IRISH MEDICINES BOARD ACT 1995, as amended

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

PPA0465/063/002A
Case No: 2086852

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Cardura 2 mg Tablet

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 **10/08/2010** until **17/09/2010**.

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

Cardura 2 mg Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains doxazosin mesilate equivalent to 2mg doxazosin.

Excipients: includes Lactose

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Product imported from the UK:
White oval tablets marked 'DXP2' on one side and 'PFIZER' on the other.

Product imported from Greece, Italy and Hungary:
White, flat bevelled edged tablets with 'CN2' and a breakline on one side and 'PFIZER' on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: Cardura is indicated for treatment of hypertension and can be used as a sole agent to control blood pressure in hypertension patients.

In patients inadequately controlled on single antihypertensive therapy, Cardura may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or angiotensin converting enzyme inhibitor.

Benign prostatic hyperplasia: Cardura is indicated as an adjunct in the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). It may therefore be of value in patients awaiting prostatic surgery or for whom surgery is not possible.

Cardura may be used in patients who are either hypertensive or normotensive.

4.2 Posology and method of administration

Adults: Cardura is used in a once daily regimen and may be administered in the morning or evening.

Hypertension: It is recommended that therapy be initiated at 1 mg given once daily for one or two weeks to minimise the potential for postural hypotension and/or syncope *(see section 4.4 Special warnings and special precautions for use)*. The dosage may then be increased to 2 mg once daily for an additional one or two weeks. If necessary the daily dosage should then be increased gradually at similar intervals to 4mg, 8 mg, and 16 mg as determined by patient response to achieve the desired reduction in blood pressure. The usual dose is 2-4mg once daily.

The maximum daily dose should not exceed 16 mg.

Diuretic therapy may be introduced, if required.

Benign prostatic hyperplasia: The recommended initial dosage of Cardura is 1mg given once daily to minimise the potential for postural hypotension and/or syncope *(see sections 4.4 Special warnings and special precautions for use).* Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4mg and up to the maximum recommended dose of 8 mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4mg once daily.

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

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

Pateints with renal impairment: Since there is no change in pharmacokinetics in patients with impaired function, the usual adult dose of Cardura is recommended. Cardura is not dialyzable.

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

4.3 Contraindications

Cardura is contra-indicated in patients with a known hypersensitivity to quinazolines, doxazosin, or any of the inert ingredients.

Use during lactation

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

4.4 Special warnings and precautions for use

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 *(see section 4.2 Posology and method of administation).* 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 patients should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of Cardura therapy, such as driving or operating machinery.

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.

Patients with renal impairment: There is no evidence that Cardura aggravates renal dysfunction. Cardura dosage introduction and adjustment should be carried out with great care.

Patients with hepatic impairment:
There is 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 wholly metabolised by the liver, Cardura should be used with care in patients with significant existing hepatic dysfunction (*see section 4.2 Posology and method of administration, and section 5.2 Pharmacokinetic properties).*

The mean terminal half-life of doxazosin is 22 hours. This may be prolonged in patients with congestive heart failure. The rate of dose adjustment may need to be slowed.

In some patients with left ventricular failure, the decrease in left ventricular filling associated with vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of doxazosin. These effects should be kept in mind when introducing therapy and continuous adjustment of dose used.

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

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.

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 indomethacin), however, the theoretical potential for interaction with other protein bound drugs should be borne in mind.

No adverse drug reactions have been observed with thiazide diuretics, frusemide, 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).*

In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1mg dose of doxazosin on day 1of a four-day regimen of oral cimetidine (400mg 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 of 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 the other hypertensives.

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 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's use during pregnancy has not yet been established. Accordingly, Cardura should be used only when, in the opinion of the physician, potential benefits outweigh the potential risks.

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 cause drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

Hypertension: In clinical studies involving patients with hypertension, the most common reactions associated with Cardura therapy were of a postural type (rarely associated with fainting), or non-specific and included:

Ear and Labyrinth Disorders: Vertigo

Gastrointestinal Disorders: Nausea

General Disorders and Administration Site Conditions: asthenia, oedema, fatigue, malaise

Nervous system disorders: dizziness, headache, postural dizziness, somnolence, syncope

Respiratory, Thoracic and Mediastinal Disorders: rhinitis

Benign prostatic hyperplasia: Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension.

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: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, dry mouth, vomiting

General Disorders and Administration Site Conditions: 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, back pain, muscle cramps, muscle weakness, myalgia.

Nervous System Disorders**:** hypoaesthesia, paraesthesia, tremor

Psychiatric Disorders: agitation, anxiety, depression, insomnia, nervousness

Renal and Urinary System Disorders: dysuria, haematuria, micturition disorder, micturition frequency, nocturia, polyuria, urinary incontinence

Reproductive System and Breast Disorder: gynaecomastia, impotence, priapism

Respiratory, Thoracic and Mediastinal Disorders: aggravated bronchospasm, coughing, dyspnoea, epistaxis

Skin and Subcutaneous Tissue Disorders: alopecia, pruritus, purpura, skin rash, urticaria

Vascular Disorders: Hot flushes, hypotension, postural 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: bradycardia, tachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, cerebrovascular accidents and cardiac arrythmias.

4.9 Overdose

Should overdose 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

Administration of Cardura reduces blood pressure due to a decrease in systemic vascular resistance. With once daily dosing, clinically significant reductions in blood pressure are maintained throughout the day and at 24 hours post-dose. During the onset of therapy, a gradual reduction in blood pressure occurs, and orthostatic effects are comparable with those of other antihypertensives.

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

Cardura is suitable to use in patients with co-existent asthma, left ventricular hypertrophy and in elderly patients.

Treatment with Cardura has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, Cardura improves insulin sensitivity in patients who have impairment.

Cardura 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.

Administration of Cardura to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the alpha-adrenoceptors located in the muscular stroma and capsule of the prostate, and in the bladder neck.

Doxazosin has been shown to be an effective blocker of the 1A subtype of the alpha-1-adrenoceptor which accounts for over 70% of the subtypes in the prostate. This accounts for the action in BPH patients.

Cardura has demonstrated sustained efficacy and safety in the long-term treatment of BPH.

5.2 Pharmacokinetic properties

Absorption: following oral administration in humans (young male adults or the elderly of either sex), doxazosin is well absorbed and approximately two thirds of the dose is bioavailable.

Biotransformation/Elimination: Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is primarily metabolized by O-demethylation and hydroxylation.

Doxazosin is extensively metabolized in man and in the animal species tested, with the faeces being the predominant route of excretion.

The mean plasma elimination half-life is 22 hours thus making the drug suitable for once daily administration.

After oral administration of doxazosin the plasma concentrations of the metabolites are low. The most active (6’ hydroxy) metabolite is present in man at one fortieth of the plasma concentration of the parent compound which suggests that the antihypertensive activity is in the main due to doxazosin.

Pharmacokinetic studies in the elderly and patients with renal insufficiency have shown no significant alterations compared to younger 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 subjects 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 40%. As with any drug wholly metabolized by the liver, use of Cardura in patients with impaired liver function should be undertaken with caution *(see section 4.4 Special warnings and special precautions for use).*

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

Lactose
Microcrystalline cellulose
Sodium laurilsulfate
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be 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 30^{o}C.

6.5 Nature and contents of container

Blister packs of 14, 28 and 30 tablets contained in an outer cardboard carton.

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

The tablets should not be broken.

7 MARKETING AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/063/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 August 2000

Date of last renewal: 18 August 2005

10 DATE OF REVISION OF THE TEXT

October 2008