SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin Teva 4 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 4 mg doxazosin (as mesilate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round biconvex film-coated tablets with bossing "DL" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.
Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

Posology

The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension:
Adults: Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin Teva can be used as a sole agent or in combination with another medicinal product e.g. a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an ACE-inhibitor.

Symptomatic treatment of prostatic hyperplasia:
Adults: Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin Teva may be used in benign prostatic hyperplasia (BPH) patients who are either hypertensive or normotensive, as the blood pressure changes in normotensive patients are clinically insignificant. In hypertensive patients both conditions are treated concomitantly. As with any other medication of this type it is prudent medical practice to monitor the patient during the initial period of therapy.

Elderly
Same dosage as for adults.

Renal impairment
Since there is no significant variation in pharmacokinetics in patients with impaired renal function the usual adult dose of doxazosin tablets is recommended.
Doxazosin tablets are not dialyzable.

Hepatic impairment
As with any drug completely metabolised by the liver, doxazosin tablets should be administered with caution to patients with evidence of impaired hepatic function (see section 4.4 Special warnings and precautions for use).

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

Method of administration
Doxazosin Teva can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The prolonged-release tablets should not be chewed, divided or crushed (see section 4.4).

4.3 Contraindications

- Known hypersensitivity to the active substance doxazosin, to other quinazolines or to any of the excipients listed in section 6.1
- 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 a history of gastro- intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract[1]
- Patients with hypotension[2]

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

[1] For patients taking the sustained release tablets only

[2] For the benign prostatic hyperplasia indication only

Information to be given to the patient: Patients should be informed that Doxazosin Teva tablets should be swallowed whole. Patients should not chew, divide or crush the tablets.

For some prolonged-release formulations the active compound is surrounded by an inert, non absorbable coating that is designed to control the release of the drug over a prolonged period. After transit through the gastrointestinal tract, the empty tablet shell is excreted. Patients should be advised not to be concerned if they occasionally observe remains in their stools that look like a tablet.

Abnormally short transit times through the gastrointestinal tract (e.g. following surgical resection) could result in incomplete absorption. In view of the long half life of doxazosin the clinical significance of this is unclear.

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 practise to monitor blood pressure on initiation of therapy to minimise the potential for postural effects. 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 anti-hypertensive 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

In hypertensive patients with one or more additional risk factors for cardiovascular disease, Doxazosin Teva should not be used as a single agent for the treatment of hypertension due to a possible increased risk for development of heart failure.

Hepatic impairment:
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 no clinical experience from patients with severe hepatic impairment exists, use in these patients is not recommended. Caution is also recommended when Doxazosin Teva is administered concomitantly with medicinal products which may influence hepatic metabolism (e.g. cimetidine).

Doxazosin Teva may influence plasma renin activity and urinary excretion of vanillylmandelic acid. This should be considered when interpreting laboratory data.

Use with PDE-5 inhibitors:

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients. In order to minimise the risk for developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of phospodiesterase-5-inhibitors.
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.

Screening for prostate cancer:
Carcinoma of the prostate causes many of the symptoms associated with BHP and the two disorders can co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with doxazosin for treatment with BPH symptoms.

Excipient(s)

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per prolonged-release tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Posphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) 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).

Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives.
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 no present.

There are no studies concerning interactions with agents influencing hepatic metabolism.

In an open-label, randomised, 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 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

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 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 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.

4.7 Effects on ability to drive and use machines

Due to undesirable effects, the ability to operate machinery or drive a motor vehicle may be impaired to a minor or moderate degree, especially when initiating therapy

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000), not known (cannot be estimated from the available data).

System Organ Class	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
Infections and infestations	Respiratory tract infection, urinary tract infection				
Blood and the lymphatic system				Leukopenia, thrombocytopenia	

System Organ Class	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
disorders					
Immune system disorders		Allergic drug reaction			
Metabolism and nutrition disorders		Anorexia, gout, increased appetite			
Psychiatric disorders		anxiety, depression, insomnia		Agitation, nervousness	
Nervous system disorders	Dizziness, headache, somnolence	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			Flush	
Respiratory, thoracic and mediastinal disorders	Bronchitis, cough, dyspnoea, rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders	Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis	Gastrointestinal obstruction		
Hepato-biliary		Abnormal liver function		Cholestasis,	

System Organ Class	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
disorders		tests		hepatitis, jaundice	
Skin and subcutaneous tissue disorders	Pruritus	Skin rash		Alopecia, purpura, urticaria	
Musculoskeletal, connective tissue and bone disorders	Back pain, myalgia	Arthralgia		Muscle cramps, muscle weakness	
Renal and urinary disorders	Cystitis, urinary incontinence	Dysuria, hematuria, micturition frequency		Micturition disorder, nocturia, polyuria, increased diuresis	
Reproductive system and breast disorders		Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions	Asthenia, chest pain, influenza-like symptoms, peripheral oedema	Pain, facial oedema		Fatigue, malaise	
Investigations		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 be immediately placed in a supine, head down position. Other supportive measures should be performed if thought appropriate in individual cases. Since doxazosin is strongly bound to plasma proteins dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists,
ATC code: C 02 CA 04

Hypertension
Administration of Doxazosin Teva in 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 24 hours post dose. The majority of patients are controlled on an initial dose of 4 mg Doxazosin Teva. In patients with hypertension, the decrease in blood pressure during treatment with Doxazosin Teva was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets for hypertension can be transferred to Doxazosin Teva and the dose titrated upwards as needed, while maintaining effect and tolerability.

Habituation has not been observed during long-term treatment with doxazosin. Increase in plasma renin activity and tachycardia have been observed rarely during long-term treatment.

Doxazosin has a beneficial effect on blood lipids with a significant increase of HDL/total cholesterol ratio (approx. 4 – 13% of baseline values) and a significant reduction in total glycerides and total cholesterol. The clinical relevance of these findings is still unknown.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation as well as enhanced capacity of tissue plasminogen-activator. The clinical relevance of these findings is still uncertain. Additionally, doxazosin improves insulin sensitivity in patients with impaired sensitivity to insulin, but also concerning this finding the clinical relevance is still uncertain.

Interim analysis of the Antihypertensive and Lipid lowering Treatment to Prevent Heart Attack Trial (ALLHAT) indicated that hypertensive patients with at least 1 other major risk factor for coronary heart disease (CHD) treated with doxazosin experienced a double risk of congestive heart failure (CHF) with a 25% higher risk of major cardiovascular disease (CVD) events as compared to chlorthalidone-treated patients. The doxazosin arm of ALLHAT was discontinued as a result of these findings. No difference regarding mortality was present. The results may be confounded by various issues such as differences in effect on systolic blood pressure and withdrawal of diuretics in the doxazosin treated group before treatment was started.

Doxazosin has shown to be free of metabolic adverse effects and is suitable for treatment of patients with coexistent asthma, diabetes, left ventricular dysfunction or gout.
In addition, doxazosin improves insulin sensitivity in patients with impaired insulin sensitivity.

Prostatic hyperplasia
Administration of Doxazosin Teva to patients with prostatic hyperplasia results in a significant improvement in urodynamics and symptoms as aresult of a selective blockade of alpha-adrenoceptors located in the prostatic muscular stroma, capsule andbladder neck.
Most of the patients with prostatic hyperplasia are controlled with the initial dose.

Doxazosin has shown to be an effective blocker of 1A subtype of alpha-adrenoceptors which make up more than 70% of the adrenergic subtypes in prostate.
Throughout the recommended dosage range, Doxazosin Teva has only minor or no effect on blood pressure in normotensive benign prostatic hyperplasia (BPH) patients.

5.2 Pharmacokinetic properties

Absorption
After oral administration of therapeutic doses, doxazosin in Doxazosin Teva prolonged release tablets is well absorbed with peak blood levels gradually reached at 8 to 9 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release doxazosin tablets. Trough levels at 24 hours are, however, similar. The pharmacokinetic properties of doxazosin in Doxazosin Teva lead to a minor variation in plasma levels. Peak/trough ratio of Doxazosin Teva is less than half that of immediate release doxazosin tablets. At steady-state, the relative bioavailability of doxazosin from Doxazosin Teva compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose.

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

Biotransformation
Doxazosin is extensively metabolised with <5% excreted as unchanged product. 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.

Elimination
The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basic for once daily dosing

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

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

Hepatic impairment
There are only limited data in patients with liver impairment and on the effects of medicinal products 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 of AUC of 43% and a decrease

in oral clearance of app. 40%. Doxazosin therapy in patients with hepatic impairment should be performed 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 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 gave an accumulation in the breast milk with a maximum concentration of about 20 times greater than the maternal plasma concentration. For further information see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Polyethylene oxide

Cellulose, microcrystalline

Povidone

Butylhydroxytoluene

α-Tocopherol

Silica, colloidal anhydrous

Sodium stearyl fumarate

Film-coating:

Methacrylic acid – ethyl acrylate copolymer

Silica, colloidal hydrated

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

14, 15, 28, 30, 50 x 1, 60, 90, 100 tablets in PVC/PVDC aluminium blisters.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1147

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10th February 2009/23.11.2011

10 DATE OF REVISION OF THE TEXT

22/12/2023