Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carsem XL 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. Doxazosin is not appropriate for first-line treatment. It may be used as a monotherapy in patients who have failed to respond to or have contraindications to other agents. Alternatively, use should be limited to second or third line treatment in combination with other antihypertensives.

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.

Carsem XL 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.

Carsem XL 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.

Older people: Same dosage as for adults.

Patients with renal impairment: Since there is no significant variation in pharmacokinetics in patients with impaired renal function the usual adult dose of Carsem XL is recommended.
Carsem XL are not dialyzable.

Patients with hepatic impairment: As with any drug completely metabolised by the liver, Carsem XL 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 Carsem XL in children and adolescents have not been established.'

Method of administration
Carsem XL 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, to other quinazolines (e.g. prazosin, terazosin) 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]
- During lactations (see section 4.6 Pregnancy and lactation)[2]
- Patients with hypotension[3]

Carsem XL is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

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[1] For patients taking the sustained release tablets only

[2] For the hypertension indication only

[3] For the benign prostatic hyperplasia indication only

4.4 Special warnings and precautions for use

Information to be given to the patient: Patients should be informed that Carsem XL 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, Carsem XL 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 Carsem XL is administered concomitantly with medicinal products which may influence hepatic metabolism (e.g. cimetidine).

Carsem XL should be used with care in patients with Diabetic Autonomic Neuropathy.
Carsem XL 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.

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.

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.

Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives. Non-steroidal antirheumatics or estrogens may reduce the antihypertensive effect of doxazosin. Sympathomimetics may reduce the antihypertensive effect of doxazosin; doxazosin may reduce blood pressure and vascular reactions to dopamine, ephedrine, epinephrine, metaraminol, methoxamine and phenylephrine.

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.

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

Doxazosin is contraindicated during lactation as the drug accumulates in the milk of lactating rats (see section 5.3) and there is no information about the excretion of the drug into the milk of lactating women. Alternatively, mothers should stop breast-feeding when treatment with doxazosin is necessary.

4.7 Effects on ability to drive and use machines

The ability to drive or use machinery 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

Postural hypotension and in rare cases syncope may occur at the beginning of therapy, especially at very high doses but also when treatment is recommenced after a break.

The occurrence of adverse reactions is mainly due to the pharmacological properties of the medicinal product. The majority of the adverse reactions were transient.

The adverse reaction profile in clinical trials with patients with benign prostatic hyperplasia corresponded to the one seen in hypertension.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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) including isolated reports, 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 disorders				Leukopenia, thrombocytopenia	
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	Introperative 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			Taste disturbances
Hepato-biliary disorders		Abnormal liver function tests		Cholestasis, 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	Cystitis,	Dysuria,		Micturition disorder,	

urinary disorders	urinary incontinence	hematuria, micturition frequency		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		Fatigue, malaise, facial oedema	
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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

4.9 Overdose

Symptoms
Headache, dizziness, unconsciousness, syncope, dyspnoea, hypotension, palpitation, tachycardia, arrhythmia. Nausea, vomiting. Possibly hypoglycaemia, hypokalaemia.

Management
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: C02 CA04

Hypertension:
Administration of Carsem XL 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 Carsem XL. In patients with hypertension, the decrease in blood pressure during treatment with Carsem XL was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets for hypertension can be transferred to Carsem XL 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.

Prostatic hyperplasia:
Administration of Carsem XL to patients with prostatic hyperplasia results in a significant improvement in urodynamics and symptoms as a result of a selective blockade of alpha-adrenoceptors located in the prostatic muscular stroma, capsule and
bladder 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.

Safety and efficacy studies (including a total of 1317 doxazosin treated patients) have only been performed in patients with baseline I-PSS>12 and maximum urinary flow rate<15 ml/sec, results indicate that those patients controlled on 1mg, 2mg, or 4mg doxazosin immediate release will be equally well controlled on Carsem XL 4mg prolonged-release tablets.

Throughout the recommended dosage range, Carsem XL 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 Carsem XL 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 Carsem XL lead to a minor variation in plasma levels. Peak/trough ratio of Carsem XL is less than half that of immediate release doxazosin tablets. At steady-state, the relative bioavailability of doxazosin from Carsem XL 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.

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

Older people
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 of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and gastrointestinal tolerance. Studies in pregnant rabbits and rats at daily doses resulting in plasma concentrations 4 and 10 times the human exposure (Cmax and AUC), respectively, revealed no evidence of harm to the foetus. A dosage regime of 82 mg/kg/day (8 times the human exposure) was associated with reduced foetal survival.

A male fertility study performed in the rat revealed that doxazosin can adversely affect fertility and reproductive performance. Alpha-adrenergic blocking agents may inhibit labor in rats.

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. Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

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 anhydrous
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 Pharma B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/072/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2009

Date of last renewal: 23rd November 2011

10 DATE OF REVISION OF THE TEXT

March 2017