Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DDAVP Desmopressin 100 micrograms/ml Nasal drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 100 micrograms desmopressin acetate equivalent to 89 micrograms desmopressin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal drops, solution.
Clear, colourless, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. For the diagnosis and treatment of cranial diabetes insipidus including post-hypophysectomy polyuria/polydipsia.

2. For the measurement of the urine concentration capacity.

4.2 Posology and method of administration

General
The rhinyle tube has a graduated scale corresponding to 2.5 µg, 5 µg, 10 µg, 15 µg and 20 µg desmopressin acetate.

Method of administration: see instruction in sections 6.5 and 6.6.

Fluid restriction should be observed (see indication specific instructions in 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
Treatment of Diabetes Insipidus:
Adults
Dosage is individual. The dose is usually10 to 20 micrograms once or twice daily (equivalent to 0.1ml to 0.2ml once or twice daily).

Children
Dosage is individual. The dose is usually 5 to 10 micrograms once or twice daily (equivalent to 0.05ml to 0.1ml once or twice daily).
A lower dose may be required for infants.

Diagnosis of Diabetes Insipidus:
Adults and children :
A single dose of 20 micrograms (0.2ml).

Renal Function Testing:
To establish renal concentration capacity, the following single doses are recommended:

Adults: 40 micrograms (0.4ml).

Children > 1 year: 20 micrograms (0.2ml).

Children < 1 year: 10 micrograms (0.1ml).

After administration of DDAVP/Desmopressin Nasal drops solution any urine collected within one hour is discarded. During the next 8 hours two portions of urine are collected for osmolality testing.

Special Populations
Elderly: see section 4.4

Renal Impairment: see section 4.3.

Hepatic Impairment: see section 4.5

Paediatric Population: DDAVP/Desmopressin Nasal drops solution is indicated for use in the paediatric population (see section 4.1) Dose recommendations are outlined in section 4.2.

4.3 Contraindications

DDAVP/Desmopressin Nasal drops solution is contraindicated in cases of :

- habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours). Before prescribing DDAVP/Desmopressin Nasal drops solution the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded
- history of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretics
- known hyponatraemia
- syndrome of inappropriate ADH secretion (SIADH)
- moderate and severe renal insufficiency (creatinine clearance below 50ml/min).
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Special warnings
DDAVP/Desmopressin Nasal drops solution should only be used in patients where orally administered formulations are not feasible.

Use of the product should be under specialist supervision with appropriate facilities available for monitoring and interpretation of responses.

When DDAVP/Desmopressin Nasal drops solution is prescribed it is recommended

- to start at the lowest dose
- to ensure compliance with fluid restrictions instructions
- to increase dose progressively, with caution
- to ensure that in children, administration is under adult supervision in order to control the dose intake.

The product should be used with caution in patients with hypertension.

Adjustment of dosage in cases immediately post-hypophysectomy should be controlled on the basis of measurements of urinary osmolality.

Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis.

Patients should be warned to avoid ingesting water while swimming.

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

In addition for renal concentration capacity testing:
When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5L 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.

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

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 known to induce SIADH e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, chlorpromazine, carbamazepine, and some antidiabetics of the sulfonylurea group particularly chlorpropamide, and in case of concomitant treatment with NSAIDs.

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

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

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

There is some evidence from post-marketing data for the occurrence of severe hyponatraemia in association with the nasal spray formulation of desmopressin, when it is used in the treatment of cranial diabetes insipidus.

4.5 Interaction with other medicinal products and other forms of interaction

Substances, which are known to induce SIADH, e.g., tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine and carbamazepine, as well as some antidiabetics of the sulfonylurea group particularly chlorpropamide, may cause an additive antidiuretic effect leading to an increased risk of fluid retention/hyponatraemia (see section 4.4 Special Warnings and Precautions for Use).

NSAIDs may induce fluid retention/hyponatraemia (see section 4.4 Special Warnings and Precautions for Use).

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/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.

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.

Breast-feeding
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.

4.7 Effects on ability to drive and use machines

DDAVP/Desmopressin Nasal drops solution 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 (5%). Anaphylactic reactions have not been seen in clinical trials but spontaneous reports have been received.

Tabulated summary of adverse reactions:
The below table is based on the frequency of adverse drug reactions reported in clinical trials with nasal desmopressin, 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 Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Not known**
Immune system disorders				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 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 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Overdose of DDAVP/Desmopressin Nasal drops solution leads to a prolonged duration of action with an increased risk of water retention and hyponatraemia.

Treatment:
Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given: Interruption of the desmopressin treatment, restrict fluid intake and symptomatic treatment as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues
ATC code: H01B A02

DDAVP/Desmopressin Nasal drops solution contains desmopressin, a structural analogue of the natural pituitary hormone arginine vasopressin. The difference lies in the desaminiation 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.

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 of desmopressin have shown that no significant amount is metabolised 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 metabolising 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. 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 hemihydrate
Hydrochloric acid (for PH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Stored in a refrigerator at 2°C to 8°C.
Do not freeze.
Keep the container in the outer carton.

6.5 Nature and contents of container

Amber, Type 1 (Ph. Eur.) glass vial fitted with a dropper closure and containing 2.5 ml (nominal volume) of a clear, aqueous solution, accompanied with a calibrated plastic tube (rhinyle) for administration. The rhinyle tube has 5 dosing marks: 0.025 ml, 0.050 ml, 0.100 ml, 0.150 ml and 0.200 ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Instructions for use of DDAVP/Desmopressin Nasal drops, solution:

1. Pull plastic tag on neck of bottle.
2. Break security seal and remove plastic cap.
3. Twist off the small knurled seal from the dropper. Use the same seal reversed to prevent subsequent leakage, especially if the bottle is not stored upright.
4. Take the calibrated part of the plastic tube (rhinyle) in one hand and place the fingers of the other hand around the cylindrical part of the dropper. Insert the top of the dropper in a downward position into the end of the rhinyle marked with an arrow and squeeze the end and dropper until the solution has reached the desired mark. If difficulty is experienced in filling the rhinyle, a diabetic or tuberculin syringe may be used to draw up the dose and load the rhinyle.
5. Hold the rhinyle with the fingers approximately ¾ inch from the end and insert it into the nostril until the tips of the fingers reach the nostril.
6. Put the other end of the rhinyle into the mouth. Hold the breath, tilt back the head and then blow with a short strong puff through the rhinyle so that the solution reaches the right place in the nasal cavity. Through this procedure, medication is limited to the nasal cavity and the preparation does not pass down into the back of the throat.
7. If this product is for a child, the dose should be given or supervised by an adult.
8. After use, close the bottle with the plastic cap, wash the rhinyle in water and shake thoroughly, until no more water is left. The rhinyle can then be used for the next application.

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd
United Drug House
Magna Drive
Magna Business Park
Citywest Road
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8 MARKETING AUTHORISATION NUMBER

PA1009/001/001

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Date of last renewal: 25th March 2006

10 DATE OF REVISION OF THE TEXT

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