CARDURA®

Doxazosin Mesylate

1. NAME OF THE MEDICINAL PRODUCT

CARDURA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: doxazosin
The tablets contain doxazosin mesylate salt equivalent to 1 mg, 2 mg and 4 mg doxazosin.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Doxazosin is indicated for the treatment of hypertension and can be used as the initial agent to control blood pressure in the majority of patients. In patients not adequately controlled on a single antihypertensive agent, doxazosin may be used in combination with another agent, such as a thiazide diuretic, a beta-blocker, a calcium antagonist or an angiotensin-converting enzyme inhibitor.

Benign Prostatic Hyperplasia

Doxazosin is also indicated for the treatment of the urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). Doxazosin may be used in BPH patients who are either hypertensive or normotensive. While the blood pressure changes in normotensive patients with BPH are clinically insignificant, patients with hypertension and BPH have had both conditions effectively treated with doxazosin monotherapy.

4.2 Posology and method of administration

Doxazosin may be administered either in the morning or in the evening.

Hypertension

The full dosage range of doxazosin is 1 mg to 16 mg daily. It is recommended that therapy be initiated at 1 mg once daily for 1 or 2 weeks to minimize the potential for postural hypotension and/or syncope (see section **4.4 Special warnings and precautions for use**). The dosage may then be increased to 2 mg once daily for an additional 1 or 2 weeks. If necessary, the daily dosage should then be increased gradually at similar intervals to 4 mg, 8 mg, and 16 mg, as determined by patient response, to achieve the desired reduction in blood pressure. The usual dose is 2 mg to 4 mg once daily.

Benign Prostatic Hyperplasia

The recommended initial dosage of doxazosin is 1 mg 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 to 4 mg once daily.

Use in Elderly

Normal adult dosage is recommended.

Use in Renally Impaired Patients

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

Use in Hepatically Impaired Patients

See section **4.4 Special warnings and precautions for use**.

Use in Children

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

4.3 Contraindications

Doxazosin is contraindicated in patients with a known hypersensitivity to quinazolines, doxazosin, or any of the inert ingredients.

4.4 Special warnings and precautions for use

Postural Hypotension/Syncope

As with all alpha-blockers, a very small percentage of patients have experienced 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**). 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 with Phosphodiesterase Type-5 Inhibitors

Concomitant administration of doxazosin with a phosphodiesterase type-5 (PDE-5) inhibitor should be used with caution as it may lead to symptomatic hypotension in some patients.

Impaired Hepatic Function

As with any drug wholly metabolized by the liver, doxazosin should be administered with caution to patients with evidence of impaired hepatic function (see section **5.2 Pharmacokinetic properties**).

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 $alpha_1$-blockers. As IFIS may lead to increased procedural complications during the operation, current or past use of alpha-blockers should be made known to the ophthalmologic surgeon in advance of surgery.

Priapism

Prolonged erections and priapism have been reported with alpha-1 blockers including doxazosin in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

4.5 Interaction with other medicinal products and other forms of interaction

Use with PDE-5 Inhibitors

(See section **4.4 Special warnings and precautions for use** - *Use with Phosphodiesterase Type-5 Inhibitors*).

CYP3A4 Inhibitors

In vitro studies suggest that doxazosin is a substrate of 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)**.

Other

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

phenytoin or indomethacin. Doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycemic drugs, uricosuric agents, or anticoagulants.

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 Pregnancy and lactation

Although no teratogenic effects were seen in animal testing with doxazosin, reduced fetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum human recommended dose.

A single case report demonstrated transfer of doxazosin into human breast milk and animal studies have shown that doxazosin accumulates in breast milk (see section **5.3 Preclinical safety data**).

As there are no adequate and well-controlled studies in pregnant or nursing women, the safety of doxazosin during pregnancy or lactation has not yet been established. Accordingly, during pregnancy or lactation, doxazosin should be used only when, in the opinion of the physician, the potential benefit outweighs the potential risk.

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 doxazosin therapy.

4.8 Undesirable effects

Hypertension

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

Ear and Labyrinth Disorders: vertigo

Gastrointestinal Disorders: nausea

General Disorders and Administration Site Conditions: edema, asthenia, fatigue, malaise

Nervous System Disorders: dizziness, headache, postural dizziness, somnolence, syncope

Respiratory, Thoracic and Mediastinal Disorders: rhinitis

Benign Prostatic Hyperplasia

Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension.

In post-marketing experience, the following additional adverse events have been reported:

Blood and Lymphatic Disorders: leukopenia, thrombocytopenia

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: blurred vision, IFIS (see section **4.4 Special warnings and precautions for use**)

Gastrointestinal Disorders: abdominal pain, constipation, diarrhea, dyspepsia, flatulence, mouth dry, vomiting

General Disorders and Administrations Site Conditions: pain

Hepatobiliary Disorders: cholestasis, hepatitis, jaundice

Immune System Disorders: allergic reaction

Investigations: abnormal liver function tests, weight increase

Metabolism and Nutrition: anorexia

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle cramps, muscle weakness, myalgia

Nervous System Disorders: hypoesthesia, paresthesia, tremor

Psychiatric Disorders: agitation, anxiety, depression, insomnia, nervousness

Renal and Urinary Disorders: dysuria, hematuria, micturition disorder, micturition frequency, nocturia, polyuria, urinary incontinence

Reproductive System and Breast Disorder: gynecomastia, impotence, priapism, retrograde ejaculation

Respiratory, Thoracic and Mediastinal Disorders: bronchospasm aggravated, coughing, dyspnea, epistaxis

Skin and Subcutaneous Tissue Disorders: alopecia, pruritus, purpura, skin rash, urticaria

Vascular Disorders: hot flushes, hypotension, hypotension postural

The following additional adverse events have been reported in marketing experience among patients treated for hypertension but these, in general, are not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin: bradycardia, tachycardia, palpitation, chest pain, angina pectoris, myocardial infarction, cerebrovascular accidents and cardiac arrhythmias.

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

Hypertension

Administration of doxazosin 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. A gradual reduction in blood pressure occurs, with maximum reductions usually occurring 2 to 6 hours after dosing. In patients with hypertension, blood pressures during treatment with doxazosin were similar in both the supine and standing positions. Unlike non-selective alpha-adrenoceptor blocking agents, tolerance has not been observed in long-term therapy with doxazosin. Elevations of plasma renin activity and tachycardia were seen infrequently in sustained therapy.

Doxazosin produces favorable effects on blood lipids, with a significant increase in the high-density lipoprotein (HDL)/total cholesterol ratio and significant reductions in total triglycerides and total cholesterol. It therefore confers an advantage over diuretics and beta-adrenoceptor blocking agents, which adversely affect these parameters. Based on the established association of hypertension and blood lipids with coronary heart disease, the favorable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in the risk of developing coronary heart disease.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation, and enhanced tissue plasminogen activator capacity. Additionally, doxazosin improves insulin sensitivity in patients who have impairment.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with asthma, diabetes, left ventricular dysfunction, and gout.

An *in vitro* study has demonstrated the antioxidant properties of the 6'- and 7'-hydroxy metabolites of doxazosin at concentrations of 5 μM.

In a controlled clinical trial in hypertensive patients, treatment with doxazosin was associated with improvement of erectile dysfunction. In addition, the patients who received doxazosin reported fewer new cases of erectile dysfunction than those who received other antihypertensive agents.

Benign Prostatic Hyperplasia

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.

Doxazosin has been shown to be an effective blocker of the 1A subtype of the alpha-1-adrenoceptor which accounts for over 70% of the subtypes in the prostate. This accounts for the action in BPH patients.

Doxazosin has demonstrated sustained efficacy and safety in the long-term treatment of BPH (i.e., up to 48 months).

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, doxazosin is well absorbed with peak blood levels occurring at about 2 hours.

Biotransformation/Elimination

The plasma elimination is biphasic, with the terminal elimination half-life being 22 hours. This provides the basis for once-daily dosing. Doxazosin is extensively metabolized, with <5% excreted as unchanged drug.

Pharmacokinetic studies in patients with renal impairment have shown 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%. As with any drug wholly metabolized by the liver, use of doxazosin in patients with altered liver function should be undertaken with caution (see section **4.4 Special warnings and precautions for use**).

Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is primarily metabolized 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

Carcinogenesis

Chronic dietary administration (up to 24 months) of doxazosin at maximally tolerated doses of 40 mg/kg/day in rats and 120 mg/kg/day in mice revealed no evidence of carcinogenic potential. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8 times and 4 times, respectively, the human AUC at a dose of 16 mg/day.

Mutagenesis

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Impairment of Fertility

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 mg/kg/day (but not 5 or 10 mg/kg/day), about 4 times the human AUC at a dose of 12 mg/day. This effect was reversible within 2 weeks of drug withdrawal. There have been no reports of any effects of doxazosin on male fertility in humans.

Lactation

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast 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 inert ingredients: sodium starch glycolate, microcrystalline cellulose, lactose, magnesium stearate and sodium lauryl sulfate.

6.2 Incompatibilities

None

6.3 Shelf-life

Observe “Expiry Date” (month/year) imprint on outer pack.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Packed in blister strips in box of 100’s.

7. Manufacturer

Pfizer Manufacturing Deutschland GmbH,
Freiburg Im Breisgau,
Germany

Date of Revision: 9 April 2025

CARDURA-0425