HPRA

CARDURA

2 Milligram Tablets

Pfizer Limited

PA0019/043/002

Main Information

Trade Name	CARDURA
Active Substances	DOXAZOSIN
Strength	2 Milligram
Dosage Form	Tablets
Licence Holder	Pfizer Limited
Licence Number	PA0019/043/002

Group Information

ATC Code	C02CA04 Alpha-adrenoreceptor antagonists

Status

Authorised/Withdrawn	Authorised
Licence Issued	21/12/1987

Supply Status	Supply through pharmacies only
Dispensing Status	Product subject to prescription which may be renewed (B)
Marketing Status	Marketed
Promotion Status	Promotion to Healthcare Professionals only
Conditions of Licence	

Documents

Summary of Product Characteristics	PDF Version
Package Leaflet	PDF Version
Public Assessment Report	No document available

Generics Information

Interchangeable List	Doxazosin 2mg Tablets
Interchangeable List Code	IC0021-006-002
Interchangeable List Document	PDF of Interchangeable List

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Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland, D02 XP77

+353 (1) 676 4971 info@hpra.ie

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

CARDURA 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxazosin mesilate 2.43 mg equivalent to 2 mg doxazosin.

Excipient with known effect:
Each tablet contains 40 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

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

Posology
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). 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 16mg

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 section 4.4). Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2mg and thereafter to 4mg and up to the maximum recommended dose of 8mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4mg once daily.

Paediatric population:
The safety and efficacy of Cardura in children and adolescents have not been established.

Elderly patients:
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 and section 5.2).

4.3 Contraindications

Doxazosin is contraindicated in:
1) Hypersensitivity to the active substance, other types of quinazolines (e.g. prazosin, terazosin) or to any of the excipients listed in section 6.1
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 (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 – In relation with the alpha-blocking properties of doxazosin, patients may experience postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy (see section 4.2). 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 and section 5.2).
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 (e.g. 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.

Priapism:
Prolonged erections and priapism have been reported with alpha-1 blockers including doxazosin in post marketing experience If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance.

Screening for Prostate Cancer: Carcinoma of the prostate causes many of the symptoms associated with BPH and the two disorders can co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin for treatment of BPH symptoms.

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). 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.

In vitro studies suggest that doxazosin is a substrate of cytochrome P450 3A4 (CYP 3A4). Caution should be exercised when concomitantly administering doxazosin with a strong CYP 3A4 inhibitor, such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole (see section 5.2).

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 Fertility, pregnancy and lactation

<u>For the hypertension indication:</u>
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, during pregnancy, 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). These doses were approximately 300 times the maximum recommended human dose.

Use during lactation: The excretion of doxazosin in breast milk was demonstrated to be very low (with the relative infant dose less than 1%) however human data is very limited. A risk to the newborn or infant cannot be excluded and therefore doxazosin should be used only when in the opinion of the physician, the potential benefit outweighs the potential risk.

<u>For the benign prostatic hyperplasia indication:</u>
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

Hypotension: 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.

The following undesirable effects have been observed and reported during treatment with Cardura with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Unknown
Infections and infestations		Respiratory tract infection, urinary tract infection				
Blood and the lymphatic system disorders					Leukopenia, thrombocytopenia	
Immune system disorders			Allergic drug reaction			
Metabolism and nutrition disorders			Gout, increased appetite, anorexia			
Psychiatric disorders			Agitation, depression, anxiety, insomnia, nervousness			
Nervous system disorders		Somnolence dizziness, headache	Cerebrovascular accident, hypoesthesia, syncope, tremor		Dizziness postural, paresthesia	
Eye disorders					Blurred vision	Intraoperative floppy iris syndrome (see section 4.4)
Ear and labyrinth disorders		Vertigo	Tinnitus			
Cardiac disorders		Palpitation, tachycardia	Angina pectoris, myocardial infarction		Bradycardia, cardiac arrhythmias	
Vascular disorders		Hypotension, postural hypotension			Hot flushes	
Respiratory, thoracic and mediastinal disorders		Bronchitis, cough, dyspnoea, rhinitis	Epistaxis		Bronchospasm	

Gastrointestinal disorders		Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, flatulence, vomiting, gastroenteritis, diarrhoea			
Hepato-biliary disorders			Abnormal liver function tests		Cholestasis, hepatitis, jaundice	
Skin and subcutaneous tissue disorders		Pruritus	Skin rash		Urticaria alopecia, purpura	
Musculoskeletal, connective tissue and bone disorders		Back pain, myalgia	Arthralgia	Muscle cramps, muscle weakness		
Renal and urinary disorders		Cystitis, urinary incontinence	Dysuria, micturition frequency, hematuria	Polyuria	Increased diuresis, micturition disorder, nocturia	
Reproductive system and breast disorders			Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions		Asthenia, chest pain, influenza-like symptoms, peripheral oedema	Pain, facial oedema		Fatigue, malaise	
Investigations			Weight increase			

Reporting of side effects
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures should be performed if thought 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

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists

ATC code: C02CA04

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 is primarily metabolised by O-demethylation and hydroxylation.

Doxazosin is extensively metabolized in the liver. In vitro studies suggest that the primary pathway for elimination is via CYP 3A4; however, CYP 2D6 and CYP 2C9 metabolic pathways are also involved for elimination, but to a lesser extent.

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 metabolised by the liver, use of Cardura in patients with impaired liver function should be undertaken with caution (see section 4.4).

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, carcinogenicity and gastrointestinal tolerance.

Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at doses approximately 300 times greater than the maximum human recommended dose.

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

For further information see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Sodium laurilsulfate
Sodium starch glycolate (type A)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Cardura 2mg Tablets are available as calendar packs of 28 tablets. Aluminium/PVC/PVdC blister strips, 14 tablets/strip, 2 strips in a carton box.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0019/043/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 December 1987

Date of latest renewal: 21 December 2007

10 DATE OF REVISION OF THE TEXT

August 2017