IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0126/160/002
Case No: 2052342

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

Clonmel Healthcare Limited

Waterford Road, **Clonmel**, **Co. Tipperary**, **Ireland**

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

Benprotan 10 mg Prolonged Release 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 **26/08/2008** until **14/12/2011**.

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

Benprotan 10 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alfuzosin hydrochloride.

Excipients:

Each tablet conains 8 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, bevelled-edge, uncoated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

The prolonged-release tablet should be swallowed whole with a sufficient amount of fluid.
The tablet should be taken immediately after the same meal each day.

Adults
1 prolonged-release tablet 10 mg once daily. The first dose should be taken at bedtime.

Elderly (over 65 years)
1 prolonged-release tablet 10 mg once daily if the recommended initial lower dose of alfuzosin hydrochloride is well tolerated and additional efficacy is required. The first dose should be taken at bedtime.

Pharmacokinetic and clinical safety data demonstrate that no dose reduction is necessary to elderly patients.

Reduced renal function
Mild to moderate renal insufficiency:
If a lower dose is not sufficient, therapy can be adjusted to 1 prolonged-release tablet 10 mg daily according to clinical response. The first dose should be taken at bedtime.

Severe renal insufficiency:
Alfuzosin 10 mg should not be given to patients with severely impaired renal function (creatinine clearance < 30 ml/min) as there are no clinical safety data available for this patient group (see section 4.4).

Hepatic insufficiency
Alfuzosin given as 10 mg prolonged release tablets are contraindicated in patients with hepatic insufficiency. After careful medical consideration, a preparation containing a low dose of alfuzosin hydrochloride (according to the relevant dosage instructions for this specific patient group) might be considered appropriate. Refer to corresponding product information for dosing instructions.

4.3 Contraindications

- Hypersensitivity to alfuzosin, other quinazolines (e.g. terazosin, doxazosin) or to any of the excipients.
- Conditions with orthostatic hypotension.
- Hepatic insufficiency.
- Combination with other alpha-1 receptor blocking agents.

4.4 Special warnings and precautions for use

Alfuzosin 10 mg should not be administered to patients with severely impaired renal function (creatinine clearance < 30 ml/min) as there are no clinical safety data available for this patient group. Alfuzosin Stada should be given with caution to patients treated with antihypertensive medicinal products. Blood pressure should be monitored regularly, especially at the beginning of treatment.

In some patients postural hypotension may develop, with or without symptoms (dizziness, asthenia, sweating) within a few hours of administration.In such cases, the patient should lie down until the symptoms have completely disappeared.This effects are usually temporary. They occur at the start of the treatment and normally do not prevent continuation the treatment. Patients should be warned about the possibility of side effects.

Caution should be exercised with alfuzosin is administered to patients who have responded with pronounced hypotension to other alpha- 1 blockers.

Treatment should be initiated gradually in patients with hypersensitivity to other alpha- 1 receptor blockers.

As with all alpha-1 receptor blockers, alfuzosin should be used with caution in patients with acute cardiac failure.

The "Intraoperative Floppy Iris Syndrome" (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports have also been received with other alpha-blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1 blockers should be made known to the opthalmic surgeon in advance of surgery.

In cardiac patients the treatment of coronary insufficiency should continue taking into account that the concomitant administration of nitrates and alfuzosin may increase the risk of occurrence of hypotension. Alfuzosin should be discontinued if angina pectoris recurs or worsens.

Patients should be instructed to swallow the tablet whole. Other methods of administration such as crushing, powdering or chewing the tablet, should be avoided. Incorrect administration may lead to undesirable release and absorption of the active substance with a risk of early undesirable effects.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Contra-indicated combinations:
Alpha-1 receptor blocking agents (see section 4.3).

Combinations requiring caution:
- Alfuzosin blood levels are increased by potent CYP3A4 inhibitors like ketoconazole, itraconazole and ritonavir.
- Antihypertensive agents (see section 4.4).
- Nitrates.

Concomitant use with antihypertensive agents or nitrates increases the risk of hypotension.
See also section 4.4.

Administration of an anaesthetic to a patient being treated with alfuzosin may lead to profound hypotension. It is recommended that the tablets be withdrawn 24 hours before surgery.

No pharmacodynamic or pharmacokinetic interactions have been observed in studies with healthy volunteers between alfuzosin and the following active substances: warfarin, digoxin and hydrochlorothiazide.

4.6 Pregnancy and lactation

Due to the type of indication this section is not applicable.

4.7 Effects on ability to drive and use machines

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

Adverse reactions such as vertigo, dizziness and asthenia may occur, especially at the beginning of treatment. This has to be taken into consideration when driving vehicles and operating machines.

4.8 Undesirable effects

The most commonly reported event is dizziness, which occurs in approximately 5% of treated patients.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000).

Nervous system disorders
Common: tiredness, dizziness, headache, vertigo.
Uncommon: Drowsiness.

Eye disorders
Uncommon: Visual disturbances.

Cardiac and vascular disorders
Common: Postural hypotension (initially, primarily with too high a dose or if treatment is resumed after a short interruption of therapy).
Uncommon: Tachycardia, palpitations, syncope (in particular at the beginning of treatment).

Very rare: Aggravation or recurrence of angina pectoris (see section 4.4).

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.

Gastrointestinal disorders
Common: Nausea, dyspepsia, dry mouth, diarrhoea, abdominal pain.
Uncommon: vomiting.

Hepato-biliary disorders
Very rare: Hepatotoxicity.

Skin and subcutaneous tissue disorders
Uncommon: Rash (urticaria, exanthema), pruritus.
Very rare: Angioedema.

Renal and urinary disorders
Uncommon: Urinary incontinence.
Very rare: Isolated cases of priapism were reported.

General disorders and administration site conditions
Common: Asthenia.
Uncommon: Hot flushes, oedema, chest pain.

4.9 Overdose

In case of overdose, conventional treatment in a hospital is recommended, e.g. i.v. fluids and vasopressors. The appropriate antidote is a vasoconstrictor that acts directly on the smooth muscle in the blood vessels such as noradrenaline.

Gastric lavage and/or administration of medicinal charcoal should be considered. Alfuzosin is not easily dialysable because of its high degree of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in benign prostate hypertrophy, alpha-adrenoreceptor antagonists.
ATC code: G04C A01

Alfuzosin, which is a racemate, is an orally acting quinazoline derivative, which selectively blocks post-synaptic alpha-1 receptors. *In vitro* studies have confirmed the selectivity of alfuzosin for alpha-1 receptors in the trigone of the urine bladder, the urethra and the prostate gland. The clinical symptoms in BPH are not only related to the size of the prostate, but also to sympathomimetic nerve impulses, which by stimulating the post-synaptic alpha receptors increase the tension of the smooth muscle of the lower urinary tract. Treatment with alfuzosin relaxes this smooth muscle, thus improving the urinary flow.

Clinical evidence of uroselectivity has been demonstrated by clinical efficacy and a good safety profile in men treated with alfuzosin, including the elderly and patients with hypertension. Alfuzosin may cause moderate anti-hypertensive effects.

In man, alfuzosin improves the voiding parameters by reducing urethral tone and bladder outlet resistance, and thus facilitates bladder emptying.

A lower frequency of acute urinary retention has been observed in patients treated with alfuzosin than in untreated patients.

In placebo-controlled studies of BPH patients, alfuzosin has:
- significantly increased maximum urinary flow (Q_{max}) in patients with Q_{max} <15 ml/s by an average of 30%. This improvement was observed from the first dose;
- significantly reduced the detrusor pressure and increased the volume producing a strong desire to void,
- significantly reduced the residual urine volume.

These urodynamic effects lead to an improvement of Lower Urinary Tract Symptoms (LUTS), i.e. filling (irritative) as well as voiding (obstructive) symptoms, which has been clearly demonstrated.

5.2 Pharmacokinetic properties

Alfuzosin shows linear pharmacokinetics in the therapeutic dose range. The peak plasma concentration is reached approx. 5 hours after administration. The kinetic profile is characterised by large interindividual fluctuations in plasma concentrations. Absorption is increased when the medication is administered after a meal.

Absorption
Prolonged release formulation:
After the first dose (fed) the mean maximum plasma concentration was 7.72 ng/ml and AUCinf was 127 ng x h/ml (fed), and tmax was 6.69 h (fed). Under steady state conditions (fed) the mean AUC over the dosing interval (AUCτ) was 145 ng x h/ml, mean Cmax was 10.6 ng/ml and Cmin was 3.23 ng/ml.

Distribution
Plasma protein binding is approximately 90%. Alfuzosin's distribution is 2.5 l/kg in healthy volunteers. It has been shown to preferentially distribute in the prostate in comparison to plasma.

Elimination
The apparent elimination half-life is approx. 8 hours. Alfuzosin is extensively metabolised in the liver (several routes), metabolites are eliminated via renal excretion and probably also via biliary excretion. Of an oral dose, 75-91% is excreted in the faeces; 35% as unchanged substance and the rest as metabolites, indicating some degree of biliary excretion. About 10% of the dose is excreted in urine as unchanged substance. None of the metabolites are pharmacologically active.

Renal or hepatic impairment
Volume of distribution and clearance increase with reduced renal function, possibly owing to a decreased degree of protein binding. The half-life, however, is unchanged. In patients with severe hepatic insufficiency the half-life is prolonged. The peak plasma concentration is doubled, and the bioavailability increases in relation to that in young, healthy volunteers.

Elderly patients
Oral absorption is more rapid, and AUC values are greater in elderly (> 75 years) than in younger subjects. The increase in plasma concentration may be explained by a reduction in the metabolic capacity of the elderly. Oral bioavailability is somewhat higher than in younger subjects. The elimination half-life remains unchanged.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential or reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E464)
Povidone K25
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister.

10, 28, 30 and 90 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

Clonmel Healthcare Ltd.
Waterford Road
Clonmel
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8 MARKETING AUTHORISATION NUMBER

PA 126/160/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

August 2008