CARDURA™

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name

CARDURA™

1.2 Strength

1, 2 and 4 mg

1.3 Pharmaceutical Dosage Form

Compressed tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Doxazosin

2.2 Quantitative Declaration

Each tablet contains doxazosin mesylate salt equivalent to 1 mg, 2 mg and 4 mg doxazosin.

3. PHARMACEUTICAL FORM

Compressed Tablets

The 1 mg tablets are white, round, biconvex tablets with “CN 1” on one side and Pfizer logo on the other side.

The 2 mg tablets are white, oblong, biconvex tablets with breaker score and code “CN” and “2” on one side and Pfizer logo on the other side.

The 4 mg tablets are white, rhombus shaped, biconvex tablets with breaker score and code “CN” and “4” on one side and Pfizer logo on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Doxazosin 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, doxazosin may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

Benign Prostatic Hyperplasia

Doxazosin is indicated for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). Doxazosin may be used in BPH patients who are either hypertensive or normotensive.

4.2 Posology and method of administration

Posology

Doxazosin may be administered in the morning or the evening.

Hypertension

Doxazosin is used in a once daily regimen: the initial dose is 1 mg, to minimize the potential for postural hypotension and/or syncope (see section 4.4 Special warnings and precautions for use). Dosage may then be increased to 2 mg after an additional one or two weeks of therapy and thereafter, if necessary, to 4 mg. The majority of patients who respond to doxazosin will do so at a dose of 4 mg or less. Dosage can be further increased if necessary, to 8 mg or the maximum recommended dose of 16 mg.

Benign Prostatic Hyperplasia

The recommended initial dosage of doxazosin is 1 mg given once daily to minimize the potential for postural hypotension and/or syncope (see section 4.4 Special warnings and precautions for use). Depending on the individual patient’s urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and up to the maximum recommended dose of 8 mg. The recommended titration interval is 1 to 2 weeks. The usual recommended dose is 2 mg to 4 mg daily.

Pediatric Population

The safety and efficacy of doxazosin in children and adolescents have not been established.

Elderly Patients

Normal adult dosage.

Patients with renal impairment

Since there is no change in pharmacokinetics in patients with impaired renal function, the usual adult dose of doxazosin is recommended.

Doxazosin 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 metabolized by the liver, doxazocin should be administered with caution to patients with evidence of impaired liver function (see section 4.4 Special warnings and precautions for use and section 5.2 Pharmacokinetic properties).

Method of Administration

Oral administration.

4.3 Contraindications

Doxazosin is contraindicated in:

- Patients with a known hypersensitivity to the active substance or other types of quinazolines (e.g. prazosin, terazosin), or to any of the excipients listed in section 6.1 List of excipients
- 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)

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 Posology and method of administration). Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimize 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 doxazosin 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 edema 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 Hepatically Impaired Patients

As with any drug wholly metabolized by the liver, doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see section 4.2 Posology and method of administration). Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

Use with Phosphodiesterase Type-5 Inhibitors

Concomitant administration of doxazosin with a Phosphodiesterase Type-5 (PDE-5) inhibitor (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.

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 benign prostatic hyperplasia symptoms.

Excipient Information

Patients with rare hereditary problems of galactose intolerance, Total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil)

Concomitant administration of doxazosin with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4 Special warnings and precautions for use – Use

with Phosphodiesterase Type-5 Inhibitors). 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).

Conventional doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, 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.

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 Pharmacokinetic properties).

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 4-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

<u>For the hypertension indication:</u>

Pregnancy

As there are no adequate and well-controlled studies in pregnant women, the safety of doxazosin during pregnancy has not yet been established. Accordingly, during pregnancy, doxazosin 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 fetal survival was observed in animals at extremely high doses (see section 5.3 Preclinical safety data).

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 drive or use machinery may be impaired, especially when initiating therapy.

4.8 Undesirable effects

Hypertension

In clinical trials involving patients with hypertension, the most common reactions associated with doxazosin 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 doxazosin with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000).

Table 1 Adverse reactions for doxazosin

System Organ Class	Common	Uncommon	Rare	Very Rare	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; Dyspnea; Rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders	Abdominal pain; Dyspepsia; Dry mouth; Nausea	Constipation; Flatulence; Vomiting; Gastroenteritis Diarrhea			
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 edema	Pain; Facial edema		Fatigue; Malaise	
Investigations		Weight increase			

4.9 Overdose

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

Mechanism of action

Doxazosin is a potent and selective post-junctional alpha-1-adrenoceptor antagonist. This action results in a decrease in systemic blood pressure. Doxazosin is appropriate for oral administration in a once daily regimen in patients with essential hypertension.

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 hyperlipidemia.

Administration of doxazosin 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.

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 extensively metabolized in man and in the animal species tested, with the feces 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.

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 metabolized by the liver, doxazosin should be administered with caution to patients with impaired liver function (see section 4.4 Special warnings and precautions for use).

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 fetal 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

Doxazosin mesylate tablets include the following excipients: sodium starch glycolate, microcrystalline cellulose, lactose, magnesium stearate and sodium lauryl sulfate.

6.2 Incompatibilities

None.

6.3 Shelf life

Please see details on carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/PVDC-Al blister containing 10 tablets in a carton of 1, 2, 3, 4, 5 and 10 blisters

7. MARKETING AUTHORIZATION HOLDER

Viatris (Thailand) Limited

8. MARKETING AUTHORIZATION NUMBER

Cardura (Tablets 1 mg) Reg. No. 1C 15120/64

Cardura (Tablets 2 mg) Reg. No. 1C 15121/64

Cardura (Tablets 4 mg) Reg. No. 1C 15122/64

9. DATE OF AUTHORIZATION

Cardura (Tablets 1 mg) 27 August 2021

Cardura (Tablets 2 mg) 27 August 2021

Cardura (Tablets 4 mg) 27 August 2021

10. DATE OF REVISION OF THE TEXT

01 March 2022