Summary of Product Characteristics

1. Name of the Medicinal Product

Doxazosin 2 mg tablets

2. Qualitative and Quantitative Composition

Each tablet contains 2.425 mg doxazosin mesilate equivalent to 2 mg of doxazosin.

Excipient(s) with known effect
Each tablet contains 40.0 mg lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Tablet
2 mg: white oblong scored tablet, "D2" engraved on one side
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

Essential hypertension.
Symptomatic treatment of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology

The duration of therapy will be decided by the physician.

Hypertension:
The usual dosage limits of doxazosin lie between 1 and 8 mg per day. The maximum recommended dosage is 16 mg per day. The initial dosage is 1 mg, to be taken before retiring to bed. This dose is maintained for 1 or 2 weeks. The dose can then be increased to 2 mg once a day for another 1 or 2 weeks. If necessary the daily dose can then be gradually increased, observing equal intervals, to 4, 8 and 16 mg once a day, depending on the patient's response.

The maximum daily dose should not exceed 16mg

Benign prostate hyperplasia:
The initial dose of doxazosin is 1 mg (1 mg tablet) on the 1st to 8th day once daily and 2 mg (2 mg tablet) on the 9th to 14th day. Subsequently, dose should be titrated individually to 4 mg and to the maximum recommended dosage of 8 mg, depending on the urodynamic parameters and the BPH symptomatology of

the patient. The recommended titration interval is 1 to 2 weeks. The usual recommended dose is 2-4 mg daily. Doxazosin is administered once a day. If the doxazosin treatment has been stopped for a number of days, the regimen should be determined again.

Renal impairment
Because the pharmacokinetics of doxazosin remain unchanged in patients with renal insufficiency, and no evidence exists that doxazosin will exacerbate an existing renal insufficiency, the application of the usual dosages is generally advised. As in rare cases an increased sensitivity cannot be ruled out, a more cautious approach with respect to initiating the treatment in such patients may be called for. As doxazosin is highly protein bound, it is not removed by dialysis.

Elderly
Normal adult dosage. In common with other drugs of this class, dosage should be kept as low as possible and increments made under close supervision.

Hepatic impairment
The doxazosin dose should be titrated particularly carefully in patients with impaired liver function. No clinical experience is available in patients with serious hepatic dysfunction (see section 4.4).

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

Method of administration
The tablets should be taken with a sufficient amount of water once daily.

4.3 Contra-indications

Doxazosin is contraindicated in:
- patients with hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 or other quinazolines (e.g. prazosin, terazosin).
- patients with history of orthostatic hypotension
- patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones
- BPH patients with hypotension.

Doxazosin is contraindicated as monotherapy in patients with overflow bladder, anuria or 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. Therefore, it is prudent medical practice 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.

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.

Use in patients with acute cardiac conditions:
As with any other vasodilatory antihypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with the following acute cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis
- heart failure at high output
- 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. Since there is no clinical experience in patients with severe hepatic impairment, using doxazosin in these patients is not recommended.

Use in patients with renal impairment:
There is no evidence that doxazosin aggravates renal dysfunction. However, doxazosin dosage introduction and adjustment should be carried out with great care.

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

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 cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Chronic heart failure
The mean terminal half-life of doxazosin is 22 hours. This may be prolonged in patients with congestive heart failure. The rate of dose adjustment may need to be slowed.

In some patients with left ventricular failure, the decrease in left ventricular filling associated with vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of doxazosin. These effects should be kept in mind when introducing therapy and continuous adjustment of dose used.

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.

Excipient(s)

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

Sodium
This medicinal product 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

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients (see section 4.4).

Most (98%) of 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 indometacin.

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).

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 and anticoagulants. However, data from formal drug/drug interaction studies are not present.

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 four-day regiment of oral cimetidine (400 mg 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
Doxazosin crosses the placenta.
As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin during pregnancy has not been established. Accordingly, during pregnancy, doxazosin should be used only if the

potential benefit outweighs the 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). These doses were approximately 300 times the maximum recommended human dose.

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 engage in activities such as operating machinery or operating a motor vehicle may be impaired, especially when initiating therapy. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

Hypotension
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.

Frequencies used are 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
- Not known (cannot be estimated from the available data)

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	Anorexia Gout Increased appetite
Psychiatric disorders	Uncommon	Anxiety

		Insomnia Nervousness Agitation Depression
Nervous system disorders	Common	Dizziness Headache Somnolence
	Uncommon	Cerebrovascular accident Hypoesthesia Syncope Tremor
	Very rare	Dizziness postural Paresthesia
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 Dyspnoea Rhinitis
	Uncommon	Epistaxis
	Very rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain Dyspepsia Dry mouth Nausea
	Uncommon	Constipation Diarrhoea Flatulence Vomiting Gastroenteritis
Hepatobiliary disorders	Uncommon	Abnormal liver function tests
	Very rare	Cholestasis Hepatitis Jaundice
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	Skin rash

	Very rare	Alopecia Purpura Urticaria
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 increased Hematuria
	Rare	Polyuria
	Very rare	Increased diuresis Micturition disorder Nocturia
Reproductive system and breast disorders	Uncommon	Impotence
	Very rare	Gynaecomastia 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 Website: 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 immediately be 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.

If this measure is inadequate, shock should be first treated with volume expanders. If necessary, vasopressor agents 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-adrenoceptor antagonists, ATC-code: C02CA04

Doxazosin is a selective and competitive antagonist of postsynaptic alpha-1-adrenergic receptors.

Administration of doxazosin will cause a significant reduction in blood pressure due to decreased peripheral vascular resistance. Following once-daily administration a clinically significant reduction in the blood pressure is maintained for up to 24 hours. After administration a gradual reduction in blood pressure will come about; orthostatic effects at the start of the treatment may occur. Maximum reduction in blood pressure will be achieved about 2-6 hours after administration.
In hypertensive patients the blood pressure during the doxazosin therapy is similar in a lying and in a standing position.

Doxazosin is suitable to 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. The clinical relevance of these findings is still uncertain. 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 co-existent diabetes mellitus, insulin resistance and gout.

Unlike the non-selective alpha adrenergic receptor blocking agents, no tolerance has been observed after a prolonged doxazosin therapy. An increase in the plasma renin activity and tachycardia have only infrequently been observed after a continued therapy.

Doxazosin produces favourable effects on blood lipids, with a significant increase in the high density lipoprotein (HDL)/total cholesterol ratio and trends to a favourable reduction in total triglycerides.

Administration of doxazosin to patients with symptomatic BPH results in a significant improvement of urodynamic symptoms. The effect is reported to be due to selective blockade of the alpha-adrenoreceptors in the smooth muscle of bladder neck, prostate capsule and urethra.

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.

5.2 Pharmacokinetic properties

Absorption
Following oral administration, doxazosin is absorbed well and approximately two thirds of the dose is bioavailable. Maximum plasma levels are reached after 2 hours and the absolute bioavailability is approximately 63%.

Distribution

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

Biotransformation/Elimination
Doxazosin is primarily metabolised 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.

Doxazosin is extensively metabolised in man and in the animal species tested, with the faeces being the predominant route of excretion with less than 5% of the dose excreted as unchanged doxazosin.

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.

Elderly/Renal impairment
Pharmacokinetic studies in the elderly and patients with renal insufficiency have shown no significant alterations compared to younger patients with normal renal function.

Hepatic impairment
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, use of doxazosin in patients with impaired liver function should be undertaken with caution (see section 4.4).

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, carcinogenicity and gastrointestinal tolerance.

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 1 mg/kg of [2-14C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

For further information see section 4.6.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose, lactose, sodium starch glycollate (type A), magnesium stearate, sodium laurylsulfate, colloidal anhydrous silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blister strips, 2, 3, 5, 10, 20 or 50 x 10 tablets or 1, 2 or 7 x 14 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

PL 00289/0358

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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