IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA1262/001/002
Case No: 2037250

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 0.2 mg Tablets

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 **18/06/2007** until **06/04/2011**.

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 0.2 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.2 mg desmopressin acetate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Uncoated, white, round, convex tablets scored on one side.
The scoreline is only to facilitate breaking for ease of swallowing in exceptional cases and not to divide into equal doses. Both half tablets should be taken as one dose.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

For the treatment of vasopressin - sensitive central diabetes insipidus.

4.2 Posology and method of administration

For oral use.

The dose of Desmopressin tablets has to be adapted individually.
Desmopressin should always be taken at the same time in relation to mealtimes, as food causes reduced absorption (see section 4.5).

Nocturnal enuresis:
A suitable initial dose is 0.2 mg at bedtime. The dose can be increased up to 0.4 mg if the lower dose is not sufficiently effective.

Fluid intake should be limited to a minimum and only to satisfy thirst from 1 hour before to 8 hours after administration of Nocutil in order to enhance the antidiuretic effect and to avoid hyperhydration (see section 4.4).

If signs or symptoms of water retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and in severe cases convulsions) occur, the treatment must be discontinued until the patient has fully recovered. The supervising specialist should decide whether or not to restart treatment in such a patient.
If the treatment is resumed, strict restriction of fluid intake is necessary, see section 4.4.

Desmopressin tablets are intended for treatment periods of up to 3 months. The need for continued treatment should be reassessed by means of a period of at least 1 week without treatment.

Diabetes insipidus:
For the different dosage regimens tablets containing 0.1 and 0.2 mg are available.
The dose of desmopressin used should be adapted to the individual.
A suitable starting dose in adults and children is 0.1 mg three times daily. The dosage regimen should then be adjusted in accordance with the patient's response. Clinical experience has shown that the daily dose varies between 0.2 and 1.2 mg. The maintenance dose for the majority of patients is 0.1-0.2 mg three times daily. If signs of water retention/hyponatraemia appear, the treatment should be temporarily discontinued until the patient has recovered and the dose adjusted accordingly.

4.3 Contraindications

Desmopressin must not be used in cases of:
- hypersensitivity to the active substance or to any of the excipients of Nocutil,
- patients over the age 65 for the treatment of primary nocturnal enuresis,
- incapacity to follow the fluid intake restriction, for instance in case of cognitive disorders, neurological disease and dementia,
- primary and psychogenic polydipsia,
- cardiac insufficiency and other conditions requiring treatment with diuretic agents,
- hyponatraemia or predisposition of hyponatraemia,
- syndrome of inappropriate ADH secretion (SIADH),
- severe classic von Willebrand disease (type IIB); patients with 5% factor VIII activity level; factor VIII antibodies.

4.4 Special warnings and precautions for use

Organic causes of polyuria or increased frequency of micturition or nocturia such as benign prostatic hyperplasia (BPH), urinary-tract infection, bladder stones/tumours, bladder sphincter disorders, polydipsia or inadequately controlled diabetes mellitus should excluded or treated appropriately.

Any adrenal or thyroid insufficiency should be corrected before the start of the desmopressin therapy.

Desmopressin tablets are not indicated for use in infants and small children under 5 years of age.

Caution is required in cases of cystic fibrosis, coronary heart disease, hypertension, chronic renal disease and pre-eclampsia.

Precautions to avoid hyponatraemia including careful attention to fluid restriction and frequent monitoring of serum sodium must be taken in case of concomitant treatment with medicinal products, which are known to induce a syndrome of inappropriate ADH (SIADH), e.g. tricyclic antidepressants, selective serotonine reuptake inhibitors, chlorpromazine, carbamazepine and in case of concomitant treatment with NSAIDs (see section 4.5).

When used to control primary nocturnal enuresis, desmopressin should only be used in patients with normal blood pressure.
Patients and their parents should be warned to avoid undue fluid intake (including during swimming) and to stop desmopressin during an episode of vomiting, diarrhoea, systemic infections and fever 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 until the next morning (at least 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.

Desmopressin therapy without concomitant limitation 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.
Particularly infants and elderly patients (depending on their general health) are at increased risk for water and electrolyte imbalance. Cerebral oedema was repeatedly reported in otherwise healthy children and young adults treated with desmopressin for nocturnal enuresis.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Indomethacin (and other NSAIDs), clofibrate and oxytocin may augment the antidiuretic effect of desmopressin and may induce water retention and hyponatraemia.

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 and/or hyponatraemia.

Concomitant treatment with loperamide may result in a three-fold increase in plasma concentrations of desmopressin, which may lead to an increased risk of fluid retention and/or hyponatraemia.Other pharmaceutical preparations, which delay peristalsis may have the same effect. This has however not been studied.

Glibenclamide and lithium may diminish the antidiuretic effect.

Desmopressin may enhance the effects of anti hypotensive medicinal products and attenuate the effects of antihypertensive medicinal products.
If hypo- or hypertensive medicinal products are used concurrently blood pressure, plasma sodium levels and excretion of urine should be monitored.

It is unlikely that desmopressin will interact with medicinal drugs affecting hepatic metabolsm, 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.

A standardised 27% fat meal administered decreased absorption (rate and extent) dose of oral desmopressin. No significant effect was, however, observed with respect to pharmacodynamic properties (urine production or osmolality). However, food intake may reduce the intensity and duration of the antidiuretic effect at low doses of desmopressin (see section 4.2).

4.6 Pregnancy and lactation

Desmopressin tablets should be given with caution in pregnancy.
Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate no adverse effects of desmopressin on pregnancy or on the health of the foetus/newborn child. There have been rare reports of malformations in children born to mothers treated for diabetes insipidus during pregnancy. 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.

Results from analyses of breast milk from mothers having received high doses of desmopressin (300 µg intranasally), show that desmopressin is excreted in breast milk, but the quantity of desmopressin which can be transferred to the child is lower than the amount necessary to influence diuresis.

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

Treatment without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with or without accompanying warning signs and symptoms (headache, nausea/vomiting, cerebral oedema, decreased serum sodium, weight gain and in severe cases convulsions).

Enuresis nocturna and diabetes insipidus

Nervous system disorders	Common (>1/100, <1/10)	Headache
Gastrointestinal disorders	Common (>1/100, <1/10)	Stomach pains, nausea
Metabolism and nutrition disorders	Very rare (<1/10,000)	Hyponatraemia
Immune system disorders	Very rare (<1/10,000)	Allergic skin reactions, general allergic reactions
Psychiatric disorders	Very rare (<1/10,000)	Emotional disturbances

These adverse reactions, 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 increase in body weight, slight hypertension, tachycardia, flush, headache, convulsions, nausea, abdominal cramps, and in severe cases cerebral oedema, generalised convulsions and coma can be expected.
Treatment should be discontinued and fluid intake restricted until serum sodium is normalised. Subsequently, the dose should be reduced.
Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given:
In cases of massive overdose with the risk of water intoxication the administration of a saluretic such as furosemide should be considered.
All cases of suspected cerebral oedema require immediate admission for intensive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antidiuretics vasopressin and analogues
ATC code: H01BA02

Desmopressin is a synthetic polypeptide that represents a structural analogue of the native posterior pituitary hormone arginine vasopressin. It has considerably longer antidiuretic action whereas the uterotonic and vasopressor actions are extremely low.
Action sets in within 1 hour of application and lasts between 6 and 14 hours.

5.2 Pharmacokinetic properties

The absolute bioavailability of orally administered desmopressin varies between 0.08% and 0.16%. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant intake of food decreases the rate and extent of absorption by 40%. Mean maximum plasma concentration is reached within 2 hours. The distribution volume is 0.2 – 0.37 l/kg. Desmopressin does not cross the blood-brain barrier. The oral terminal half-life varies between 2 and 3 hours.

As the elimination of desmopressin is delayed in patients with reduced renal function, lower doses are required.

About 65 % of the amount of desmopressin absorbed after oral administration are recovered in the urine within 24 hours.

No gender-related differences regarding pharmacokinetics have been observed for desmopressin.

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

Lactose monohydrate
Potato starch
Povidone
Magnesium stearate
Colloidal anhydrous silica.

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 package. Keep the container tightly closed.

6.5 Nature and contents of container

30 ml High Density Polyethylene (HDPE) bottle with a tamper-proof,
child-resistant, twist-off Polypropylene (PP) closure with a silica gel desiccant insert.

Each bottle contains 15, 28, 30, 90 or 100 tablets.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Gebro Pharma GmbH
6391 Fieberbrunn
Austria

8 MARKETING AUTHORISATION NUMBER

PA 1262/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th April 2006

10 DATE OF REVISION OF THE TEXT

June 2007