SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

CARDURA XL 8mg prolonged release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

9.70mg doxazosin mesilate equivalent to 8mg doxazosin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet

White film coated, round, biconvex shaped tablets with a hole in one side, marked CXL8.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Benign Prostatic Hyperplasia: Cardura XL is indicated for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH).

Cardura XL may be used in BPH patients who are either hypertensive or normotensive. While the blood pressure changes in normotensive patients with BPH are not usually clinically significant, patients with hypertension and BPH have had both conditions effectively treated with doxazosin monotherapy.

4.2 Posology and method of administration

Posology

Hypertension and benign prostatic hyperplasia: The initial dose of Cardura XL is 4mg once daily. Over 50% of patients with mild to moderate severity hypertension will be controlled on Cardura XL 4mg once daily. Optimal effect of Cardura XL may take up to 4 weeks. If necessary, the dosage may be increased following this period to 8mg once daily according to patient response.

The maximum recommended dose of Cardura XL is 8mg once daily.

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

Elderly patients: Normal adult dosage.

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

Patients with hepatic impairment: 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 sections 4.4 and 5.2).

Method of administration

Cardura XL can be taken with or without food.

The tablets should be swallowed whole with a sufficient amount of liquid. Patients should not chew, divide or crush the tablets (see section 4.4).

4.3 Contraindications

Cardura XL is contraindicated in:

1) Patients with known hypersensitivity to doxazosin, quinazolines 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) Patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.
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

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 (see section 4.2).

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 the empty tablet shell is excreted. 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:
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. 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.

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
- high-output cardiac failure
- right-sided heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

Use in patients with hepatic impairment:
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 sections 4.2 and 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 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.

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

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.

Excipient information:
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil)</u>
Concomitant administration of doxazosin 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 indomethacin).

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 interactions in clinical experience with thiazide diuretics, frusemide, 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 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 C_{max} 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

For the hypertension indication:

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, during pregnancy, Cardura XL 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).

Breast-feeding

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.

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.

4.8 Undesirable effects

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

The following undesirable effects have been observed and reported during treatment with Cardura XL 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), Not known (cannot be estimated from the available data).

System Organ Class	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		Anorexia, gout, increased appetite			
Psychiatric disorders		Anxiety, depression, insomnia		Agitation, nervousness	
Nervous system disorders	Dizziness, headache, somnolence	Cerebrovascular accident, hypoesthesia, syncope, tremor		Dizziness postural, paresthesia	
Eye disorders				Blurred vision	Intropera tive floppy iris syndrome (see Section 4.4)
Ear and labyrinth disorders	Vertigo	Tinnitus			
Cardiac	Palpitation,	Angina		Bradycardia,	

disorders	tachycardia	pectoris, myocardial infarction		cardiac arrhythmias	
Vascular disorders	Hypotension, postural hypotension			Flush	
Respiratory, thoracic and mediastinal disorders	Bronchitis, cough, dyspnea, rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders	Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis	Gastrointestinal obstruction		
Hepato-biliary disorders		Abnormal liver function tests		Cholestasis, hepatitis, jaundice	
Skin and subcutaneous tissue disorders	Pruritus	Skin rash		Alopecia, purpura, urticaria	
Musculoskeletal, connective tissue and bone disorders	Back pain, myalgia	Arthralgia		Muscle cramps, muscle weakness	
Renal and urinary disorders	Cystitis, urinary incontinence	Dysuria, hematuria, micturition frequency		Micturition disorder, nocturia, polyuria, increased diuresis	
Reproductive system and breast disorders		Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions	Asthenia, chest pain, influenza-like symptoms, peripheral edema	Pain, facial oedema		Fatigue, malaise	
Investigations		Weight increase			

Reporting of suspected adverse reactions

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 the Yellow Card Scheme at

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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. 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

Mechanism of action
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, the decrease in blood pressure during treatment with Cardura XL was similar in both the sitting and standing position.

Subjects treated with immediate release doxazosin tablets can be transferred to Cardura XL 4mg and the dose titrated upwards as needed.

Pharmacodynamic effects

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 co-existent 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, in addition to its antihypertensive effect, has in long term studies produced a modest reduction in plasma total cholesterol, LDL-cholesterol and triglyceride concentrations and therefore may be of particular benefit to hypertensive patients with concomitant hyperlipidaemia.

Administration of Cardura XL 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 prostatic muscular stroma, capsule and bladder neck.

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 doxazosin tablets. Trough levels at 24 hours are, however, similar.

Peak/trough ratio of Cardura XL is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from Cardura XL compared to 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 basic for once daily dosing. Doxazosin is extensively metabolised with <5% excreted as unchanged drug.

Pharmacokinetic studies with doxazosin 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 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%.

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.

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.

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 radioactive doxazosin indicate that doxazosin accumulates in rat milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

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

PVC/PVDC blister with aluminium foil

2 years.

Blister strips of aluminium foil/aluminium foil

3 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

PVC/PVDC blister with aluminium foil strips of 7, 14 and 10 tablets in pack size of 28 or 30 tablets.

Blister strips of aluminium foil/aluminium foil of 7, 14 and 10 tablets in pack size of 28 or 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Upjohn UK Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 50622/0010

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04/01/2021