SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxzogen 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 tablets embossed with ‘DL’

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:
Adult patients
Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxzogen XL 4 mg prolonged-release tablets can be used as 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:
Adult patients
Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily. It can take up to 4 weeks to reach the full effect.

Doxzogen XL 4 mg prolonged-release tablets 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.

Elderly patients
Same dosage as for adults.

Renal impairment
Since there is no change in pharmacokinetics in patients with impaired renal function, and since there are no signs that doxazosin aggravates existing renal impairment, the usual dose can be used in these patients.

Hepatic impairment
Doxazosin should be given with particular caution to patients with evidence of impaired liver function. In patients with severe hepatic impairment clinical experience is lacking and therefore the use of doxazosin is not recommended. (see section 4.4).

Paediatric population
The safety and efficacy of doxazosin in children below 18 years of age has not yet been established. Doxzogen XL 4 mg prolonged-release tablets are not recommended for patients under the age of 18 years.

Method of administration
Doxzogen XL 4 mg prolonged-release tablets 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

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1 or quinazolines (e.g. prazosin, terazosin)
- Patients with a history of orthostatic hypotension
- Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infections 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.
- Patients with hypotension[1]

Doxazogen is contraindictaed as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

[1] 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 doxazosin 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.

Gastrointestinal diseases
There have been rare incidences of obstructive symptoms in patients with known stricture in connection with the ingestion of other medicinal products that are formulated in the same way as Doxazosin 4 mg prolonged release tablets that is, with a non-deformable shell and modified excretion.

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 practice 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.

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 heart diseases:

- pulmonary oedema as a result of aortic or mitral stenosis,
- heart failure at high output,
- right sided heart failure as a result of pulmonary embolism or pericardial effusion and left sided ventricular heart insufficiency with low filling pressure.

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

On initiation of therapy or increasing of dose the patient should be monitored to minimise the potential for postural effects, e.g. hypotension and syncope. In patients treated for benign prostatic hyperplasia and without hypertension mean blood pressure changes are small, but hypotension, dizziness, fatigue occur in 10 – 20% of the patients and oedema and dyspnoea occur in less than 5% of patients. Special care should be taken with hypotensive patients or patients with known orthostatic dysregulation taking doxazosin to treat benign prostatic hyperplasia (BPH). They should be informed about the potential risk form injuries and measures of precaution to minimize orthostatic symptoms.

Use in Hepatically Impaired Patients
As with any drug wholly metabolised by the liver, doxazosin should be administered with particular caution in patients with evidence of hepatic impairment (see section 5.2). Since there is no clinical experience in patients with severe hepatic impairment, use in these patients is not recommended.

Caution is also recommended when doxazosin is administered concomitantly with medicinal products, which may influence hepatic metabolism (e.g. cimetidine).

Doxazosin should be used with care in patients with Diabetic Autonomic Neuropathy.

Doxazosin 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 administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) should be done with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. In order to minimize the risk for developing orthostatic hypotension the patient should be haemodynamically stabilised 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.

In addition, physicians should advise patients what to do in the event of orthostatic hypotensive symptoms.

Inoperative 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 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 α-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

Prostate cancer causes many of the symptoms that can be associated with benign prostatic hyperplasia (BPH), and the two conditions can occur at the same time. Prostate cancer should be ruled out before the treatment of BPH symptoms with doxazosin is started.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

4.5 Interactions with other medicinal products and other forms of interaction

Doxazosin is highly bound to plasma proteins (98%). *In vitro* data in human plasma indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin.

In vitro studies suggest that doxazosin is a substrate of cytochrome P450 3A4 (CYP 3A4). Caution should therefore be exercised when co-administering doxazosin and 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 together with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory medicinal products, antibiotics, oral hypoglycaemic agents, uricosuric agents, or anticoagulants without adverse drug interactions. However, data from formal drug/drug interaction studies are not present.

Doxazosin potentiates the blood pressure lowering effect 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.

Concomitant administration of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients (see section 4.4). No studies have been conducted with doxazosin prolonged release formulations.

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 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 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 data 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. Animal studies have shown reduced foetal survival at extremely high doses (see section 5.3). Doxzogen XL 4 mg prolonged-release tablets should not be used during pregnancy unless clearly needed.

Breast-feeding
It has been shown that the excretion of doxazosin in human milk is very low (the relative dose in infants is less than 1%), but the amount of human data is very limited. It cannot be ruled out that there will be a risk for newborns or infants and doxazosin may only be used if the doctor estimates that the potential benefit is greater than the potential risk.

For benign prostatic hyperplasia indication:
This section is not applicable

4.7 Effects on ability to drive and use machines

Doxzogen XL 4 mg prolonged-release tablets may impair the ability to drive and use machines, especially at the beginning of therapy.

4.8 Undesirable effects

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 following undesirable effects have been observed and reported during treatment with Doxzogen 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) and not known (frequency cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	Respiratory tract infection, urinary tract infection				
Blood and lymphatic system disorders				Leukopenia, thrombocytopenia, erythrocytopenia	
Immune system disorders		Allergic drug reaction			

Metabolism and nutrition disorders		Anorexia, gout, increased appetite, hypokalaemia, thirst	Hypoglycaemia	Increase in serum urea.	
Psychiatric disorders	Apathy	Anxiety, depression, insomnia, nightmares, amnesia, emotional stability		Agitation, nervousness	
Nervous system disorders	Dizziness, headache, somnolence	Cerebrovascular accident, hypoesthesia, syncope, tremor		Dizziness postural, paraesthesia	
Eye disorders	Accommodation disturbances	lacrimation, photophobia		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, oedema	Peripheral ischaemia		Flush	
Respiratory, thoracic and mediastinal disorders	Bronchitis, cough, dyspnoea, rhinitis	Epistaxis, pharyngitis	Oedema of larynx	Bronchospasm	
Gastrointestinal disorders	Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis, taste disturbances	Gastrointestinal obstruction		
Hepatobiliary disorders		Abnormal liver function tests		Cholestasis, hepatitis, jaundice, icterus, increased liver values	
Skin and subcutaneous tissue disorders	Pruritus	Skin rash		Alopecia, purpura, urticaria	
Musculoskeletal, and connective tissue disorders	Back pain, myalgia,	Arthralgia, muscle stiffness		Muscle cramps, muscle weakness	
Renal and urinary disorders	Cystitis, urinary incontinence	Dysuria, haematuria, micturition frequency		Micturition disorder, nocturia, polyuria, increased diuresis, increase of serum creatinine	
Reproductive	Delayed	Impotence		Gynaecomastia,	Retrograde

system and breast disorders	ejaculation			priapism	ejaculation
General disorders and administration site conditions	Asthenia, chest pain, influenza-like symptoms, peripheral oedema	Pain, facial oedema, fever/shiver, paleness, general oedema		Fatigue, malaise, low body temperature in elderly	
Investigations		Weight increase			

Particular caution:
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.

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 www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Treatment:
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

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists, ATC code: C02CA04

Hypertension:
Administration of doxazosin 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 at 24-hours post dose. The majority of patients are controlled on the

initial dose of 4 mg doxazosin. In patients with hypertension, the decrease in blood pressure during treatment with Doxzogen XL prolonged-release tablets was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to doxazosin prolonged-release tablets 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 rarely been seen during long-term treatment.

Doxazosin has a beneficial effect on blood lipids with significant increase of HDL/total cholesterol ratio (app. 4-13% of base line values), and 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 thrombocyte aggregation as well as enhanced capacity of tissue plasminogen-activator. The clinical relevance of these findings is still uncertain. No placebo-controlled studies investigating the effect of conventional doxazosin tablets or doxazosin prolonged release tablets on cardiovascular morbidity and mortality have been completed. An interim analysis of the study ‘Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial’ (ALLHAT) showed that patients with hypertension and at least one other clinical risk factor for coronary heart disease treated with doxazosin had a doubled risk for chronic heart failure compared to patients treated with chlortalidone. Furthermore, they had a 25% higher risk of developing clinically significant cardiovascular events. The doxazosin arm was discontinued based on these findings.

Apart from this, doxazosin improves insulin sensitivity in patients with decreased insulin sensitivity, but also concerning this finding the clinical relevance is still uncertain.

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 doxazosin 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. This is thought to be the mechanism of action in this patient group.

Throughout the recommended dosage range, doxazosin has only a 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 prolonged-release tablets is well absorbed and reach maximum blood concentration about 8 to 9 hours after ingestion. Peak plasma levels are approximately one third of those of the same dose of immediate release doxazosin tablets. Trough levels at 24 hours after ingestion are, however, similar. The pharmacokinetic properties of doxazosin in prolonged release tablets lead to a minor variation in plasma levels. Peak/trough level ratio of Doxzogen XL 4 mg prolonged release tablets is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from prolonged-release tablets compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose. Pharmacokinetic studies with doxazosin prolonged release tablets in elderly patients have not shown any significant differences compared to younger patients.

Distribution
App. 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 metabolised in the liver. *In vitro* studies suggest that the primary route of excretion is via CYP 3A4 and to a lesser extent via CYP 2D6 and CYP 2C9.

Elimination
The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basis 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.

Liver 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. Although a teratogenic effect has not been seen in animal studies, decreased foetal survival has been seen in animals that have been given doses that are app. 300 times the maximum dose recommended for humans.

Studies in lactating rats showed that a single dose of 1 mg/kg [2-^{14}C] doxazosin accumulates in the mother's milk at a concentration 20 times higher than the maternal plasma concentration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Macrogol
Cellulose, microcrystalline
Povidone K 29-32
Butylhydroxytoluene (E321)
α-Tocopherol
Silica, colloidal anhydrous
Sodium stearyl fumarate

Tablet coat:
Methacrylic acid - ethyl acrylate copolymer (1:1) Dispersion 30 per cent
Silica, colloidal anhydrous
Macrogol 1300-1600
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC/aluminium blisters

Pack sizes: 10, 20, 28, 30, 50, 56, 60, 90, 98, 100, 140 (10 x 14) tablets

Calendar packs of 28 and 98

Unit dose 50 x 1

HDPE tablet container

Pack sizes: 100, 250 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Limited t/a Mylan
Station Close
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0743

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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16/07/2019