**IRISH MEDICINES BOARD ACT 1995**

**MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998**

**(S.I. No.142 of 1998)**

**PA1262/001/003**
Case No: 2024528

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Gebro Pharma GmbH**

**6391 Fieberbrunn**, **Austria**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Nocutil 0.1 mg/ml Nasal Spray, solution, Desmopressin acetate**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **28/11/2006** until **27/04/2011**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Nocutil 0.1 mg/ml Nasal Spray, solution, Desmopressin acetate

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml nasal spray, solution contains 0.1 mg desmopressin acetate (corresponding to 0.089 mg desmopressin).
One spray delivers 10micrograms desmopressin acetate.

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Nasal spray, solution [Nasal spray]
Clear, colourless solution

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the treatment of nocturnal enuresis in children (from 5 years of age) following exclusion of organic causes
- as part of a global therapeutic management (e.g. if other, non-pharmaceutical treatment measures have failed)

For the treatment of vasopressin - sensitive cranial diabetes insipidus.

### 4.2 Posology and method of administration

For nasal use.

Before application blow the nose. Place nozzle just inside the nostril and press once. One spray delivers a dose of 10 µg. If higher doses are prescribed use alternating nostrils. While spraying breathe in slightly. Replace the protective cap after use.

Nocturnal enuresis:
The dosage should be adjusted within the range of 10 - 40 µg daily.
The usual initial dose in children from 5 years of age is 20 µg at bedtime.
In the event of non-response to the lowest dose, the following scheme for incremental dosing is recommended: after starting with 20 µg for 1-2 weeks, increase to 30 µg in the 3rd week and if necessary to 40 µg no earlier than the 4th week.
If a single bedtime dose of 20µg is effective, a dose reduction to a single spray (10µg) can be assessed.

The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without treatment.

Diabetes insipidus:
The dosage should be adjusted individually according to need.
In children: the average daily dose is 10µg,
in adults: the average daily dose ranges between 10 and 20µg,
once or twice daily.
If signs of water retention/hyponatraemia appear, the treatment should be temporarily discontinued and the dose

adjusted.

The voided volume and the osmolality of urine should be determined in order to titrate the optimal dose.

## 4.3 Contraindications

Due to the dose of 10 µg desmopressin acetate delivered per spray Nocutil is not indicated for use in infants and children under 5 years of age.

Desmopressin must not be used in cases of:
- hypersensitivity to the active substance or to any of the excipients,
- toxaemia of pregnancy,
- primary and psychogenic polydipsia or polydipsia in alcoholics,
- von Willebrand's disease (subtype II), Thrombotic Thrombocytopenic Purpura (TTP),
- cardiac insufficiency and other conditions requiring treatment with diuretic agents,
- hyponatremia,
- renal insufficiency.

## 4.4 Special warnings and precautions for use

Desmopressin therapy without concomitant adjustment of fluid intake may lead to fluid retention and hyponatraemia, accompanied by symptoms such as weight gain, headache, nausea and oedema. In severe cases cerebral oedema, convulsions and coma may occur. Rare cases of cerebral oedema were reported in otherwise healthy children and young adults treated with desmopressin for nocturnal enuresis.

Patients and their parents should be warned to avoid fluid overload (including during swimming) and to stop desmopressin during an episode of vomiting or diarrhoea until fluid balance is normal. The risk of hyponatraemia convulsions can also be minimised by keeping to the recommended starting doses and by avoiding concomitant use of substances which increase secretion of vasopressin (see Section 4.5).

As a precautionary measure to prevent hyperhydration and hyponatraemia, fluid intake should be reduced, especially in very young and elderly patients, in conditions characterised by fluid and electrolyte imbalance and by increased intracranial pressure.
During the treatment of nocturnal enuresis fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after administration.

Fluid retention can be monitored by weighing the patient or by the measurement of plasma sodium or osmolality.

An increase in body weight may be due to overdosage or**,** more often**,** due to increased fluid intake.

Care should be taken in cases of cystic fibrosis, coronary heart disease, hypertension and chronic renal disease.

When used to control primary nocturnal enuresis, desmopressin should only be used in patients with normal blood pressure.

Absorption may be irregular in patients with oedema, scarring or other abnormal conditions of the nasal mucosa.

## 4.5 Interaction with other medicinal products and other forms of interaction

Indomethacin (and possibly other NSAIDs), clofibrate and oxytocin may augment the antidiuretic effect of Nocutil.

Substances which are known to release antidiuretic hormone, for example, tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect and increase the risk of water retention.

Glibenclamide and lithium may diminish the antidiuretic effect.

If hypo- or hypertensive drugs are used concurrently blood pressure, plasma sodium levels and excretion of urine should be monitored.

## 4.6 Pregnancy and lactation

Pregnancy
Data from a limited number (n=53) of pregnant women who have been treated for diabetes insipidus, do not indicate any harmful effects for desmopressin on pregancy or on the health of the fetus/newborn infant.
No other relevant epidemiological data is available. Animal studies do not show any direct or indirectly harmful effects relating to pregnancy, embryonal/fetal development, delivery or post natal development.
Desmopressin should not be used during pregnancy unless considered essential by the physician and should be given with caution to pregnant patients, although the oxytocic effect of desmopressin is very low.

Lactation
Results from analyses of breast milk from mothers having received high doses of desmopressin (300µg intranasally), show that desmopressin passes over in breast milk, but the quantity of desmopressin which can be transferred to the child is lower than the amount necessary to influence diuresis.
Desmopressin may be used during breast-feeding.

## 4.7 Effects on ability to drive and use machines

No studies on the effect of the ability to drive and use machines have been performed.

## 4.8 Undesirable effects

The following undesirable effects have been observed with the use of desmopressin. Adverse reactions are listed according to the following categories:

Very common: ≥ 10%
Common: ≥ 1% and < 10%
Uncommon: ≥ 0,1% and < 1%
Rare: > 0,01% and < 0,1%
Very rare: < 0,01%

<u>Respiratory , thoracic and mediastinal disorders:</u>
Uncommon: nasal congestion, epistaxis, rhinitis

<u>Eye disorders:</u>
Common: conjunctivitis

<u>Gastrointestinal disorders:</u>
Uncommon: nausea, abdominal cramps, vomiting

<u>Nervous system disorders:</u>
Uncommon: headache
Rare: cerebral oedema, hyponatremic seizures

<u>Skin/General disorders:</u>
Common: asthenia
Very rare: allergic and hypersensitivity reactions (e.g. pruritus, exanthema, fever, bronchospasms, anaphylaxis) as reported with peptides in general. On the other hand, these may represent hypersensitivity to the preservative benzalkonium chloride.

Cardiac / vascular disorders
Due to increased water reabsorption blood pressure may rise and in some cases hypertension may develop. In patients with coronary heart disease angina pectoris may occur.

These adverse effects, except for allergic reactions, may be prevented or disappear if the desmopressin dose is reduced.

## 4.9 Overdose

An overdose increases the risk of hyperhydration. Therefore symptoms such as slight hypertension, tachycardia, flush, headache, convulsions, nausea and abdominal cramps are to be expected.
Treatment should be discontinued and fluid intake restricted until serum sodium is normalised. Subsequently, the dose should be reduced.
In cases of massive overdose with the risk of water intoxication the administration of furosemide should be considered.
All cases of suspected cerebral oedema require immediate admission for intensive care measures.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiuretics
ATC code: H01BA02 – Vasopressin and analogues

Desmopressin is a synthetic polypeptide that represents a structural analogue of the native posterior pituitary hormone arginine vasopressin. It has considerably longer antidiuretic action and at the same time diminished vasopressor activity.

Action sets in within 1 hour of application and lasts between 8 and 12 hours.

## 5.2 Pharmacokinetic properties

Intranasal absorption of desmopressin is fast, but incomplete. Interindividual differences regarding the rate of absorption from the nasal mucosa and the duration of the presence of the active ingredient in the plasma result in variations in plasma half-life of 2.5 - 4.5 hours.

The systemic bioavailability is approximately 3-5%. The maximal plasma concentrations are reached after approximately 1 hour and does not increase in proportion to the administered dose.
The distribution volume is approximately 0.2-0.37 L/kg. Desmopressin does not pass the blood-brain barrier.
In-vitro studies with human liver microsomes have shown that no significant amount of desmopressin is metabolised in the liver. It is therefore not likely that desmopressin is metabolised in the liver in-vivo.

About 45% of an intravenous injection of desmopressin is recovered in the urine within 24 hours. The eliminaition half-life is approximately 2-3 hours.

## 5.3 Preclinical safety data

Preclinical effects, e.g. nephrotoxicity, were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Studies on carcinogenicity and mutagenicity (except one negative Ames-Test) are not available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Benzalkonium chloride

Malic acid
Sodium hydroxide
Sodium chloride
Purified water

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf Life

3 years
After first opening 56 days.

## 6.4 Special precautions for storage

Do not store above 25 °C.
Keep container in outer carton and store in an upright position.

## 6.5 Nature and contents of container

Package sizes of:
2.5 ml, 3.5 ml, 5 ml, 6 ml, 7 ml and 8.4 ml - amber, type 1 (transparent) glass bottle.
The fill volumes include overages to allow delivery of the declared doses.
Multiple packs: 3x5 ml, 4x5 ml, 3x6 ml
Closure: Spray head with metered-dose valve, applicator and protective cap.

Not all pack sizes may be marketed.

## 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 first use:
Remove the protective cap and prime the spray several times until the first consistent spray is seen. Spray is now ready for use.

# 7 MARKETING AUTHORISATION HOLDER

Gebro Pharma GmbH
6391 Fieberbrunn
Austria

# 8 MARKETING AUTHORISATION NUMBER

PA 1262/1/3

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28th April 2006

# 10 DATE OF REVISION OF THE TEXT

November 2006