Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cardura 2 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.43mg doxazosin mesilate equivalent to 1mg doxazosin.

Each tablet also contains lactose monohydrate. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Product imported from the UK:
White **oblong** biconvex tablets: marked “CN 2” and scored on one side and marked with the Pfizer logo on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: Cardura 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 may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an 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 BPH 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 4 mg, 8 mg, and l6 mg as determined by patient response to achieve the desired reduction in blood pressure. The usual dose is 2-4 mg 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 1 mg given once daily to minimise the potential for postural hypotension and/or syncope (see section 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 4 mg and up to the maximum recommended dose of 8 mg.
The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4 mg once daily.

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

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

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

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 precautions for use, and section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Doxazosin is contraindicated in:

1) Patients with a known hypersensitivity to quinazolines (e.g. prazosin, terazosin, doxazosin), 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) During lactation (please see section 4.6)
5) Patients with hypotension (for benign prostatic hyperplasia indication only)

Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

4.4 Special warnings and precautions for use

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 (see section 4.2 Posology and method of administration). 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 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:
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 administered with particular caution to patients with evidence of impaired hepatic function (see section 4.2 Posology and method of administration, and 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 with PDE-5 Inhibitors:
Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (eg sildenafil, tadalafil, and vardenafil) should be done 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 with Renal Impairment:
There is no evidence that Cardura aggravates renal dysfunction. However, Cardura dosage introduction and adjustment should be carried out with great care.

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.

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.

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

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 doxazosin prolonged release formulations.

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 interaction in clinical experience with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, and anticoagulants. However, data from formal drug/drug interaction studies are not present.

Doxazosin potentiates 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: Doxazosin crosses the placenta.

As there are no adequate and well-controlled studies in pregnant women, the safety of Cardura during pregnancy has not yet been established. Accordingly, Cardura should be used only when, in the opinion of the physician, the potential benefit outweighs the potential risk. 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).

For the benign prostatic hyperplasia indication: This section is not applicable.

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

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

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

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	gout, increased appetite Anorexia

Psychiatric Disorders	Uncommon	Agitation, depression Anxiety, insomnia, nervousness
Nervous System Disorders	Common	somnolence Dizziness, headache
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Dizziness postural, paresthesia,
Eye Disorders	Very Rare	Blurred vision
	Unknown	Intraoperative 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 flushes
Respiratory, Thoracic and Mediastinal Disorders	Common	Bronchitis, cough, dyspnea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Bronchospasm
Gastrointestinal Disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea,
	Uncommon	Constipation, flatulence, vomiting, gastroenteritis diarrhoea
Hepatobiliary Disorders	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
	Uncommon	Skin rash,
	Very Rare	urticaria alopecia, purpura
Musculoskeletal and Connective Tissue Disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia,
	Rare	muscle cramps, muscle weakness
Renal and Urinary Disorders	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, micturition frequency, hematuria
	Rare	polyuria
	Very Rare	Increased diuresis, micturition disorder, nocturia
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 oedema,
	Uncommon	Pain, facial oedema
	Very Rare	fatigue, malaise
Investigations	Uncommon	Weight increase

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.

If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressor should then be used. Renal function should be monitored and supported as needed.
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 high density lipoprotein (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 in primarily metabolised by O-demethylation and hydroxylation.

Doxazosin is extensively metabolised 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 safety 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
magnesium stearate
microcrystalline cellulose
sodium lauril sulfate
sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date of this product shall be the date shown on the blister strip 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.

6.5 Nature and contents of container

Cardura 1 mg tablets are available as calendar packs of 28 tablets.
Aluminium foil/aluminium foil blister strips contained in a 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

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

IPS Healthcare Limited
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1659/12/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010

10 DATE OF REVISION OF THE TEXT