Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DDAVP/Desmopressin 4 micrograms/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml DDAVP/Desmopressin 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 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. (Injection)
Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

DDAVP/Desmopressin Injection is indicated for:
1. For the diagnosis and treatment of cranial diabetes insipidus.
2. In the control of bleeding in patients with mild to moderate haemophilia and von Willebrand's disease type I and IIA undergoing surgery or following trauma.
3. To establish renal concentration capacity.

4.2 Posology and method of administration

Posology
Treatment of Cranial Diabetes Insipidus:
By subcutaneous, intramuscular or intravenous injection.

The injection may be used when the intranasal or oral administration is considered unsuitable. Individualise dosage after testing of the effect on urine osmolality and diuresis at different dose levels.

Adults: The usual dose is 1 to 4 micrograms given once daily.

Children: Doses from 0.4 micrograms (0.1ml) may be used.

Diagnosis of Cranial Diabetes Insipidus:
The diagnostic dose in adults and children is 2 micrograms given by subcutaneous or intramuscular injection. Failure to elaborate a concentrated urine after water deprivation, followed by the ability to do so after the administration of desmopressin confirms a diagnosis of cranial diabetes insipidus. Failure to concentrate after the administration suggests nephrogenic diabetes insipidus.

When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 litres to quench thirst from 1 hour before until 8 hours after administration.

Mild to moderate haemophilia and von Willebrand's disease
By intravenous administration.

The dose for adults and children is 0.4 micrograms per kilogram body weight administered by intravenous infusion. Further doses may be administered at 12 hourly intervals so long as cover is required.

As some patients have shown a diminishing response to successive doses, it is recommended that monitoring of Factor VIII levels should continue. The dose should be diluted in 50 ml of 0.9 % sodium chloride for injection and given over 20 minutes. This dose should be given immediately prior to surgery or following trauma.

Renal Concentration Capacity Test
By subcutaneous or intramuscular injection
Adults and children: a single dose of 2 micrograms.

When used for diagnostic purposes the fluid intake must be limited to a maximum of 0.5 litres to quench thirst from 1 hour before until 8 hours after administration.

Special Populations
Renal impairment
DDAVP/Desmopressin Injection should be used with caution in patients with moderate and severe renal insufficiency (see section 5.2).

Hepatic impairment
No dose adjustment is needed for patients with hepatic impairment (see section 5.2).

Paediatric population
DDAVP/Desmopressin Injection is indicated for use in the paediatric population (see section 4.1). Dose recommendations are outlined in section 4.2.

Method of administration
The injection is normally administered intravenously but may, if needed, also be given intramuscularly or subcutaneously (see Posology, section 4.2).

For instructions for use and handling of the medicinal product, see section 6.6.

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)
- 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 II B where the administration of desmopressin may result in pseudothrombocytopenia due to the release of clotting factors which cause platelet aggregation.
- Renal Concentration Capacity Test: hypertension, heart disease

4.4 Special warnings and precautions for use

Special Warnings
DDAVP/Desmopressin Injection should only be administered under the supervision of a Specialist with appropriate laboratory facilities available for monitoring of the patient.

When DDAVP/Desmopressin 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 4.8.

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.

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

In addition for renal concentration capacity testing:
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 haemostatic 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 4.8). 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 DDAVP/Desmopressin Injection interrupted.

DDAVP/Desmopressin Injection does not reduce prolonged bleeding time in thrombocytopenia.

During infusion of DDAVP/Desmopressin Injection for haemostatic use, it is recommended that the patient's blood pressure is monitored continuously.

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 DDAVP/Desmopressin 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 4.5). In patients with chronic therapy with drug(s) affecting water and/or sodium homeostasis, DDAVP/Desmopressin 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).

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

When repeated doses are used to control bleeding in haemophilia or von Willebrand's disease, care should be taken to prevent fluid overload. Fluid should not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or determining plasma sodium or osmolality.

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

4.5 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 4.4).

It is unlikely that DDAVP/Desmopressin Injection will interact with drugs affecting hepatic metabolism, since DDAVP/Desmopressin 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.

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, 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 of 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. Therefore it is not considered necessary to stop breastfeeding.

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

4.7 Effects on ability to drive and use machines

DDAVP/Desmopressin Injection has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reaction with DDAVP/Desmopressin 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 4.4).

Rare cases of serious hypersensitivity reactions including anaphylactoid shock and reaction have been reported in association with DDAVP/Desmopressin Injection (see section 4.4).

Tabulated list of adverse reactions
The below table is based on the frequency of adverse drug reactions reported in clinical trials with DDAVP/Desmopressin Injection conducted in adults for treatment of central diabetes insipidus and haematological indications (n=129), combined with the post marketing experience for desmopressin 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 < 1/1000)**	**Very rare (< 1/10,000)**	**Not known[4]**
Immune system disorders				Hypersensitivity reactions including anaphylactic reaction and other serious allergic conditions
Metabolism and nutrition disorders			Hyponatraemia	Water intoxication[1] Weight increased[1]
Psychiatric disorders				Confusional state[1]
Nervous system disorders	Headache[2]	Dizziness[2]		Coma[1] Loss of consciousness[1,3] Hyponatraemic encephalopathy[1] Brain oedema[1,3] Convulsions[1]
Cardiac disorders	Tachycardia			Myocardial infarction[3] Angina pectoris[3] Chest pain[3]
Vascular disorders	Flushing Hypotension			Deep vein thrombosis[3] Cerebrovascular accident and disorder (stroke)[3] Cerebral thrombosis[3] Hypertension[3]
Respiratory, thoracic and mediastinal disorders				Dyspnoea Pulmonary embolism[3]
Gastrointestinal disorders	Nausea[2] Abdominal pain[1]			Vomiting[2]
Skin and subcutaneous tissue disorders				Rash maculo-papular Rash erythematous Rash macular Urticaria Erythema Pruritus Rash
General disorders and administration site conditions	Fatigue			Generalized or local oedemas[2] (peripheral, face) Injection/infusion site reactions including swelling, pain, extravasation, erythema, bruising and nodules Chills[3] 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 desmopressin injections 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 desmopressin injections 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 4.4.

Hyponatraemia is reversible. Treatment should be individualised and rapid overcorrection should be avoided to reduce the risk of further complications (see sections 4.2 and 4.4).

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 desmopressin injection. Allergic reactions usually occur rapidly after drug administration and may occur during first time usage or after repeated exposure of desmopressin 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 desmopressin 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 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

Symptoms
Overdose of DDAVP/Desmopressin 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 DDAVP/Desmopressin treatment, fluid restriction and symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues
ATC code: H01B A02

DDAVP/Desmopressin 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.

5.2 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%). Plasma half-life varies between 3 and 4 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.

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
Water for injections

6.2 Incompatibilities

This medical product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Do not freeze.
Keep container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Box containing 10 x 1 ml clear, colourless Type I (Ph. Eur.) borosilicate, glass ampoules.

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

Single use only. Discard any unused contents.

For intravenous infusion, the dose should be diluted in 50 ml of 0.9% sodium chloride for injection.

7 MARKETING AUTHORISATION HOLDER

Ferring Ireland Ltd.
United Drug House
Magna Drive
Magna Business Park
Citywest Road
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA1009/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 February 1977
Date of last renewal: 17 February 2007

10 DATE OF REVISION OF THE TEXT

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