SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxatan XL 4 mg Prolonged Release Tablets.

2. QUALITATIVE AND QUANTITIATIVE COMPOSITION

Each tablet contains doxazosin 4 mg (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

Doxatan XL is indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

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

4.2 Posology and method of administration

The initial dose of Doxatan XL is 4 mg once daily. A significant number of patients will be controlled on this dose. If necessary, the dosage may be increased to 8 mg once daily according to patient response.

The maximum recommended dose is 8 mg once daily.

Doxatan XL can be taken with or without food.

The tablets should be swallowed whole with a sufficient amount of liquid.

Elderly: In common with other drugs of this class, the dosage should be kept as low as possible and increments made under close supervision.

Use in Renally Impaired Patients: Since the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual dosages may be used in these patients. Doxatan XL is not dialysable.

Use in Hepatically Impaired Patients: Doxatan XL should be used with care in patients with significant existing hepatic dysfunction (see section 4.4. "Special Warnings and Precautions for Use").

Paediatric populations: The safety and efficacy of Doxatan XL in children and adolescents have not been established.

4.3 Contraindications

Doxatan XL is contra-indicated in patients with a known hypersensitivity to quinazolines (e.g. doxazosin, prazosin, terazosin) or any constituents of Doxatan XL.

Doxatan XL is contra-indicated in patients with a history of gastro-intestinal obstruction, oesophageal obstruction or any degree of decreased lumen diameter of the gastro-intestinal tract.

Use during lactation: Animal studies have shown that doxazosin accumulates in breast milk. The clinical safety of Doxatan XL during lactation has not been established; consequently Doxatan XL is contra-indicated in nursing mothers.

Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones.

4.4 Special warnings and precautions for use

Information for the Patient: Patients should be informed that Doxatan XL should be swallowed whole. Patients should not chew, break or crush the tablets.

Impaired Renal Function: There is no evidence that Doxatan XL aggravates renal dysfunction. However, Doxatan XL dosage introduction and adjustment should be carried out with great care.

Impaired Hepatic Function: As with any drug wholly metabolised by the liver, Doxatan XL should be administered with caution to patients with evidence of impaired hepatic function (see 5.2. Pharmacokinetic Properties).

An excessive hypotensive effect may occur in some patients following soon after initial treatment often in persons who have shown evidence of overreaction with other antihypertensives and usually with the initial dose. It is recommended that the initial dosage should be given when the patient is not required to undertake any activity such as driving or operating machinery.

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.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and Doxatan XL 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.

Patients on a low sodium diet or treated with diuretics seem more sensitive for the potential for postural effects.

Because of its vasodilator action, doxazosin should be used with caution in patients with any of the following cardiac emergencies:

- pulmonary oedema due to aortic or mitral stenosis
- high output cardiac insufficiency
- right ventricular heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

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

4.5 Interaction with other medicinal products and other forms of interactions

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

indometacin), however, the theoretical potential for interaction with other protein bound drugs should be borne in mind. No adverse interactions have been observed with thiazide diuretics, frusemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents or anticoagulants.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and Doxatan XL may lead to symptomatic hypotension in some patients (see section 4.4).

4.6 Fertility, pregnancy and lactation

Use during pregnancy:
Doxazosin crosses the placenta. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum recommended human dose. As there are no adequate and well controlled studies in pregnant women, the safety of Doxatan XL use during pregnancy has not yet been established. Accordingly, Doxatan XL should be used only when, in the opinion of the physician, potential benefit outweighs potential risk.

Use during lactation:
Doxatan XL is contraindicated during lactation.

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

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

Frequencies used are as follows: Very common ≥ 1/10, Common ≥ 1/100 and < 1/10, Uncommon ≥ 1/1,000 and < 1/100, Rare ≥ 1/10,000 and < 1/1,000, Very rare < 1/10,000

MedDRA **System Organ Class**	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Very Rare	Leukopenia, thrombocytopenia
Immune System Disorders	Uncommon	Allergic drug reaction
Metabolism and Nutrition Disorders	Uncommon	Anorexia, gout, increased appetite
Psychiatric Disorders	Uncommon	Anxiety, depression, insomnia
	Very Rare	Agitation, nervousness
Nervous System Disorders	Common	Dizziness, headache, somnolence
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Dizziness postural, paraesthesia

Eye Disorders	Very Rare	Blurred vision
	Unknown	Intraoperative floppy iris syndrome (see Section 4.4)
Ear and Labyrinth Disorders	Common	Vertigo
	Uncommon	Tinnitus
Cardiac Disorders	Common	Palpitation, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very Rare	Bradycardia, cardiac arrhythmias
Vascular Disorders	Common	Hypotension, postural hypotension
	Very Rare	Hot Flush
Respiratory, Thoracic and Mediastinal Disorders	Common	Bronchitis, cough, dyspnoea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Aggravated Bronchospasm
Gastrointestinal Disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
	Uncommon	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis
Hepatobiliary Disorders	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
	Uncommon	Skin rash
	Very Rare	Alopecia, purpura, urticaria
Musculoskeletal and Connective Tissue Disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia
	Very Rare	Muscle cramps, muscle weakness
Renal and Urinary Disorders	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, hematuria, micturition frequency
	Very Rare	Micturition disorder, nocturia, polyuria, increased diuresis
Reproductive System and Breast Disorders	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Unknown	Retrograde ejaculation
General Disorders and	Common	Asthenia, chest pain, influenza-like

Administration Site Conditions		symptoms, peripheral edema
	Uncommon	Pain, facial oedema
	Very Rare	Fatigue, malaise,
Investigations	Uncommon	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 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-adrenoceptor antagonists
ATC code: C02CA04

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

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

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.

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. Additionally, doxazosin improves insulin sensitivity in patients with impaired sensitivity to insulin.

Doxazosin has shown to be free of metabolic adverse effects and is suitable for treatment of patients with co-existent asthma, diabetes, left ventricular dysfunction or gout.

Prostatic hyperplasia:
Administration of Doxatan 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.

Throughout the recommended dosage range, Doxatan XL has only a minor or no effect on blood pressure in normotensive benign prostatic hyperplasia (BPH) patients.

In controlled clinical investigations with patients with sexual dysfunction, the therapy with doxazosin was associated with an improvement of the sexual function.

5.2 Pharmacokinetic properties

Absorption:
After oral administration of therapeutic doses, doxazosin in Doxatan XL 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 in Doxatan XL lead to a minor variation in plasma levels. Peak/trough ratio of Doxatan XL is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from Doxatan 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 drug. 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 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 on patients with liver impairment and on the effects of drugs 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 approx. 40%.

Doxazosin therapy in patients with hepatic impairment should be performed with caution (see section 4.4. “Special warnings and precautions for use”).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, carcinogenicity and gastrointestinal tolerance (see section 4.6 “Pregnancy and lactation”).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Polyethylene oxide
Microcrystalline cellulose
Povidone
Butylhydroxytoluene (E321)
α-Tocopherol
Silica, colloidal anhydrous
Sodium stearyl fumarate

Coating:
Methacrylic acid copolymer (Eudragit L30 D-55)
Macrogol 1300-1600
Titanium dioxide (E171)
Silica, colloidal anhydrous

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 containers

Transparent PVC/PVdC and Aluminium blister strips.

Blister packs of 10, 14, 15, 28, 30, 56, 60 and 100 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

Clonmel Healthcare Ltd.,
Waterford Road,
Clonmel,
Co. Tipperary.

8. MARKETING AUTHORISATION NUMBER

PA0126/202/004

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

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Date of last authorisation: 29th July 2010

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