IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/033/002
Case No: 2044942

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

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

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

Noctissin 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 **22/05/2009** until **21/05/2014**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Noctissin 0.2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.2 mg desmopressin acetate corresponding to 0.178 mg desmopressin

Excipients: Lactose monohydrate

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet.

White, round tablets, scored on one side, and “D2” engraved on the other side. Diameter 8 mm.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Central diabetes insipidus.
Nocturnal enuresis in children above the age of 5 years.
Treatment of nocturia due to nocturnal polyuri in adults.

4.2 Posology and method of administration

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

Diabetes insipidus:
Adults and children:
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 mg and 1.2 mg. The maintenance dose for the majority of patients is 0.1 mg – 0.2 mg three times daily. If signs of water retention/ hyponatraemia appear, the treatment should be temporarily discontinued and the dose adjusted.

Nocturnal enuresis:
Children above the age of 5:
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.

In connection with long-term treatment, a treatment-free period of at least one week should be introduced every three months to assess whether spontaneous healing has occurred.

Fluid intake must be restricted and monitored. If signs or symptoms of fluid retention and/or hyponatraemia (headache, nausea/vomiting, weight gain and, in serious cases, convulsions, coma) arise, treatment should be discontinued until the patient is fully recovered. When treatment is restarted, fluid restriction must be observed (see section 4.4).

Nocturia:
Recommended initial dose is 0.1 mg at bedtime. If the effect is inadequate, the dose may be increased weekly to 0.2 mg and subsequently up to 0.4 mg. Fluid intake must be restricted and monitored (see section 4.4).

Before a diagnosis of nocturnal polyuria can be made, the frequency and volume of urine production should be measured for at least 48 hours. If nocturnal urine production exceeds the bladder capacity or exceeds 1/3 of the urine production during 24 hours, nocturnal polyuria is indicated.

If signs or symptoms of fluid retention and/or hyponatraemia (headache, nausea/vomiting, weight increase and, in serious cases, convulsions, coma) arise, treatment should be discontinued until the patient is fully recovered. When treatment is restarted, fluid restriction must be observed and serum sodium levels monitored (see section 4.4).

If the desired clinical effect is not achieved after 4 weeks of dose titration, treatment should be discontinued.

Treatment of elderly patients should be followed closely due to increased risk of hyponatraemia. Serum sodium should be measured at baseline, three days after onset of treatment or at any dose increase and regularly during prolonged therapy.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients.
Habitual and psychogenic polydipsia (resulting in urinary production exceeding 40 ml/kg/24 hours).
Cardiac insufficiency or other conditions requiring treatment with diuretics.
Moderate or serious renal failure (creatinine clearance <50 ml/min).
Known hyponatraemia.
SIADH – a condition involving inappropriately high ADH production.

4.4 Special warnings and precautions for use

In connection with treatment of nocturnal enuresis and nocturia, fluid intake must be restricted as much as possible from 1 hour before administration at bed time until the next morning and in any case for at least 8 hours after administration. Treatment without simultaneous fluid restriction may result in fluid retention and/or hyponatraemia with or without concurrent warning signs or symptoms (headache, nausea/vomiting, weight gain and, in serious cases, convulsions, coma). Cerebral edema has repeatedly been reported in children and young adults treated with demospressin for nocturnal enuresis.

In patients with urge incontinence, organic causes of increased frequency of micturition or nocturia (e.g. benign prostatic hyperplasia (BPH), urinary-tract infection, bladder stones/tumours, bladder sphincter disorders), polydipsia and inadequately controlled diabetes mellitus, the specific cause of the problems should primarily be treated resp. excluded.

Precaution should be taken to avoid hyponatraemia, e.g. fluid restriction and serum sodium measurements if Noctissin is taken concomitantly with medicinal products capable of inducing SIADH, e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), chlorpromazine, carbamazepine or NSAIDs.

Older people and patients with low serum sodium may have an increased risk of hyponatraemia.

In case of illnesses characterised by a fluid and/or electrolyte imbalance, treatment with desmopressin should be discontinued (e.g. in case of systemic infections, fever or gastroenteritis).

Serious bladder dysfunction and outlet obstruction should be considered before onset of treatment.

The medicinal product should be administered with caution and dose should be reduced if necessary in patients with cardiovascular disorders or patients affected by asthma, epilepsy and migraine.

During treatment with desmopressin, body weight, serum sodium and/or blood pressure may have to be monitored.

Contains lactose. 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

Medicinal products known to induce SIADH, e.g. tricyclic antidepressants, SSRIs, chlorpromazine and carbamazepine may have an additive antidiuretic effect and thus increase the risk of fluid retention/hyponatraemia.

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

Concomitant treatment with loperamide may lead to a trebling of the desmopressin plasma concentration, which may result in an increased risk of fluid retention/hyponatraemia. Other medicinal products that retard intestinal transport may have the same effect. However, this has not been studied.

Desmopressin is unlikely to interact with medicinal products affecting hepatic metabolism since *in vitro* studies involving human microsomes do not show any significant hepatic metabolism. However, no *in vivo* interaction studies have been conducted.

Concomitant treatment with dimeticone may reduce the absorption of desmopressin.

A standardised meal with 27% fat significantly reduced the absorption (rate and extent) of orally administered desmopressin by approximately 40%. No significant effect was observed in pharmacodynamics (urine production or osmolality). However, it can not be excluded that certain patients achieve a different effect when Noctissin is taken with food. At low doses, food intake may reduce the antidiuretic effect duration.

4.6 Pregnancy and lactation

Pregnancy:

Data from studies carried out on a limited number (n=53) of pregnant women with diabetes insipidus indicate rare cases of malformations in children exposed during pregnancy. To date, no further relevant epidemiological data have been made available. Studies carried out on animals reveal no direct or indirect harmful effects on pregnancy, foetal formation and development, birth or postnatal development.
Caution should be exercised in prescribing desmopressin to pregnant women. Blood pressure monitoring is recommended due to the increased risk of preeclampsia.

Lactation:

Results of analyses conducted on milk from lactating mothers treated with high doses of desmopressin (300 µg intranasal) show that the amount of desmopressin that can be passed to the infant is considerably less than the amount required to affect diuresis.

Desmopressin may be used during lactation.

4.7 Effects on ability to drive and use machines

No studies have been conducted to determine the effects of desmopressin on the ability to drive or use machines. Desmopressin has no known effect on the ability to drive or use machines.

4.8 Undesirable effects

Treatment without concomitant restriction of fluid intake may result in fluid retention/hyponatraemia with or without concurrent warning signs or symptoms. The symptoms concerned include headache, nausea/vomiting, reduced serum sodium, weight gain and, in serious cases, convulsions, coma. (See section 4.4)

The frequency of adverse events listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Nocturnal enuresis and diabetes insipidus:

The most common include headache and gastrointestinal disorders.

Immune system disorders Not known	Allergic reactions.
Metabolism and nutrition disorders Very rare	Hyponatraemia.
Psychiatric disorders Very rare	Emotional disturbances.
Nervous system disorders Common	Headache.
Gastrointestinal disorders Common	Abdominal pain, nausea.
Skin and subcutaneous tissue disorders Very rare	Allergic skin reactions.

Nocturia:

In clinical trials, approx. 35% of the patients experienced undesirable effects during dose titration. 8% of patients stopped treatment due to undesirable effects during dose titration and 2% stopped treatment in the following double-blind period (0.63% in the desmopressin group and 1.45% in the placebo group).
During long-term treatment, approx. 24% of the patients experienced undesirable effects.
The most common undesirable effect is headache. Fifteen percent of patients experienced headache during dose titration and 6% experienced headache during long-term treatment.

Metabolism and nutrition disorders Common	Hyponatraemia (dose titration).
Nervous system disorders Very common Common	Headache (dose titration). Headache (long-term treatment). Dizziness.
Cardiac disorders Common	Peripheral oedema (long-term treatment).
Gastrointestinal disorders Common	Nausea. Weight gain (long-term treatment). Abdominal pain (dose titration). Dry mouth (dose titration).

Renal and urinary disorders Common	Frequent urination (long-term treatment).

4.9 Overdose

Overdose may lead to prolonged effects and increased risk of fluid retention and hyponatraemia.

Symptoms of serious fluid retention:
Convulsions and unconsciousness.

Treatment:

Treatment of hyponatraemia should be individualised, but the following general guidelines can be given:
Hyponatraemia is treated by discontinuing desmopressin therapy, restricting fluid intake and treating symptomatically if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vasopressin and analogues, ATC code: H 01 BA 02

Desmopressin is a synthetic analogue to the natural hormone arginine vasopressin. Desmopressin is distinguished from the natural hormone by two chemical differences: deamination of 1-cysteine and substitution of 8-L-arginin by 8-D-arginin. This change considerably prolongs the antidiuretic effect and almost eliminates the pressor effect at therapeutic doses. Desmopressin is a potent agent with an EC_{50} value of 1.6 pg/ml for the antidiuretic effect. An effect lasting 6-14 hours or more can be expected after oral administration.

Clinical trials of desmopressin tablets for nocturia showed the following:

- 39% of the patients experienced a reduction of at least 50% in night-time urination. The corresponding reduction for patients receiving placebo treatment was 5% ($p<0.0001$).
- The average number of night-time urination decreased by 44% in the desmopressin group compared with 15% in the placebo group ($p<0.0001$).
- The average duration of the first undisturbed sleep increased by 64% in the desmopressin group compared with 20% in the placebo group ($p<0.0001$).
- The average duration of the first undisturbed sleep increased by two hours when desmopressin was administered compared with 31 minutes when placebo was administered ($p<0.0001$).

5.2 Pharmacokinetic properties

The absolute bioavailability following oral administration of desmopressin varies between 0.08% and 0.16%.
Bioavailability of desmopressin varies moderately to substantially in both the individual and between individuals.
Concomitant intake of food reduces the rate and extent of absorption by 40%.
The average maximum plasma concentration is achieved within two hours after administration. The distribution volume is 0.2-0.3 l/kg. The plasma half-life is 2-3 hours. Half-life following oral administration is between 2 and 3 hours. Desmopressin does not pass the blood-brain barrier.

In vitro studies conducted using human liver microsomes have shown that no significant amounts of desmopressin are metabolised in the liver. In vivo metabolism in the liver is therefore unlikely.

Following intravenous administration, 45% of the administered desmopressin is found in the urine within 24 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and toxicity to reproduction.
Impairment of renal function, with a rise in serum creatinine as well as hyaline degeneration of tubule epithelia, has been demonstrated in rats at a daily dose of 47.4 micrograms/kg body weight, i.e. at exposures considered sufficiently in excess of the maximum human exposure. The alterations were reversible after termination of desmopressin treatment. Investigations on the carcinogenic properties are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Potato starch
Povidone K30
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container. Keep the container tightly closed in order to protect from moisture.
The desiccant should not be removed.

6.5 Nature and contents of container

HDPE container with HDPE/LDPE cap and desiccant capsule.

Pack sizes: 10, 15, 20, 30, 60, 90, 100 and 250 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

Tablets may be crushed, but must not be suspended in water.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/33/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd May 2009

10 DATE OF REVISION OF THE TEXT