Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Desmospray, Desmopressin Nasal Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Desmospray contains 10 micrograms of demopressin acetate per actuation (0.1 ml), equivalent to 8.9 micrograms desmopressin.

Excipients:
1ml Desmospray contains 0.1 mg benzalkonium chloride.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, solution.
Clear, colorless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Desmospray is indicated for:

i. The treatment of nocturia associated with multiple sclerosis.
ii. The diagnosis and treatment of vasopressin-sensitive cranial diabetes insipidus.
iii. Establishing renal concentration capacity.

4.2 Posology and method of administration

General

One dose of the spray provides 0.1 ml which corresponds to 10 μg desmopressin acetate.

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

Only use Desmospray in patients where oral formulations are not feasible and always start at the lowest dose (see section 4.4).

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 Nocturia associated with multiple sclerosis
For multiple sclerosis patients up to 65 years of age with normal renal function suffering from nocturia the dose is one or two sprays intranasally (10 to 20 micrograms) at bedtime. Not more than one dose should be used in any 24 hour period. If a dose of two sprays is required, this should be as one spray into each nostril.

Fluid restriction should be observed, please see section *4.4 Special Warnings and Precautions for Use.* In the event of signs of fluid retention/hyponatraemia, treatment should be interrupted.

Treatment of Diabetes Insipidus:
Dosage is individual but clinical experience has shown that the average maintenance dose in adults and children is one or two sprays (10 to 20 micrograms) once or twice daily. If a dose of two sprays is required, this should be as one spray into each nostril.

Diagnosis of Diabetes Insipidus:
The diagnostic dose in adults and children is two sprays (20 micrograms). Failure to elaborate concentrated urine after water deprivation, followed by the ability to do so after the administration of Desmospray confirms the diagnosis of cranial diabetes insipidus. Failure to concentrate after the administration suggests nephrogenic diabetes insipidus.

Fluid restriction should be observed, please see section *4.4 Special Warnings and Precautions for Use.*

Renal Function Testing

To establish renal concentration capacity, the following single doses are recommended.

Adults: Two sprays into each nostril (a total of 40 micrograms).
Children: (1–15 years): One spray into each nostril (a total of 20 micrograms).
Infants (to 1 year): One spray (10 micrograms).

Adults and children with normal renal function can be expected to achieve concentrations above 700mOsm/kg in the period of 5–9 hours following administration of Desmospray. It is recommended that the bladder should be emptied at the time of administration. After administration of Desmospray, any urine collected within one hour is discarded. During the next 8 hours two portions of urine are collected for osmolality testing. Fluid restriction should be observed, please see section *4.4 Special Warnings and Precautions for Use.*

In normal infants a urine concentration of 600mOsm/kg should be achieved in the 5 hour period following the administration of Desmospray. The fluid intake at the two meals following the administration should be restricted to 50% of the ordinary intake in order to avoid water overload.

Special Populations

Older people:

The initiation of treatment in older patients (over 65 years) is contraindicated in patients being treated for nocturia associated with multiple sclerosis.

Dosage recommendation for older patients suffering from central diabetes insipidus is the same as for other age groups.

Renal Impairment

Desmospray is contraindicated in case of moderate and severe renal insufficiency (creatinine clearance below 50 ml/min) (see section 4.3)

Hepatic Impairment

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. Thus human liver metabolism *in vivo* by the cytochrome P450 system is unlikely to occur. The effect of desmopressin on the pharmacokinetics of other drugs is likely to be minimal due to its lack of inhibition of the cytochrome P450 drug metabolising system (see section 4.5).

Paediatric Population

Desmospray is indicated for use in the paediatric population (see section 4.1). Dose recommendations are outlined in section 4.2.

4.3 Contraindications

Desmospray is contraindicated in cases of:

- Habitual or psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours). Before prescribing Desmospray the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.
- History of known or suspected cardiac insufficiency and other conditions requiring treatment with diuretic agents
- Known hyponatraemia
- Syndrome of inappropriate ADH secretion (SIADH)
- Moderate and severe renal insufficiency (creatinine clearance below 50ml/min).
- Hypersensitivity to desmopressin, the preservative benzalkonium chloride or any of the excipients.

When used to control nocturia in patients with multiple sclerosis, desmopressin should not be used in patients with hypertension or cardiovascular disease.

Desmopressin should not be prescribed to patients over the age of 65 for the treatment of nocturia associated with multiple sclerosis.

4.4 Special warnings and precautions for use

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

Desmospray 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

Desmospray should only be used in patients where orally administered formulations are not feasible.

When Desmospray is prescribed it is recommended
- To start at the lowest dose
- To ensure compliance with fluid restriction instructions
- To increase dose progressively, with caution
- To ensure that in children, administration is under adult supervision in order to control the dose intake.

When used for the treatment of nocturia associated with multiple sclerosis, fluid intake must be limited to a minimum from 1 hour before until 8 hours after administration. 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).

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.

When Desmospray is used in the treatment of nocturia associated with multiple sclerosis, periodic assessments should be made of blood pressure and weight to monitor the possibility of fluid overload.

All patients and, when applicable, their guardians should be carefully instructed to adhere to the fluid restrictions.

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.

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 suspected to induce SIADH e.g. tricyclic antidepressants, selective serotonine 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, and 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 central diabetes insipidus.

Due to the presence of benzalkonium chloride this product may cause bronchospasm.

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).

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

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) and in women with known 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 µg 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

Desmospray 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 Desmospray 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, restriction of fluid intake and symptomatic treatment as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues
ATC code: H01B A02

Desmospray 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

Benzalkonium chloride solution
Sodium chloride
Citric acid monohydrate
Disodium phosphate dihydrate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original carton. Store in an upright position.

6.5 Nature and contents of container

The spray pack comprises of a 10ml amber glass injection vial fitted with a snap-on tamper-proof pre-compression spray pump, to which a 20 mm nasal applicator is attached. The fill volume is 7.1ml including overage to allow delivery of 60 doses of 0.1ml.

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

Before Desmospray is used for the first time, prime the pump by pressing downward 4 times or until an even spray is obtained. If the spray has not been used for a week it will be necessary to prime the pump again by pressing it downwards once or until an even spray is obtained.

Instructions for use:

The patient should blow his/her nose before using the spray

1. Remove the protection cap.
2. Control that the end of the tube inside the bottle is submerged in the liquid.
3. Re-prime the pump if the spray has not been used within the last week.
4. Once it has been primed, the pump delivers one dose each time pressure is applied.
5. The head must be tipped back slightly while inserting the applicator straight into the nostril.
6. When a higher dose is needed, spray alternatively into each nostril.
7. Replace cap after use and store the bottle in an upright position.

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

If there is any doubt concerning the correct intake of the dose, the spray should not be re-administered 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 Ireland Ltd
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1009/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 09 July 2007

10 DATE OF REVISION OF THE TEXT

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