SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

CARDURA® XL 4 mg TABLETS

CARDURA® XL 8 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

Excipients with known effect:

Each CARDURA XL 4 mg tablet contains 29,0 mg sodium chloride.

Each CARDURA XL 8 mg tablet contains 58,0 mg sodium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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”.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 patients with BPH who are either hypertensive or normotensive.

4.2 Posology and method of administration

Posology

The initial dose of CARDURA XL in patients with hypertension and/or BPH is 4 mg once daily in the morning with food. Depending on the patient's symptomatic response and tolerability, the dose may be increased to 8 mg, the maximum recommended dose.

If CARDURA XL is discontinued for several days, therapy should be restarted using a 4 mg once daily dose.

If switching from CARDURA to CARDURA XL, therapy should be initiated with the lowest dose (4 mg once daily). Prior to starting therapy with CARDURA XL, the final evening dose of CARDURA should not be taken.

Hypertension

The majority of patients will be controlled on CARDURA XL 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 medicine, CARDURA XL may be used in combination with a thiazide diuretic or a beta-adrenoceptor blocking medicine.

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 3 – 4 weeks. Blood pressure should be evaluated routinely in these patients.

Special populations

Elderly population

Normal adult dosage is recommended. Due to an enhanced propensity to orthostasis in the elderly, or to an increased sensitivity to vasodilator medicines in the elderly, caution should be exercised in prescribing CARDURA XL to elderly patients, especially those who are ≥ 70 years of age (see section 5.2).

Renal impairment

Since the pharmacokinetics of doxazosin is 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.

Hepatic impairment

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.

Paediatric population

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

Method of administration

For oral use.

CARDURA XL should be taken with food. The tablets should be swallowed whole with a sufficient amount of liquid and must not be chewed, divided, cut, or crushed.

In CARDURA XL, the medicine 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.

4.3 Contraindications

CARDURA XL is contraindicated in:

- Patients with a known hypersensitivity to doxazosin, quinazolines or any of the excipients (listed in section 6.1).
- Pregnancy and lactation (see section 4.6).
- Patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract.

4.4 Special warnings and precautions for use

Postural hypotension/syncope

Postural hypotension may occur with initiation of therapy with CARDURA XL, 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 phosphodiesterase-5 (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 Gastrointestinal Therapeutic System (GITS).

Impaired hepatic function

CARDURA XL should be administered with particular caution to patients with evidence of impaired hepatic function (see sections 4.2 and 5.2).

Cataract surgery

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients on or previously treated with alpha-1 adrenoceptor blockers. This variant of small pupil syndrome is characterised by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilatation with standard mydriatic medicines, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's surgeon should be prepared for possible modifications to their surgical technique, such as the utilisation of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 adrenoreceptor blocker therapy prior to cataract surgery.

Priapism

Prolonged erections (priapism) have been reported with alpha-1 adrenoceptor blockers including CARDURA XL in post-marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent erectile dysfunction. Therefore, patients should be advised about the seriousness of the condition and seek immediate medical assistance.

Sodium

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

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of CARDURA XL with a PDE-5 inhibitor may lead to an additive hypotensive effect and symptomatic hypotension (see section 4.4). No studies have been conducted with doxazosin GITS.

CARDURA XL is highly bound to plasma proteins (98 %). *In vitro* data in human plasma indicate that CARDURA XL has no effect on protein binding of digoxin, phenytoin, warfarin or indomethacin.

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

No adverse interaction has been noted in clinical experience to date with thiazide diuretics, furosemide, beta-adrenoceptor blocking medicines, antibiotics, oral hypoglycaemic medicines, non-steroidal anti-inflammatory drugs (NSAIDs), uricosuric products or anticoagulants. Administration of CARDURA XL may reduce serum concentrations of triglycerides, total and LDL-cholesterol and increase HDL-cholesterol. These potentially favourable effects on lipids persist when a thiazide-like diuretic is given concurrently. The long-term consequences of these medicine-induced changes in lipids are not known.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

CARDURA XL's safety and efficacy in pregnancy and lactation have not been formally established (see section 4.3). Doxazosin is known to transfer into breast milk and to cross the placental barrier.

Fertility

Fertility in males: Studies in rats after oral administration of doxazosin base showed reduced fertility in males, which was reversible after two weeks of treatment termination at doxazosin base exposure of 13-fold above the human exposure (AUC) at the MHRD of 8 mg CARDURA XL. There have been no reports of any effects of doxazosin on male fertility in humans.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated summary of adverse reactions

Adverse events have been categorised as follows: 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).

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**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Nervous system disorders	Common	Dizziness, headache, somnolence
Ear and labyrinth disorders	Common	Vertigo
Cardiac disorders	Common	Palpitation, tachycardia
Vascular disorders	Common	Hypotension, postural hypotension
Respiratory, thoracic and mediastinal disorders	Common	Bronchitis, coughing, dyspnoea, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
Skin and subcutaneous tissue disorders	Common	Pruritus
Musculoskeletal and connective tissue disorders	Common	Back pain, myalgia
Renal and urinary disorders	Common	Cystitis, urinary incontinence
General disorders and administration site conditions	Common	Asthenia, chest pain, influenza like symptoms, peripheral oedema

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

conventional doxazosin (54 %). The adverse event profile in elderly (> 65 years) patients with BPH 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, thrombocytopenia
Immune system disorders	Allergic reactions
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Anxiety, depression, insomnia, agitation, nervousness
Nervous system disorders	Cerebrovascular accident[a], hypoaesthesia, syncope, tremor, postural dizziness, paraesthesia
Eye disorders	Blurred vision, IFIS (Intraoperative Floppy Iris Syndrome)
Ear and labyrinth disorders	Tinnitus
Cardiac disorders	Palpitation, tachycardia, angina pectoris, myocardial infarction, bradycardia, cardiac dysrhythmia
Vascular disorders	Hypotension, hot flushes
Respiratory, thoracic and mediastinal disorders	Coughing, dyspnoea, epistaxis, bronchospasm aggravated
Gastrointestinal disorders	Dyspepsia, dry mouth, constipation, diarrhoea, flatulence, vomiting, gastrointestinal obstruction
Hepatobiliary disorders	Cholestasis, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Pruritus, skin rash, alopecia, purpura, urticaria
Musculoskeletal and connective tissue disorders	Arthralgia, muscle cramps, muscle weakness
Renal and urinary disorders	Urinary incontinence, dysuria, haematuria, micturition frequency, micturition disorder, nocturia, polyuria
Reproductive system and breast	Impotence, gynaecomastia, priapism, retrograde ejaculation

disorders	
General disorders and administration site conditions	Chest pain, pain, fatigue, malaise
Investigations	Abnormal liver function tests, weight increase

[a] Cerebrovascular accident was categorised by combining the frequencies of "cerebral infarct", "cerebral ischaemia" and "cerebrovascular accident".

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypotensive, antihypertensive medicines include other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS, etc

Mechanism of action

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

Administration of doxazosin GITS 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-adrenoceptors 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 doxazosin GITS was similar in both the sitting and standing positions.

Subjects treated with conventional doxazosin can be transferred to doxazosin GITS and the dose titrated upwards as needed.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, doxazosin GITS is well absorbed with peak blood levels gradually reached at 8 to 9 hours after dosing. Peak plasma levels (C_{max}) are approximately one third of those of the same dose of conventional doxazosin tablets. Trough levels at 24 hours are, however, similar.

Peak/trough blood level fluctuation of doxazosin GITS is significantly lower and less than half that of conventional doxazosin tablets.

At steady state, the relative bioavailability of doxazosin from doxazosin GITS compared to the conventional form was 54 % with the 4 mg dose and 59 % with the 8 mg dose.

Pharmacokinetic studies with doxazosin GITS in the elderly have shown no significant alterations compared to younger patients.

Biotransformation/elimination

The plasma elimination of doxazosin is biphasic with the terminal elimination half-life being 22 hours, hence providing the basis for once daily dosing. Doxazosin is extensively metabolised, with < 5 % excreted as unchanged medicine.

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 medicines 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.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Doxazosin is extensively metabolised 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hydroxypropyl methylcellulose

Magnesium stearate

Polyethylene oxide

Red ferric oxide

Sodium chloride

Film-coat

Black ink (ammonium hydroxide, iron oxide black, isopropyl alcohol, modified pharmaceutical glaze, n-butyl alcohol, propylene glycol)

Cellulose acetate

Polyethylene glycol

Opadry White (hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

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

Protect from moisture and humidity.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Tel.: +27(011) 451 1300 / +27(071) 281 2503 (24 hours)

Manufacturer: Viatris Pharmaceuticals LLC, Barceloneta, Puerto Rico

8. REGISTRATION NUMBERS

CARDURA XL 4 mg TABLETS: 32/7.1/0556

CARDURA XL 8 mg TABLETS: 32/7.1/0557

9. DATE OF FIRST AUTHORISATION

28 June 2000

10. DATE OF REVISION OF THE TEXT

11 July 2021

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 – Reg. No.: 2001/12.3.1/3952

CARDURA XL 8 mg – Reg. No.: 2001/12.3.1/3953