 20159 Milano

8. MARKETING AUTHORISATION NUMBER

A.I.C. N. 023892033

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

May 2010

10. DATE OF REVISION OF THE TEXT

30 November 2018