PROFESSIONAL INFORMATION

CARZIN XL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CARZIN XL 4 mg, prolonged release film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains doxazosin mesylate equivalent to 4 mg doxazosin.

Each tablet contains sugar (lactose monohydrate 74,27 mg).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged release, film coated tablets.

White, round, slightly biconvex, film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARZIN XL is indicated for:

- treatment of mild to moderate hypertension
- the treatment of symptoms in benign prostatic hyperplasia (BPH) and for reduced urinary flow associated with BPH. CARZIN XL may be used in patients with BPH who are either hypertensive or normotensive.

4.2 Posology and method of administration

The orthostatic hypotension effect of CARZIN XL following the initial dose can be avoided by starting treatment with a low dose, preferably at night.

The initial dose of CARZIN 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.

Should CARZIN XL be discontinued for several days, therapy should be restarted using a 4 mg once daily dose.

Hypertension

The usual dose is one CARZIN XL 4 mg tablet once daily; (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 the patient's response.

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

Benign Prostatic Hyperplasia

The usual dose is one CARZIN XL 4 mg tablet once daily. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 8 mg once daily.

The recommended titration interval is 3 - 4 weeks. Blood pressure should be evaluated routinely in these patients.

Special populations

Use in elderly

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 CARZIN XL to elderly patients, especially those who are ≥ 70 years of age.

Use in renally impaired patients

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

Use in hepatically impaired patients

CARZIN XL is wholly metabolised by the liver and should be administered with caution to patients with evidence of impaired hepatic function. Use in patients with severe hepatic impairment is not recommended.

Paediatric population

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

Method of administration

Oral use.

CARZIN 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.

4.3 Contraindications

CARZIN XL is contraindicated in

- hypersensitivity to doxazosin, other quinazolines or to any of the ingredients of CARZIN XL
- patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract
- pregnancy and lactation (see section 4.6)
- patients with a history of orthostatic hypotension
- patients with benign prostatic hyperplasia and concomitant congestion of the upper

urinary tract, chronic urinary tract infection or bladder stones

- patients with hypotension (for benign prostatic hyperplasia indication only).

CARZIN XL 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

There is a potential for dizziness, weakness, and syncope after an initial dose or after an increase in dosage strength when CARZIN XL is administered to patients with symptomatic hypotension (see sections 4.2, 4.5 and 4.8).

Upon initiation of therapy, 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 and should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of CARZIN XL therapy.

Concomitant use with phosphodiesterase-5 (PDE-5) inhibitors

Concomitant administration of CARZIN 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).

Hepatic impairment

Care should be taken when CARZIN XL is administered to patients with mild or moderately impaired hepatic or renal function. These conditions may increase exposure to CARZIN XL and may increase the hypotensive effect. Use in patients with severe hepatic impairment is not recommended.

Coronary insufficiency

Caution should be used when CARZIN XL is administered to patients with coronary

insufficiency. If symptoms of angina pectoris should newly appear or worsen, CARZIN XL should be discontinued.

Acute cardiac conditions

As with any other vasodilatory antihypertensive medicine, it is prudent medical practice to advise caution when administering CARZIN XL 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.

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 alpha-1 blockers, therefore the possibility of a class effect cannot be excluded. 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

Post marketing experience indicates prolonged erections and priapism have been reported with alpha-1 blockers including CARZIN XL. 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

Prostate cancer should be ruled out prior to commencing CARZIN XL therapy.

General

Orthostatic hypotension (which may be preceded by tachycardia and followed by syncope) can be avoided by starting treatment with a low dose, preferably at night (see section 4.2).

Hypotensive effects may be increased by alcohol ingestion, exercise, and heat.

Information on excipients of CARZIN XL

CARZIN XL contains lactose. Patients with the rare hereditary conditions of galactose intolerance, e.g., galactosaemia, total lactase deficiency or glucose-galactose malabsorption should not take CARZIN XL.

CARZIN XL contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of CARZIN XL with a PDE-5 inhibitors may lead to symptomatic hypotension in some patients (see section 4.4). No studies have been conducted with doxazosin prolonged release formulations.

The hypotensive effects of CARZIN XL may be enhanced by use with diuretics and other antihypertensives, alcohol and other medicines that cause hypotension. The risk of first-dose hypotension may be increased in patients receiving beta-blockers or calcium channel blockers.

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

Concomitant administration of antidepressants or antipsychotics may enhance the hypotensive effects of CARZIN XL.

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 CARZIN 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.

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety in pregnancy has not been established (see section 4.3).

Breastfeeding

Safety in lactation has not been established (see section 4.3).

Doxazosin is known to transfer into breast milk and to cross the placental barrier. A risk to the

new-born or infant cannot be excluded.

Fertility

Fertility in males: Studies in rats after oral administration of doxazosin base showed reduced fertility in males. This 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 CARZIN 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 operating a motor vehicle may be impaired, especially when initiating therapy.

4.8 Undesirable effects

a) Summary of the safety profile

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

The most common reactions associated with CARZIN XL are of a postural type, (rarely associated with fainting) or non-specific.

b) Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	Frequent	Respiratory tract infection, urinary tract infection, influenza-like symptoms
Metabolism and nutrition disorders	Less frequent	Gout, increased appetite

Nervous system disorders	Frequent	Dizziness, headache, somnolence, sleep disturbances including drowsiness
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Frequent	Palpitations, tachycardia
Vascular disorders	Frequent	Hypotension, postural hypotension
Respiratory, thoracic, and mediastinal disorders	Frequent	Bronchitis, coughing, dyspnoea, rhinitis
Gastrointestinal disorders	Frequent	Abdominal pain, dyspepsia, dry mouth, nausea
Hepatobiliary disorders	Less frequent	Abnormal liver function tests
Skin and subcutaneous tissue disorders	Frequent	Pruritus
Musculoskeletal, connective tissue and bone disorders	Frequent	Back pain, myalgia
Renal and urinary disorders	Frequent	Cystitis, urinary incontinence
General disorders and administrative site conditions	Frequent Less frequent	Asthenia, chest pain, peripheral oedema Facial oedema

Post-marketing studies

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequency unknown	Leukopenia, thrombocytopenia
Immune system disorders	Frequency unknown	Allergic reactions, angioedema
Metabolism and nutrition disorders	Frequency unknown	Anorexia, diaphoresis
Psychiatric disorders	Frequency unknown	Anxiety, depression, insomnia, agitation, nervousness, hallucinations, paranoia, confusion
Nervous system disorders	Frequency unknown	Cerebrovascular accident, hypoaesthesia, syncope, tremor, postural dizziness, paraesthesia, cerebrovascular accident was categorised by combining the frequencies of ‘cerebral infarct’, ‘cerebral ischaemia’ and ‘cerebrovascular accident’
Eye disorders	Frequency unknown	Blurred vision, IFS (Intraoperative Floppy Iris Syndrome)
Ear and labyrinth disorders	Frequency unknown	Tinnitus

Cardiac disorders	Frequency unknown	Angina pectoris, myocardial infarction, bradycardia, cardiac dysrhythmia
Vascular disorders	Frequency unknown	Hypotension, hot flushes
Respiratory, thoracic, and mediastinal disorders	Frequency unknown	Dyspnoea, coughing, epistaxis, aggravated bronchospasm, nasal congestion
Gastrointestinal disorders	Frequency unknown	Dyspepsia, dry mouth, vomiting, constipation, flatulence, diarrhoea, faecal incontinence, gastrointestinal obstruction
Hepatobiliary disorders	Frequency unknown	Hepatitis, pancreatitis, cholestasis, jaundice
Skin and subcutaneous tissue disorders	Frequency unknown	Pruritus, skin rash, alopecia, purpura, urticarial, reddened sclera, lichen planus
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Arthralgia, muscle cramps, muscle weakness
Renal and urinary disorders	Frequency unknown	Urinary incontinence, dysuria, haematuria, micturition frequency, micturition disorder, nocturia, polyuria
Reproductive system and breast disorders	Frequency unknown	Priapism, gynaecomastia, impotence, erectile dysfunction, retrograde ejaculation

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

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the online service for adverse drug reaction reporting by following the link: https://www.sahpra.org.za/Publications/Index/8 or http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problemreporting-form/. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Management of overdose:

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Doxazosin is highly protein bound; therefore, it is not removed by dialysis. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists

ATC code: C02CA04

Pharmacological classification: A.7.1 Vasodilators, hypotensive medicines.

Mechanism of action

Doxazosin produces peripheral vasodilatation primarily through its selective blockage of alpha1-adrenergic receptors. The result is a fall in blood pressure because of the decreased peripheral vascular resistance.

Blockade of alpha1-adrenergic receptors may also result in a reduction in urethral resistance and pressure, bladder outlet resistance, and urinary symptoms.

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:

Doxazosin is well absorbed after oral administration, with peak plasma concentrations for the slow-release formulation 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.

Distribution:

Oral bioavailability is about 54 %.

Doxazosin is about 98 % bound to plasma proteins.

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

Biotransformation/elimination:

Doxazosin is extensively metabolised in the liver mainly by hydroxylation and O-demethylation and excreted in faeces as metabolites and less than 5 % unchanged doxazosin.

The plasma elimination of doxazosin is biphasic with the terminal elimination half-life being 22 hours, hence providing the basis for once daily dosing.

The duration of action of doxazosin may extend up to 36 hours.

Pharmacokinetics in special patient groups

Patients with hepatic impairment

In clinical studies, after a single dose of doxazosin, an increase in AUC of 43 % and a decrease in oral clearance of 40 % were reported in patients with moderate hepatic impairment.

Patients with renal impairment

Pharmacokinetic studies with doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Calcium hydrogen phosphate

Hypromellose

Lactose monohydrate

Magnesium stearate

Film coating – Composition of Opadry White Y-1-7000:

Hypromellose

Macrogol 400

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at or below 30 ^{o}C

Protect from light and moisture.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

CARZIN XL is available in pack sizes of 30 tablets packed in blister strips of OPA/AL/PVC film and aluminium foil, in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House

Steenberg Office Park

Silverwood Close

Westlake

Cape Town, 7945

South Africa

8. REGISTRATION NUMBER(S)

A41/7.1/0557

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of registration: 04 December 2009

Latest approval: 12 June 2015

10. DATE OF REVISION OF THE TEXT

17 January 2023

NAM NS2 10/34/0376

MOZ C6197