Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxane XL 4mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 4 mg doxazosin (as mesilate)
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
White, round, biconvex tablets marked with “DL”

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Essential hypertension
- Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

The tablets can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The tablets should not be chewed, divided or crushed.

The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension:
Adults: Usually 4 mg doxazosin once daily. It may take up to four weeks to reach optimal effect. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

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

Doxazosin 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: Same dosage as for adults.

Patients with 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 (see section 4.4).

Patients with 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 Doxazosin is not recommended for use in children and adolescents due to a lack of clinical experience.

4.3 Contraindications

Doxazosin is contraindicated in

- patients with a known hypersensitivity to quinazolines (e.g. prazosin, terazosin, doxazosin), or 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 gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract
- during lactation (see section 4.6) [1]
- patients with hypotension [2]

Doxazosin is contraindicated as monotherapy in patients with either over flow bladder or anuria with or without progressive renal insufficiency.

[1] For the hypertension indication only

[2] 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.

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 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 use in these patients is not recommended.

Use with PDE-5 inhibitors:
Concomitant administration of doxazosine 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.

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). No studies have been conducted with doxazosin prolonged release formulations.

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.

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 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

Pregnancy
For the hypertension indication:
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).

Breast-feeding
Doxazosin is contraindicated during lactation as the drug accumulates in milk of lactating rats 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 (Please see section 5.3).

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.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with Doxazosine with the following frequencies:
Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10, 000, <1/1,000); very rare (<1/10,000)

System Organ Class	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)	Unknown
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	Intraoperative floppy iris syndrome (see Section 4.4)
Ear and labyrinth		Vertigo	Tinnitus			

disorders						
Cardiac disorders		Palpitation, tachycardia	Angina pectoris, myocardial infarction		Bradycardia, cardiac arrhythmias	
Vascular disorders		Hypotension, postural hypotension			Flush	
Respiratory, thoracic and mediastinal disorders		Bronchitis, cough, dyspnea, 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 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 edema	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 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

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 doxazosin 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 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 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.
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.

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 Doxane XL 4mg Prolonged-release Tablets and associated names is well absorbed with peak blood levels gradually reached at 6 to 8 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 lead to a minor variation in plasma levels. Peak/trough ratio of doxazosin prolonged-release is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from doxazosin prolonged-release compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose.

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.

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.

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 studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. Studies in pregnant rabbits and rats at daily doses resulting in plasma concentrations 4 and 10 times the human exposure (C_{max} 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.

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

Core
Macrogol 200

Macrogol 900,
Butylhydroxytoluene (E321)
Cellulose microcrystalline,
Povidone K 30,
α-Tocopherol (E307),
Colloidal anhydrous silica,
Sodium stearyl fumarate

Coating
Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%
Silica colloidal, hydrated
Macrogol 1300-1600
Titanium dioxide (E 171).

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

PVC/PVDC//Al blister: 14, 28, 30, 56 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd.,
Bantry,
Co. Cork.

8 MARKETING AUTHORISATION NUMBER

PA0711/103/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th January 2007

Date of last renewal: 22nd May 2012

10 DATE OF REVISION OF THE TEXT

February 2017