SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin 4mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Doxazosin Mesylate 4.85 mg equivalent to 4 mg doxazosin.
Excipient with known effect: Also contains 80 mg of Anhydrous Lactose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

White, oblong, uncoated tablets debossed “D4” and score line on the same side. The scoreline is not intended for breaking the tablet.

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

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

Benign Prostatic Hyperplasia: The recommended initial dosage of Doxazosin is 1mg given once daily to minimise the potential for postural hypotension and/or syncope (see section 4.4). Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2mg and thereafter to 4mg and up to the maximum recommended dose of 8mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4mg daily.

Paediatric population: The safety and efficacy of Doxazosin mesylate in children and adolescents have not been established.

Elderly: 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, doxazosin should be administered with caution to patients with evidence of impaired liver function (see section 4.4 and section 5.2).

Method of administration

Oral administration

Doxazosin may be administered in the morning or the evening.

4.3 Contraindications

Doxazosin is contraindicated in:

(1) 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
(2) Patients with a history of orthostatic hypotension
(3) Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones.

(4) During lactation (for the hypertension indication only see section 4.6)
(5) 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). Therefore, it is prudent medical practise to monitor blood pressure on initiation of therapy to minimise 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 antihypertensive agent it is prudent medical practise to advise caution when administering doxazosin 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

Use in Hepatically Impaired Patients:
As with any drug wholly metabolised by the liver, doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see section 4.2). Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

Use with PDE-5 inhibitors:
Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (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 BPH symptoms.

Important information regarding the ingredients of this medicine
Doxazosin Tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil):</u>
Concomitant administration of doxazosin with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4). 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-blockers, 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).

Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives.

In an open-label, randomised, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400mg twice daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean Cmax 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

For the hypertension indication:

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 foetal survival was observed in animals at extremely high doses (see section 5.3).

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 (≥ 1/1,000 to < 1/100), Rare (≥ 1/10,000 to < 1/1,000), Very rare (< 1/10,000), Not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Very Rare	Leukopenia, thrombocytopenia
Immune System Disorders	Uncommon	Allergic drug reaction
Metabolism and Nutrition Disorders	Uncommon	Gout, increased appetite, anorexia
Psychiatric Disorders	Uncommon	Agitation, depression, anxiety, insomnia, nervousness
Nervous System Disorders	Common	Dizziness, headache, somnolence
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Dizziness postural, paraesthesia
Eye Disorders	Very Rare	Blurred vision
	Not known	Intraoperative floppy iris syndrome (see Section 4.4)

Ear and Labyrinth Disorders	Common	Vertigo
	Uncommon	Tinnitus
Cardiac Disorders	Common	Palpitation, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very rare	Bradycardia, cardiac arrhythmias
Vascular Disorders	Common	Hypotension, postural hypotension
	Very Rare	Hot flushes
Respiratory, Thoracic and Mediastinal Disorders	Common	Bronchitis, cough, dyspnea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Bronchospasm
Gastrointestinal Disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
	Uncommon	Constipation, flatulence, vomiting, gastroenteritis, diarrhoea
Hepatobiliary Disorders	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
	Uncommon	Skin rash
	Very rare	Urticaria, alopecia, purpura
Musculoskeletal and Connective Tissue Disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia,
	Rare	Muscle cramps, muscle weakness
Renal and Urinary Disorders	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, micturition frequency, hematuria,
	Rare	Polyuria
	Very Rare	Increased diuresis, micturition disorder, nocturia

Reproductive System and Breast Disorders	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Not known	Retrograde ejaculation
General Disorders and Administration Site Conditions	Common	Asthenia, chest pain, influenza-like symptoms, peripheral oedema,
	Uncommon	Pain, facial oedema
	Very Rare	Fatigue, malaise
Investigations	Uncommon	Weight increase

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor 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 hyperlipidaemia.

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 metabolised in man and in the animal species tested, with the faeces 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 metabolised by the liver, Doxazosin

should be administered with caution to patients with impaired liver function (see section 4.4).

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 foetal 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

Anhydrous lactose
Magnesium stearate
Microcrystalline cellulose
Sodium lauryl sulfate
Sodium starch glycollate
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

PVC/PVdC - Aluminium blisters in pack sizes of 28 tablets

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

BRISTOL LABORATORIES LIMITED

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NORTHBRIDGE ROAD

BERKHAMSTED

HERTS

HP4 1EG

UNITED KINGDOM

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