

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxane XL 4 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the 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

Hypertension: Doxane XL is indicated for the treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients.

In patients inadequately controlled on single antihypertensive therapy, Doxane XL may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

Benign prostatic hyperplasia: Doxane XL is indicated for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH).

Doxane XL may be used in BPH patients who are either hypertensive or normotensive. While the blood pressure changes in normotensive patients with BPH are not usually clinically significant, patients with hypertension and BPH have had both conditions effectively treated with doxazosin monotherapy.

4.2 Posology and method of administration

Posology

Hypertension

The initial dose is 4 mg doxazosin once daily. A significant number of patients will be controlled on this dose. It may take up to four weeks to reach optimal effect. If necessary, the dose may be increased to 8 mg doxazosin once daily according to patient response.

The maximum recommended dose is 8 mg once daily.

Benign prostatic hyperplasia

The initial dose is 4 mg doxazosin once daily. Optimal effect may take up to 4 weeks. The dose may be increased following this period to 8 mg doxazosin once daily according to patient response.

The maximum recommended dose is 8 mg once daily.

Elderly

In common with other medicinal products of this class, the dose should be kept as low as possible and increments made under close supervision.

Renal impairment

Since the pharmacokinetics of doxazosin is unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual doses may be used in these patients (see section 4.4). Doxazosin is not dialysable.

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). As with any active substance metabolised wholly by the liver, doxazosin should be used with care in patients with significant existing hepatic dysfunction (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of doxazosin in children and adolescents have not been established.

Method of administration

Oral use

The tablets can be taken with or without food. The tablets should be swallowed whole with a sufficient amount of liquid. Patients should not chew, divide or crush the tablets (see section 4.4).

4.3 Contraindications

Doxazosin is contraindicated in

- patients with a known hypersensitivity to the active substance or to other types of 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 stone
- patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract
- patients with hypotension (for the benign prostatic hyperplasia indication only)

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

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 (see section 4.2).

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 active substance over a prolonged period. After transit through the gastrointestinal tract, the empty tablet shell is excreted. Patients should be advised that they should not 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.

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, such as driving or operating machinery.

Use in patients with acute cardiac conditions:

As with any other vasodilatory anti-hypertensive medicinal product 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 patients with hepatic impairment:

As with any active substance wholly metabolised by the liver, doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see sections 4.2 and 5.2). Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.

Use in patients with impaired renal function:

There is no evidence that doxazosin aggravates renal dysfunction. However, doxazosin dose introduction and adjustments should be carried out with great care.

Use with phosphodiesterase type-5 inhibitors:

Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, and vardenafil) should be done with caution as both medicinal products 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:

Intraoperative 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.

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.

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.

Special warnings regarding excipients

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 interactions

Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil)

Concomitant administration of an alpha blocker with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4). No studies have been conducted with doxazosin prolonged-release formulations.

Doxazosin is highly bound to plasma proteins (98%). *In vitro* data in human plasma indicate that doxazosin has no effect on protein binding of the medicinal products tested (digoxin, warfarin, phenytoin or indomethacin). However, the theoretical potential for interaction with other protein-bound drugs should be borne in mind.

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).

Immediate-release doxazosin has been administered without any adverse drug interactions in clinical experience with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory medicinal products, antibiotics, oral hypoglycaemic

medicinal products, uricosuric medicinal products, or 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 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 yet been established. Accordingly, during pregnancy, doxazosin should be used only when, in the opinion of the physician, the potential benefit outweighs the potential risk. Doxazosin crosses the placenta. 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 medicinal product 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

In clinical trials, the most common reactions associated with doxazosin prolonged-release therapy were of a postural type (rarely associated with fainting) or non-specific.

The undesirable effects for doxazosin prolonged-release tablets are similar to those with immediate release doxazosin tablets. The following undesirable effects have been observed and reported during treatment with doxazosin prolonged-release tablets with the following frequencies:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data)

System Organ Class	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ 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			

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Metabolism and nutrition disorders			Anorexia, gout, increased appetite			
Psychiatric disorders			Anxiety, depression, insomnia		Agitation, nervousness	
Nervous system disorders		Dizziness, headache, somnolence	Cerebrovascular accident, hypoaesthesia, 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			Hot flushes	
Respiratory, thoracic and mediastinal disorders		Bronchitis, cough, dyspnea, rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders		Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis	Gastrointestinal obstruction		
Hepatobiliary 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, haematuria, micturition frequency		Micturition disorder, nocturia, polyuria, increased diuresis	
Reproductive system and breast disorders			Impotence		Gynaecomastia, 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 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 overdose lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases. Since doxazosin is highly protein-bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists
ATC code: C02CA04

Hypertension:

Mechanism of action

Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist. 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 supine and standing position.

Patients treated with immediate-release doxazosin tablets can be transferred to doxazosin prolonged-release and the dose titrated upwards as needed.

Responder data from the 2 primary hypertension efficacy studies (including a total of 630 doxazosin treated patients) indicate that those patients controlled on 1 mg, 2 mg or 4 mg doxazosin immediate-release tablets would be equally well controlled on 4 mg doxazosin prolonged-release tablets.

Pharmacodynamic effects

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with coexistent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with coexistent 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. Additionally, doxazosin improves insulin sensitivity in patients with impairment.

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. It therefore confers an advantage over diuretics and beta-adrenoceptor blocking agents which adversely affect these parameters. Based on the established association of hypertension and blood lipids with coronary heart disease, the favourable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in risk of developing coronary heart disease.

Prostatic hyperplasia:

Administration of doxazosin to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the 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 dose 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 from 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 characteristics of doxazosin will lead to a smoother plasma profile.

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

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

Biotransformation/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. 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.

Other special populations

Elderly

Pharmacokinetic studies with doxazosin prolonged-release tablets in the elderly have shown no significant alterations compared to younger patients.

Renal impairment

Pharmacokinetic studies with immediate-release 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 hepatic impairment and on the effects of medicinal products known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients 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 30% (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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol 200
Macrogol 900
Butylhydroxytoluene (E 321)
Cellulose microcrystalline
Povidone K 30
All-rac- α tocopherol
Colloidal anhydrous silica
Sodium stearyl fumarate
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

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

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

November 2019