IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PPA1473/006/002
Case No: 2066413

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

McDowell Pharmaceuticals

4 Altona Road, **Lisburn**, **N. Ireland**, **BT27 5QB**

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 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 **08/12/2009**.

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 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;
Cardura XL 8mg are white, round, biconvex shaped tablets with an orifice on one side marked ‘CXL8’ and plain on the other.

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:

1) Patients with a known hypersensitivity to quinazolines (e.g. doxazosin, prazosin, terazosin), or any of the excipients.
2) Patients with a history of orthostatic hypotension.
3) Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones.
4) Patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
5) During lactation (please see section 4.6).

Doxazosin is contraindicated in hypertensive patients with concomitant benign prostatic hyperplasia with either overflow bladder or anuria with or without progressive renal insufficiency**.**

4.4 Special warnings and precautions for use

Information to be given to 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 active compound is surrounded by an inert, non-absorbable shell that has been specially designed to control the release of the drug over a prolonged period. After transit through the gastrointestinal tract, when this process is completed the empty tablet shell is eliminated from the body. Patients should be advised that they should not be concerned if they occasionally observe remains in their stools that look like a tablet.

Abnormally short transit times through the gastrointestinal tract (e.g. following surgical resection) could result in incomplete absorption. In view of the long half life of doxazosin the clinical significance of this is unclear.

Postural Hypotension / Syncope:
Initiation of therapy - 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. Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimise the potential for postural effects.

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 operating machinery.

Use in patients with Acute Cardiac Conditions:
As with any other vasodilatory anti-hypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with the following acute cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis
- heart failure at high output
- right-sided heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

Use in Hepatically Impaired Patients: As with any drug wholly metabolised by the liver, Cardura XL should be administered with particular caution to patients with evidence of impaired hepatic function (see section 5.2 Pharmacokinetic properties). Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

Use in patients with 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.

Use with PDE-5 Inhibitors*:* Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, and vardenafil) should be used with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. To reduce the risk of orthostatic hypotension it is recommended to initiate the treatment with phosphodiesterase-5-inhibitors only if the patient is hemodynamically stabilized on alpha-blocker therapy. Furthermore, it is recommended to initiate phosphodiesterase-5-inhibitor treatment with the lowest possible dose and to respect a 6-hour time interval from intake of doxazosin. No studies have been conducted with doxazosin prolonged release formulations.

Use in patients undergoing 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-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

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.

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.

Conventional doxazosin has been administered without any adverse drug interactions in clinical experience with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or anticoagulants. However, data from formal drug/drug interaction studies are not present.

Doxazosin can potentiate the blood pressure lowering activity of other alpha-blockers and other antihypertensives.

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.

4.6 Pregnancy and lactation

For the hypertension indication:

Use during pregnancy: 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.
Doxazosin crosses the placenta. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses (see Section 5.3: Preclinical Safety Data). These doses were approximately 300 times the maximum recommended human dose.

Use during lactation: Doxazosin is contraindicated during lactation as animal studies have shown that doxazosin accumulates in milk of lactating rats, and there is no information about the excretion of the drug into the milk of lactating women. The clinical safety of Cardura during lactation has not been established, consequently Cardura is contra-indicated in nursing mothers.

Alternatively, mothers should stop breast-feeding when treatment with doxazosin is necessary (Please see section 5.3: Preclinical Safety Data).

4.7 Effects on ability to drive and use machines

The ability to engage in activities such as operating machinery or operating a motor vehicle 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.

Frequencies used are as follows: Very common ≥ 1/10, Common ≥ 1/100 and < 1/10, Uncommon ≥ 1/1,000 and < 1/100, Rare ≥ 1/10,000 and < 1/1,000, Very rare < 1/10,000.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Very Rare	Leukopenia, thrombocytopenia
Immune System Disorders	Uncommon	Allergic drug reaction
Metabolism and Nutrition Disorders	Uncommon	Anorexia, gout, increased appetite
Psychiatric Disorders	Uncommon	Anxiety, depression, insomnia
	Very Rare	Agitation, nervousness
Nervous System Disorders	Common	Dizziness, headache, somnolence
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Dizziness postural, paresthesia
Eye Disorders	Very Rare	Blurred vision
	Unknown	Intropeative floppy iris syndrome (see Section 4.4)
Ear and Labyrinth Disorders	Common	Vertigo
	Uncommon	Tinnitus
Cardiac Disorders	Common	Palpitation, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very Rare	Bradycardia, cardiac arrhythmias
Vascular Disorders	Common	Hypotension, postural hypotension
	Very Rare	Hot Flush
Respiratory, Thoracic and Mediastinal Disorders	Common	Bronchitis, cough, dyspnea, rhinitis
	Uncommon	Epistaxis

	Very Rare	Aggravated Bronchospasm
Gastrointestinal Disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
	Uncommon	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis
Hepatobiliary Disorders	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
	Uncommon	Skin rash
	Very Rare	Alopecia, purpura, urticaria
Musculoskeletal and Connective Tissue Disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia
	Very Rare	Muscle cramps, muscle weakness
Renal and Urinary Disorders	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, hematuria, micturition frequency
	Very Rare	Micturition disorder, nocturia, polyuria, increased diuresis
Reproductive System and Breast Disorders	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Unknown	Retrograde ejaculation
General Disorders and Administration Site Conditions	Common	Asthenia, chest pain, influenza-like symptoms, peripheral edema
	Uncommon	Pain, facial oedema
	Very Rare	Fatigue, malaise,
Investigations	Uncommon	Weight increase

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 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°C.
Store in the original package.

6.5 Nature and contents of container

Aluminium foil blister strips in a 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

McDowell Pharmaceuticals
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Lisburn
N Ireland BT27 5QB

8 Parallel Product Authorisation Number

PPA 1473/6/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 20th February 2009

10 DATE OF REVISION OF THE TEXT

December 2009