SCHEDULING STATUS: S3

PROPRIETARY NAMES (AND DOSAGE FORM):

CARDURA® XL 4 mg TABLETS

CARDURA® XL 8 mg TABLETS

COMPOSITION:

Each 4 mg CARDURA XL tablet contains 5,093 mg doxazosin mesylate equivalent to 4 mg doxazosin.

Each 8 mg CARDURA XL tablet contains 10,185 mg doxazosin mesylate equivalent to 8 mg doxazosin.

Sugar free.

CARDURA XL tablets contain the following inert ingredients: polyethylene oxide, sodium chloride, hydroxypropyl methylcellulose, red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, polyethylene glycol and black ink.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators, hypotensive medicines

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Doxazosin exerts a vasodilator effect via selective and competitive blockade of post-junctional alpha 1-adrenoceptors.

Pharmacokinetic properties:

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

Doxazosin is extensively metabolised primarily by O-demethylation and hydroxylation with less than 5 % excreted as the unchanged substance.

Peak/trough ratio of CARDURA XL is less than half that of conventional doxazosin tablets.

The plasma elimination of CARDURA XL is biphasic with the terminal elimination half-life being 22

hours, hence providing the basis for once daily dosing.

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 %.

Most (98 %) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicates that doxazosin has no effect on protein binding of the agents tested (digoxin, phenytoin, warfarin or indomethacin).

INDICATIONS:

CARDURA XL is indicated for the treatment of mild to moderate hypertension.

CARDURA XL is also indicated for the treatment of symptoms in Benign Prostatic Hyperplasia (BPH) and for reduced urinary flow associated with BPH. CARDURA XL may be used in BPH patients who are either hypertensive or normotensive.

CONTRAINDICATIONS:

CARDURA XL is contraindicated in:

- Patients with a known hypersensitivity to quinazolines, doxazosin or any of the inert ingredients.
- Pregnancy and lactation. See PREGNANCY AND LACTATION.
- Patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract.

WARNINGS AND SPECIAL PRECAUTIONS:

Postural hypotension/syncope:

Postural hypotension may occur with initiation of therapy with this agent, evidenced by dizziness and weakness or rarely loss of consciousness (syncope) particularly with the commencement of therapy. When instituting therapy with CARDURA XL, the patient should be advised on how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. Patients should be warned about this. 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 with PDE-5 Inhibitors:

Concomitant administration of CARDURA XL with a PDE-5 inhibitor should be used with caution as it may lead to symptomatic hypotension in some patients. No studies have been conducted with doxazosin GITS.

Impaired hepatic function:

Special precaution must be taken in patients with impaired liver function (see PHARMACOLOGICAL ACTION).

Intraoperative Floppy Iris Syndrome:

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 CARDURA XL and other alpha-1 blockers. As IFIS may lead to increased procedural complications during the operation, current or past use of CARDURA XL should be made known to the ophthalmologic surgeon in advance of surgery.

Driving/use of machinery:

The ability to engage in activities such as operating machinery or driving a motor vehicle may be impaired especially when initiating therapy.

INTERACTIONS:

Concomitant administration of CARDURA XL with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients. See WARNINGS. No studies have been conducted with doxazosin GITS.
No adverse interaction has been noted in clinical experience to date with thiazide diuretics, furosemide, beta-blocking agents, antibiotics, oral hypoglycaemic medicines, non-steroidal anti-inflammatory drugs (NSAIDs), uricosuric agents or anticoagulants. Administration of CARDURA XL may reduce plasma concentrations of triglycerides, total and LDL-cholesterol and increase HDL-cholesterol. These potentially favourable effects on lipids persist when a thiazide-type diuretic is given concurrently. The long-term consequences of these medicine-induced changes in lipids are not known.

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation have not been established.

DOSAGE AND DIRECTIONS FOR USE:

Patients established on conventional CARDURA tablets 1 mg to 4 mg daily may be controlled on CARDURA XL 4 mg daily.

Those patients established on conventional CARDURA 8 mg daily may be controlled on CARDURA XL 8 mg daily.

Hypertension:

The majority of patients will be controlled on 4 mg daily. If necessary, the dosage may be increased to 8 mg once daily according to patient response.

In patients not adequately controlled on a single antihypertensive agent, CARDURA XL may be used in combination with a thiazide diuretic or a beta-blocking agent.

Benign Prostatic Hyperplasia:

The recommended dosage of CARDURA XL is 4 mg once daily. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 8 mg daily.

The recommended titration interval is 1 – 2 weeks. Blood pressure should be evaluated routinely in these patients.

CARDURA XL can be taken with or without food. The tablets should be swallowed whole with a sufficient amount of liquid.

INFORMATION FOR 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 medication is contained within a non-absorbable shell that has been specially designed to slowly release the medicine. When this process is completed the empty tablet is eliminated from the body. Patients should be advised that they should not be concerned if they occasionally observe the empty tablet in the stools.

USE IN ELDERLY:

Normal adult dosage is recommended. Pharmacokinetic studies with CARDURA XL in the elderly have shown no significant alterations compared to younger patients.

USE IN HEPATICALLY IMPAIRED PATIENTS:

There are only limited data in patients with liver impairment and on the effects of medicines known to influence hepatic metabolism (e.g. cimetidine).

Doxazosin is wholly metabolised by the liver and should be administered with caution to patients with evidence of impaired hepatic function.

USE IN RENALLY IMPAIRED PATIENTS:

Since the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that CARDURA XL aggravates existing renal dysfunction, the usual dosages may be used in these patients.

USE IN CHILDREN:

The safety and efficacy of CARDURA XL in children have not been established.

SIDE EFFECTS:

The adverse event profile in elderly (> 65 years) BPH patients showed no difference from the profile in the younger population.

Adverse events have been categorised as follows:

Very common: ≥ 1/10 (≥ 10 %); Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %); Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %); Rare: ≥ 1/10 000 and < 1/1 000 (≥ 0,01 % and < 0,1 %); Very rare: < 1/10 000 (< 0,01 %).

In controlled clinical trials, the most common reactions associated with CARDURA XL were of a postural type (rarely associated with syncope) or non-specific and included:

MedDRA System Organ Class	**Frequency**	**Undesirable effects**
Cardiac disorders	Common	Palpitation, tachycardia
Ear and labyrinth disorders	Common	Vertigo
Gastrointestinal disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
General disorders and administration site conditions	Common	Asthenia, chest pain, peripheral oedema
Infections and infestations	Common	Respiratory tract infection, urinary tract infection, Influenza-like symptoms

Musculoskeletal and connective tissue disorders	Common	Back pain, myalgia
Nervous system disorders	Common	Dizziness, headache, somnolence
Renal and urinary disorders	Common	Cystitis, urinary incontinence
Respiratory, thoracic and mediastinal disorders	Common	Bronchitis, coughing, dyspnoea, rhinitis
Skin and subcutaneous tissue disorders	Common	Pruritus
Vascular disorders	Common	Hypotension, postural hypotension

The incidence of adverse events following treatment with CARDURA XL (41 %) in clinical studies of patients with BPH was broadly similar to that following placebo (39 %) and less than that following standard doxazosin (54 %). The adverse event profile in elderly (< 65 years) BPH patients showed no difference from the profile in the younger population.

In post-marketing experience, the following additional adverse events were reported.

MedDRA System Organ Class	**Undesirable effects**
Blood and lymphatic system disorders	Leukopenia, thrombocytopaenia
Cardiac disorders	Palpitation, tachycardia, angina pectoris, myocardial infarction, bradycardia, cardiac dysrhythmia
Ear and labyrinth disorders	Tinnitus
Eye disorders	Blurred vision, IFIS (Intraoperative Floppy Iris Syndrome)
Gastrointestinal disorders	Dyspepsia, dry mouth, constipation, diarrhoea, flatulence, vomiting
General disorders and administration site conditions	Chest pain, pain, fatigue, malaise
Hepatobiliary disorders	Cholestasis, hepatitis, jaundice
Immune system disorders	Allergic reactions
Investigations	Abnormal liver function tests, weight increase

Metabolism and nutrition disorders	Anorexia
Musculoskeletal and connective tissue disorders	Arthralgia, muscle cramps, muscle weakness
Nervous system disorders	Cerebrovascular accident, hypoaesthesia, syncope, tremor, dizziness postural, paraesthesia
Psychiatric disorders	Anxiety, depression, insomnia, agitation, nervousness
Renal and urinary disorders	Urinary incontinence, dysuria, haematuria, micturition frequency, micturition disorder, nocturia, polyuria
Reproductive system and breast disorders	Impotence, gynaecomastia, priapism, retrograde ejaculation
Respiratory, thoracic and mediastinal disorders	Coughing, dyspnoea, epistaxis, bronchospasm aggravated
Skin and subcutaneous tissue disorders	Pruritus, skin rash, alopecia, purpura, urticaria
Vascular disorders	Hypotension, hot flushes

[1] Cerebrovascular accident was categorised by combining the frequencies of “cerebral infarct”, “cerebral ischaemia” and “cerebrovascular accident”.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position.

Since doxazosin is highly protein bound, dialysis is not indicated.

Treatment is symptomatic and supportive.

IDENTIFICATION:

CARDURA XL 4 mg TABLETS: A round, biconvex shaped white film coated tablet, approximately 9,0 mm in diameter with an orifice on one side imprinted with “CXL 4”.

CARDURA XL 8 mg TABLETS: A round, biconvex shaped white film coated tablet, approximately 11,4 mm in diameter with an orifice on one side imprinted with “CXL 8”.

PRESENTATION:

CARDURA XL 4 mg and CARDURA XL 8 mg TABLETS: Blister strips of 30, 60, 90, 120, 240, 360 or 500 Tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light.

Protect from moisture and humidity.

Keep out of reach of children.

REGISTRATION NUMBERS:

CARDURA XL 4 mg TABLETS: 32/7.1/0556

CARDURA XL 8 mg TABLETS: 32/7.1/0557

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

Manufacturer: Pfizer Pharmaceuticals LLC, Barceloneta, Puerto Rico

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 March 2015

BOTSWANA: S2

CARDURA XL 4 mg – Reg. No.: BOT0700932

CARDURA XL 8 mg – Reg. No.: BOT0700933

NAMIBIA: NS2

CARDURA XL 4 mg – Reg. No.: 04/7.1/1222

CARDURA XL 8 mg – Reg. No.: 04/7.1/1223

ZAMBIA: POM

CARDURA XL 4 mg – Reg. No.: 120/039

CARDURA XL 8 mg – Reg. No.: 120/040

ZIMBABWE: PP10

CARDURA XL 4 mg: 2001/12.3.1/3952