Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Octostim 1.5 mg/ml Nasal Spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 1.5mg desmopressin acetate equivalent to 1.34mg desmopressin.
Excipients: contains benzalkonium chloride solution 0.1mg/ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Nasal Spray, Solution

A clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

OCTOSTIM nasal spray is indicated as follows:

1) To test for Fibrinolytic response.
2) Shortening or normalisation of prolonged bleeding time prior to an invasive therapeutic or diagnostic operation, or for therapeutic control of bleeding in patients with prolonged bleeding time
3) For the therapeutic control of bleeding and bleeding prophylaxis in connection with minor surgical procedures in patients with mild haemophilia A and von Willebrand's disease who respond positively to the test dose. Even moderate forms of the disease can be treated.
4) Factor VIII-release in plasma donors.

4.2 Posology and method of administration

Posology
One dose of spray provides 100 microlitres, which corresponds to 150 micrograms desmopressin acetate.

Therapeutic control of bleeding or bleeding prophylaxis; shortening or normalisation of prolonged bleeding time:

300 micrograms (1 dose of spray in each nostril) is given at bleeding or half an hour before the operation. The dose may be repeated every 12^{th} hour for a maximum of 2-3 days. For surgical procedures parenteral administration of desmopressin is primarily recommended.

A desired increase of VIII:C is appraised by the same criterion as in the treatment with Factor VIII-concentrate. However, the concentration of VIII:C is expected to increase for 1-2 hours after the administration. The effect of OCTOSTIM thus differs from a passive supply of factor VIII, where the VIII:C-concentration begins to fall immediately after the administration.

Plasma levels of VIII:C and vWF:Ag increase substantially after the desmopressin administration. However, it has not been possible to establish any correlation between the plasma concentration of these factors and the bleeding time, either before or after desmopressin. The effect of desmopressin on the bleeding time should therefore, if possible, be tested in the individual patient. Determination of bleeding time and plasma levels of the coagulation factors should be conducted in co-operation or consultation with a coagulation laboratory.

Blood donation: 300 micrograms (1 dose of spray in each nostril) 60-90 minutes before tapping. Should not be given more than once every second week.

Method of Administration
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.

4.3 Contraindications

OCTOSTIM nasal spray is contraindicated in cases of:

- habitual and psychogenic polydipsia (resulting in a urine production exceeding 40 ml/kg/24 hours).
- a history of 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 IIB.
- hypersensitivity to the active substances or to any of the excipients.

Fibrinolytic response testing should not be carried out in patients with hypertension, heart disease, cardiac insufficiency and other conditions requiring treatment with diuretic agents.

4.4 Special warnings and precautions for use

Special warnings:
When OCTOSTIM Nasal Spray is prescribed it is recommended to ensure compliance with fluid restriction instructions. Treatment without concomitant reduction of fluid intake may lead to fluid retention/hyponatraemia with or without accompanying signs and symptoms (headache, nausea/vomiting, decreased serum sodium, weight gain, and in severe cases, convulsions).
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). If 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 130mmol/L or plasma osmolality to below 270 mOsm/kg body weight, the fluid intake must be reduced drastically and the administration of OCTOSTIM interrupted.

OCTOSTIM nasal spray does not reduce prolonged bleeding time in thrombocytopenia.

When used for blood donation, to compensate for the increased release of plasminogen activator due to OCTOSTIM nasal spray, 50mg tranexamic acid is added to plasma in the blood bag.

OCTOSTIM Nasal Spray contains benzalkonium chloride, which is an irritant and may cause skin reactions.

Precautions:
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 illnesses characterised by fluid and/or electrolyte imbalance (such as systemic infections, fever, gastroenteritis), and the fluid and electrolyte balance should be carefully monitored, especially in situations with excessive bleeding.

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.

Precautions must be taken in patients with moderate and severe renal insufficiency (creatinine clearance below 50 ml/min).

Precautions to avoid hyponatraemia including careful attention 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 serotonin reuptake inhibitors, chlorpropamide, and in case of concomitant treatment with NSAIDs.

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 and increased risk of water retention/hyponatraemia. (S*ee section 4.4*).

NSAIDs may induce fluid retention/hyponatraemia (S*ee 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) 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 (300 micrograms intranasally), indicate that the amount 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

OCTOSTIM 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 signs and symptoms such as 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.

Spontaneous reports on severe general allergic reactions and allergic skin reactions have been received.

Tabulated summary of adverse reactions

There is no systematic safety data available from clinical development programme of OCTOSTIM nasal spray in haematological indications. Adverse reactions only seen in post marketing or in other desmopressin formulations have been added in the 'Not known' frequency column.

MedDRA Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Very rare (<1/10,000)**	**Not known**
Immune system disorders				Allergic reaction
Metabolism and nutrition disorders			Hyponatraemia	Weight increased*
Psychiatric disorders				Confusional state*
Nervous system disorders	Headache*			Coma*, Convulsions*, Dizziness*
Eye disorders	Eye redness			
Cardiac disorders	Tachycardia			
Vascular disorders	Flushing			
Respiratory, thoracic and mediastinal disorders	Nasal congestion, rhinitis, epistaxis			
Gastrointestinal disorders	Nausea*, abdominal pain*			Vomiting*
Skin and subcutaneous tissue disorders				Pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders				Muscle spasms*
General disorders and administration site conditions				Peripheral oedema*, fatigue*

* Reported in connection with hyponatraemia

Description of selected adverse reactions:

The most serious adverse reaction with desmopressin is hyponatraemia, which is reported with very rare frequency.

Paediatric population:

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; Email: medsafety@hpra.ie.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin & analogues, ATC code H01B A02

OCTOSTIM nasal spray 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 300 micrograms administered intranasally generally leads to at least a twofold 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 plasminogen activator (PA). The effect on the coagulation profile is of the same magnitude as for the 0.2 micrograms/kg intravenously administered desmopressin.

A prolonged bleeding time is shortened to the same extent after intranasal administration of 300 micrograms desmopressin as after an intravenous dose of 0.3 micrograms/kg bodyweight.

The release of factor VIII after intranasal administration of OCTOSTIM may, according to experience from Swedish blood banks, be used for preparation of factor VIII concentrate with increased content of VIII:C but in other respects with unchanged *in vitro* and *in vivo* properties. The yield of factor VIII:C will increase two – to fourfold after desmopressin stimulation in blood donors. No residues of desmopressin or tranexamic acid have been found in the factor VIII concentrate.

By administration of desmopressin instead of factor VIII concentrates, the risk of transmission of HIV-infection is avoided and hepatitis virus is avoided.

5.2 Pharmacokinetic properties

Absorption
The bioavailability, relative to intravenous administration, is 3-5%. Maximum plasma concentration following a dose of 300 micrograms desmopressin acetate is reached after approximately 1 hour and amounts to 400pg/ml on 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 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 in the urine was 52% (44-60%).

5.3 Preclinical safety data

There were no unusual findings during the examination of the safety profile of Desmopressin.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

In-use shelf life: 6 months.

6.4 Special precautions for storage

Do not store above 25°C. Keep vial in the outer carton.

Do not freeze. Store in an upright position.

6.5 Nature and contents of container

Brown Type I glass vial with pre-compression pump.
Pack size: 1 x 2.5ml (25 sprays)
Octostim nasal spray is operated by a manual dose pump without propellant. The spray pump is designed to deliver 100 microlitres solution (=150 micrograms desmopressin acetate) per actuation.

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 OCTOSTIM nasal spray is used for the first time, the pump must be primed by pressing it downwards 4 times or until an even spray is obtained. When the spray has not been used for a week it is necessary to prime the pump again by pressing downwards once or until an even spray appears.

When the nasal spray is used it is important to make sure that the end of the dip tube inside the bottle always is submerged in the liquid and that the nasal applicator is inserted parallel to the dorsal ridge of the nose at the same time as the head is leaning slightly backwards.

The bottle should always be stored in an upright position.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1009/014/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28 April 2006

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10 DATE OF REVISION OF THE TEXT

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