IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PPA1500/024/001
Case No: 2083742

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

Profind Wholesale Ltd.

Unit 625, Kilshane Avenue, **Northwest Business Park**, **Dublin 15**, **Ireland**

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

Xatral 10mg Prolonged Release Tablets

the particulars of which are set out in 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 **28/07/2010**.

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

Xatral 10mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alfuzosin hydrochloride.

Fora full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Product imported from the UK:
Round biconvex three layer tablet: one white layer between two yellow layers.
Product imported from the Italy:
Round biconvex three layer tablet: one white layer between two yellow layers.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of the functional symptoms of benign prostatic hypertrophy.

Adjunctive therapy with urethral catheterization for Acute Urinary Retention related to BPH.

4.2 Posology and method of administration

Xatral 10 mg prolonged release tablets are for oral administration.

Xatral 10 mg Prolonged Release Tablets should be swallowed whole.

BPH: The recommended dose is one 10mg tablet once daily to be taken after a meal.

AUR: One 10mg tablet daily after a meal to be taken from the first day of catheterisation.

4.3 Contraindications

- Hypersensitivity to the alfuzosin or any component.
- History of orthostatic hypotension.
- Combination with other alpha$_1$ -blockers.
- Hepatic insufficiency.

4.4 Special warnings and precautions for use

Warnings
As with all alpha$_1$-blockers in some subjects, in particular patients receiving antihypertensive medications, postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administrations. In such cases, the patient should lie down until the symptoms have completely disappeared.

These effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. The patient should be warned of the possible occurrence of such events.

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-1 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 ophthalmic surgeon in advance of surgery.

Precautions
Treatment should be initiated gradually in patients with hypersensitivity to another alpha$_1$ blocker.
Xatral should be administered carefully to patients being treated with antihypertensives. Blood pressure should be monitored regularly, especially at the beginning of treatment.

In patients with coronary insufficiency specific therapy for coronary insufficiency should be continued. If angina pectoris reappears or worsens Xatral should be discontinued.

Patients should be warned that the tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated:
- Alpha1-receptor blockers (see section 4.3)

Combinations to be taken into account:
- Antihypertensive drugs (see section 4.3)
- Nitrates
- Potent CYP3A4 inhibitors, such as ketoconazole, Itraconazole and ritonavir since alfuzosin blood levels are increased (see section 5.2)

Concomitant use with other alpha$_1$ -receptor blockers should be avoided and antihypertensive agents should be used with caution because of the risk of a hypotensive effect.

The administration of general anaesthetics to patients receiving Xatral® 10mg Prolonged Release Tablets could cause profound hypotension. It is recommended that the tablets be withdrawn 24 hours before surgery.

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

There are no data available on the effect on driving vehicles. Adverse reactions such as vertigo, dizziness and asthenia may occur. Some subjects particularly those on antihypertensive medication may experience postural hypotension, which may or may not result in symptoms such as dizziness and fatigue.

This has to be taken into account when driving vehicles and operating machinery.

4.8 Undesirable effects

CNS and Psychiatric disorders
Common: faintness/dizziness or malaise, headache
Uncommon: vertigo

Cardiovascular disorders
Uncommon: tachycardia, hypotension (postural). Syncope, palpitations

Very rare: Angina pectoris in patients with pre-existing coronary artery disease (see section 4.4 Special warnings and Precautions for Use)

Respiratory system disorders
Uncommon: rhinitis

Gastro-intestinal disorders
Common: nausea, abdominal pain
Uncommon: diarrhoea

Skin and appendages
Uncommon: rash, pruritus
Very rare: urticaria, angiodema

Body as a whole
Common: asthenia
Uncommon: flushes, oedema, chest pain

Eye disorders
Uncommon: Vision abnormal
Unknown: intraoperative floppy iris syndrome (see section 4.4 Special warnings and precautions for use)

Hepato-bilary disorders
Unknown: hepatocellular injury, cholestatic liver disease.

Reproductive system and breast disorders
Unknown: priapism

4.9 Overdose

In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.

Alfuzosin is not dialyzable because of its high degrees of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Alfuzosin is an orally active quinazoline derivative. It is a selective, peripherally acting antagonist of postsynaptic alpha$_1$ -adrenoceptors.

In vitro pharmacological studies have documented the selectivity of alfuzosin for the alpha$_{1-}$ adrenoceptors located in the prostate, bladder base and prostatic urethra.

Clinical manifestations of Benign Prostatic Hyprtrophy are associated with infra vesical obstruction which is triggered by both anatomical (static) and functional (dynamic) factors. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by alpha$_1$ -adrenoceptors. Activation of alpha$_1$ -adrenoceptors stimulates smooth muscle contraction, thereby increasing the tone of the prostate, prostatic capsule, prostatic urethra and bladder base, and, consequently, increasing the resistance to bladder outflow. This in turn leads to outflow obstruction and possible secondary bladder instability.

Alpha-blockade decreases infra vesical obstruction via a direct action prostatic smooth muscle.

In vivo, animal studies have shown that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin inhibits the hypertonic response of the urethra more readily than that of vascular muscle and shows functional uroselectivity in conscious normotensive rats by decreasing urethral pressure at doses that do not affect blood pressure.

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

In placebo controlled studies in BPH patients, alfuzosin:

- Significantly increases peak flow rate (Q_{max}) in patients with $Q_{max} \leq 15$ml/s by a mean of 30%. This improvement is observed from the first dose,
- Significantly reduces the detrusor pressure and increases the volume producing a strong desire to void,
- Significantly reduces the residual urine volume.

In addition, the efficacy on peak flow rate is maintained up to 24 hours after intake.

These favourable urodynamic effects lead to an improvement of lower urinary tract symptoms i.e. filling (irritative) as well as voiding (obstructive) symptoms.
Alfuzosin may cause moderate antihypertensive effects.

A lower frequency of acute urinary retention is observed in the alfuzosin treated patient than in the untreated patient. In addition, alfuzosin significantly increases the success rate of spontaneous voiding after catheter removal in men with an episode of AUR related to BPH.

5.2 Pharmacokinetic properties

Prolonged-release formulation:

The mean value of the relative bioavailability is 104.4% versus the immediate release formulation (2.5 mg tid) in middle-aged healthy volunteers and the maximum plasma concentration is being achieved 9 hours after administration compared to 1 hour for the immediate release formulation.

The apparent elimination half-life is 9.1 hours.

Studies have shown that consistent pharmacokinetic profiles are obtained when the product is administered after a meal.

Under fed conditions, mean C_{max} and C_{trough} values are 13.6 (SD=5.6) and 3.2 (SD=1.6) ng/ml respectively. Mean AUC_{0-24} is 194 (SD=75) ng.h/ml. A plateau of concentrations is observed from 3 to 14 hours with concentrations above 8.1 ng/ml (Cav) for 11 hours.

Compared to healthy middle aged volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly patients.

Compared to subjects with normal renal function, mean C_{max} and AUC values are moderately increased in patients with renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore, this does not necessitate a dosing adjustment.

The binding of alfuzosin to plasma proteins is about 90%. Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the parent compound being excreted unchanged in the urine. The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91%).

The pharmacokinetic profile of alfuzosin is not affected by chronic cardiac insufficiency.

Metabolic interactions: CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin. Ketoconazole is a strong-potency inhibitor of CYP3A4. Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in an increase of the C_{max} (2.11-fold) and AUClast (2.46-fold) of alfuzosin 10mg OD under fed conditions. Other parameters such as t_{max} and $tl_{/2Z}$ were not modified. The 8-day repeated administrations of ketoconazole 400mg daily increased C_{max} of alfuzosin by 2.3-fold, AUC_{last} and AUC by 3.2 and 3.0, respectively (see section 4.5)

5.3 Preclinical safety data

No data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethylcellulose
Hydrogenated castor oil
Hypromellose
Yellow ferric oxide (E172)
Magnesium stearate
Microcrystalline cellulose
Povidone
Silica colloidal hydrated
Mannitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25^{o}C.
Keep in original package.

6.5 Nature and contents of container

PVC/foil blister strips of 10 tablets contained in an over-labelled cardboard carton. Pack size 30 tablets.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

Profind Wholesale Ltd
Unit 625, Kilshane Avenue
Northwest Business Park
Dublin 15
Ireland

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/24/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st July 2009

10 DATE OF REVISION OF THE TEXT

July 2010