IRISH MEDICINES BOARD ACT 1995, as amended

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

PPA1500/001/002
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

Cardura XL 8mg 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

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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

Cardura XL 8mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8mg doxazosin (as mesilate).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablets.

Product imported from the UK:

White, round, biconvex shaped tablets with an orifice on one side marked CXL8 and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cardura XL is indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.
In patients inadequately controlled on single antihypertensive therapy, Cardura XL may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

4.2 Posology and method of administration

The initial dose of Cardura XL is 4mg once daily. A significant number of patients will be controlled on this dose. If necessary, the dosage may be increased to 8mg once daily according to patient response.
The maximum recommended dose is 8mg once daily.
Cardura XL can be taken with or without food.
The tablets should be swallowed whole with a sufficient amount of liquid. They should not be cut or chewed.

Elderly: In common with other drugs of this class, the dosage should be kept as low as possible and increments made under close supervision.

Use in renally impaired patients: Since the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual dosages may be used in these patients. Cardura XL is not dialysable.

Use in hepatically impaired patients: There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug metabolised wholly by the liver, Cardura XL should be used with care in patients with significant existing hepatic dysfunction. (see section 4.4 Special warnings and precautions for use, and section 5.2 Pharmacokinetic properties).

Use in children: There is insufficient experience to recommend the use of Cardura XL in children under 12 years of age.

4.3 Contraindications

Cardura XL is contraindicated in patients with a known hypersensitivity to quinazolines (e.g. doxazosin, prazosin, terazosin), or any of the inert ingredients of Cardura XL.

Cardura XL is contra-indicated in patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.

Use during lactation: Animal studies have shown that doxazosin accumulates in breast milk. The clinical safety of Cardura XL during lactation has not been established, consequently Cardura XL is contra-indicated in nursing mothers.

4.4 Special warnings and precautions for use

Information for the patient: Patients should be informed that Cardura XL tablets should be swallowed whole. Patients should not chew, divide or crush the tablets.
In Cardura XL the medication is contained within a non-absorbable shell that has been specially designed to slowly release the drug. When this process is completed the empty tablet is eliminated from the body. Patients should be advised that they should not be concerned if they occasionally observe in the stools something that looks like a tablet.

Use with PDE-5 Inhibitors: Concomitant administration of an alpha blocker with a PDE-5 inhibitor should be used with caution as it may lead to symptomatic hypotension in some patients. No studies have been conducted with Cardura XL.

Impaired renal function: There is no evidence that Cardura XL aggravates renal dysfunction. However, Cardura XL dosage introduction and adjustments should be carried out with great care.

Impaired liver function: As with any drug wholly metabolised by the liver, Cardura XL should be administered with caution to patients with evidence of impaired hepatic function (see section 5.2 Pharmacokinetic properties).

Postural Hypotension / Syncope: As with all alpha-blockers, a very small percentage of patients have experienced postural hypotension evidenced by dizziness and weakness or rarely loss of consciousness (syncope), particularly with the commencement of therapy. When instituting therapy with any effective alpha-blocker, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result should dizziness or weakness occur during the initiation of Cardura XL therapy, such as driving or operation machinery.

Cataract Surgery: 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 ophthalmic surgeon in advance of surgery

4.5 Interaction with other medicinal products and other forms of interaction

Doxazosin is highly bound to plasma proteins (98%). In vitro data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indometacin). However, the theoretical potential for interaction with other protein bound drugs should be borne in mind. No adverse interactions have been observed with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or anticoagulants.
Concomitant administration of an alpha blocker with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4 Special Warnings and Special Precautions for Use). No studies have been conducted with Cardura XL.
In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean Cmax and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.
Doxazosin can potentiate the blood pressure lowering activity of other antihypertensives

4.6 Pregnancy and lactation

Use during pregnancy: Doxazosin crosses the placenta. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum recommended human dose. As there are no adequate and well-controlled studies in pregnant women, the safety of Cardura XL during pregnancy has not yet been established. Accordingly, Cardura XL should be used only when, in the opinion of the physician, the potential benefit outweighs the potential risk.

Use during lactation: Contraindicated. See section 4.3 Contraindications above.

4.7 Effects on ability to drive and use machines

The ability to drive or use machinery may be impaired, especially when initiating therapy. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

In clinical trials, the most common reactions associated with Cardura XL were of a postural type (rarely associated with fainting) or non-specific and included:
Cardiac disorders: palpitation, tachycardia
Ear and Labyrinth Disorders: vertigo

Gastrointestinal Disorders: abdominal pain, dry mouth,nausea
General Disorders and Administration Site Conditions: asthenia, chest pain, peripheral oedema
Musculoskeletal and Connective Tissue Disorders: back pain, myalgia
Nervous System Disorders: dizziness, headache
Respiratory, Thoracic and Mediastinal Disorders: coughing, bronchitis
Skin and Subcutaneous Tissue Disorders: pruritis
Renal and Urinary Disorders: urinary incontinence, cystitis
Vascular Disorders: postural hypotension

In post-marketing experience the following additional adverse events have been reported:

Blood and Lymphatic Disorders: leucopenia, thrombocytopenia
Ear and Labyrinth Disorders: tinnitus
Eye Disorders: blurred vision
Gastrointestinal Disorders: constipation, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth
General Disorders and Administration Site Conditions: fatigue, malaise, pain
Hepatobiliary Disorders: cholestasis, hepatitis, jaundice
Immune System Disorders: allergic reaction
Investigations: abnormal liver function tests, weight increase
Metabolism and Nutrition: anorexia
Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle cramps, muscle weakness
Nervous System Disorders: postural dizziness, hypoaesthesia, paraesthesia, syncope, tremor
Psychiatric Disorders: agitation, anxiety, depression, insomnia, nervousness
Renal and Urinary Disorders: dysuria, haematuria, micturition disorder, micturition frequency, nocturia, polyuria, urinary incontinence
Reproductive System and Breast Disorders: gynaecomastia, impotence, priapism, retrograde ejaculation
Respiratory, Thoracic and Mediastinal Disorders: aggravated bronchospasm, dyspnoea, epistaxis, coughing
Skin and Subcutaneous Tissue Disorders: alopecia, purpura, skin rash, urticaria, pruritus
Vascular Disorders: hot flushes, hypotension

The following additional adverse events have been reported in marketing experience among patients treated for hypertension.

In general, these are not distinguishable from symptoms that might have occurred in the absence of exposure to Cardura XL: bradycardia, tachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, cerebrovascular accidents and cardiac arrhythmias.

The undesirable effects for Cardura XL are similar to those with immediate release Cardura tablets.

4.9 Overdose

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases. Since doxazosin is highly protein bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist.

Administration of Cardura XL to hypertensive patients causes a clinically significant reduction in blood pressure as a result of a reduction in systemic vascular resistance. This effect is thought to result from selective blockade of the alpha-1-adrenoreceptors located in the vasculature. With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24 hours post dose. The majority of patients are controlled on the initial dose. In patients with hypertension, blood pressure during treatment with Cardura XL was similar in both the supine and standing position.

Responder data from the 2 primary hypertension efficacy studies (including a total of 630 doxazosin treated patients) indicate that those patients controlled on 1mg, 2mg or 4mg doxazosin immediate release tablets would be equally well controlled on 4mg Cardura XL.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with coexistent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with coexistent asthma, left ventricular hypertrophy and in elderly patients. Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, doxazosin improves insulin sensitivity in patients with impairment.

Doxazosin produces favourable effects on blood lipids, with a significant increase in the HDL/total cholesterol ratio and trends to a favourable reduction in total triglycerides. It therefore confers an advantage over diuretics and beta adrenoceptor blocking agents which adversely affect these parameters. Based on the established association of hypertension and blood lipids with coronary heart disease, the favourable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in risk of developing coronary heart disease.

5.2 Pharmacokinetic properties

Absorption: After oral administration of therapeutic doses, Cardura XL is well absorbed with peak blood levels gradually reached at 8 to 9 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release Cardura tablets. Trough levels at 24 hours are, however, similar.
The pharmacokinetic characteristics of Cardura XL will lead to a smoother plasma profile.
Peak/trough ratio of Cardura XL is less than half that of immediate release Cardura tablets.
At steady-state, the relative bioavailability of doxazosin from Cardura XL compared to the immediate release form was 54% at the 4mg dose and 59% at the 8mg dose.
Pharmacokinetic studies with Cardura XL in the elderly have shown no significant alterations compared to younger patients.

Biotransformation / Elimination: The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basis for once daily dosing. Doxazosin is extensively metabolised with <5% excreted as unchanged drug.

Pharmacokinetic studies with immediate release Cardura in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 30%. (See also 4.4 Special warnings and special precautions for use).

Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. For further information see section 4.6 Pregnancy and lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene oxide

Sodium chloride

Hypromellose

Red ferric oxide (E172)

Titanium dioxide (E171)

Magnesium stearate

Cellulose acetate

Macrogol

Pharmaceutical glaze

Black iron oxide (E172)

Ammonium hydroxide

Propylene glycol

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original package.

6.5 Nature and contents of container

Aluminium foil blister strips in an over-labelled cardboard carton. Calendar packs of 28 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 1500/1/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th May 2009

10 DATE OF REVISION OF THE TEXT

July 2010