Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxatan 4mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg doxazosin (as mesilate).

Excipient with known effect
Each tablet contains 80 mg lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

White, oblong tablet, scored on one side, embossed 'D4' on one side.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxatan 4mg are indicated for the treatment of essentialhypertension.

4.2 Posology and method of administration

Posology

Unless prescribed otherwise, the following dosage regimen is recommended:
Start therapy with 1mg of doxazosin once daily. Depending on the individual patient's blood pressure response, dosage may, after 1–2 weeks, be increased to 2mg of doxazosin once daily, if necessary, then to 4mg of doxazosin once daily, and eventually to 8mg of doxazosin once daily.
Average daily dose for maintenance therapy: 2–4mg of doxazosin once daily.
Maximum daily dose: 16mg of doxazosin.

Special populations

Elderly people and patients with renal impairment:
As the pharmacokinetic properties of doxazosin are unchanged in elderly patients and those with renal impairment, these patients can be treated with the usual dose.
However, dosage should be kept as low as possible and increments made under close supervision.
As doxazosin is highly protein bound, it is not removed by dialysis.

Hepatic impairment:
The doxazosin dose should be titrated particularly carefully in patients with impaired liver function. No clinical practice experience is available in patients with serious hepatic dysfunction (see section 4.4).

Doxazosin tablets can be used as monotherapy or in combination with a thiazide diuretic, beta-blocking agents when treatment with these alone has not given the desired effect or is unsuitable.

Paediatric population

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

Method of administration
The tablets should be taken with a sufficient amount of water in the morning. The duration of therapy will be decided by the treating doctor.

4.3 Contraindications

Doxatan 4mg are contraindicated

- in patients with hypersensitivity to the active substance, other types of quinazolines (e.g. prazosin, terazosin) or to any of the excipients listed in section 6.1.
- during lactation (see section 4.6).
- in patients with a history of orthostatic hypotension.
- in patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones.
- as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

4.4 Special warnings and precautions for use

Initiation of therapy:
In relation with the alpha-blocking properties of doxazosin, in the initial phase of therapy, patients may experience circulatory disturbances with a tendency for blood pressure fall on postural change (orthostatic hypotension) evidenced by dizziness and weakness, or rarely loss of consciousness (syncope). To minimise the risk of blood pressure fall on postural change, patients should be monitored at the start of therapy. As the likelihood of such responses is greater with a higher than recommended starting dose, the recommended dosage regimen should be followed carefully. The patient should be cautioned to avoid situations where injury could result should dizziness or weakness occur during the initiation of doxazosin therapy.

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

Patients with acute cardiac conditions:
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

Patients with hepatic impairment:
Doxazosin should be used with particular caution in patients with liver function impairment. As there is no clinical practice experience in patients with severe hepatic dysfunction, use in such patients is not recommended.

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

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 as both drugs have vasodilating effects. In order to minimise the risk for developing postural hypotension the patient should be haemodynamically stable on the alpha-blocker therapy before initiating use of phosphodiesterase-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.

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.

Paediatric population
As there is inadequate clinical practice experience in children, use of doxazosin in children is not recommended.

Excipients:
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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).

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 indomethacin.

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.

Doxatan potentiates the blood pressure lowering effect of other alpha-blockers and antihypertensive drugs.
The antihypertensive effect may be increased, when doxazosin is administered concomitantly with vasodilators and nitrates.
As for other antihypertensive agents, non-steroidal anti-rheumatics or oestrogens 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.

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 inter-subject variation (27%) of the mean AUC for doxazosin with placebo.

Doxazosin may increase plasma renin activity and urinary excretion of vanillylmandelic acid. This should be considered when interpreting laboratory data.

4.6 Fertility, pregnancy and lactation

As there are no adequate and well-controlled studies in pregnant women and nursing mothers, safe use of Doxatan during pregnancy and lactation has not been established. Doxatan, therefore, should be used in pregnant women only after the doctor has carefully weighed expected benefits against potential risks. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at high doses.

It is not known, whether doxazosin is excreted into human breast milk. 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. Therefore, doxazosin is contraindicated during lactation.

Alternatively, mothers must stop breast-feeding when treatment with doxazosin is necessary.

4.7 Effects on ability to drive and use machines

Regular medical monitoring is necessary during treatment of high blood pressure with Doxatan. Individually different reactions may reduce mental alertness to such an extent that the ability to actively participate in road traffic, operate machines or work without a firm support is impaired, especially at the start of therapy, when increasing the dose, switching medications or using alcohol at the same time.

4.8 Undesirable effects

Undesirable effects arise mainly from the pharmacological properties of the preparation. Most of the side-effects have been transient or have been tolerated on continued treatment.
In this section frequencies of undesirable effects are defined as follows: 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); not known (cannot be estimated from the available data).

Infections and infestations
Common: Respiratory tract infection, urinary tract infection

Blood and lymphatic system disorders
Very rare: Decrease of erythrocytes, leukocytes and thrombocytes

Immune system disorders
Uncommon: Allergic drug reaction

Metabolism and nutrition disorders
Common: Anorexia
Uncommon: Thirst, hypokalaemia, gout, increased appetite
Rare: Hypoglycaemia

Psychiatric disorders
Common: Nervousness
Uncommon: Anxiety, insomnia, nightmares, agitation, depression, memory loss, emotional lability

Nervous system disorders
Very common: Dizziness, headache
Common: Paraesthesia, tiredness, somnolence, apathy, postural dizziness
Uncommon: Tremor, muscle stiffness, cerebrovascular accident, hypoaesthesia, syncope
Rare: Cerebrovascular disturbances
Not known: Dysgeusia

Eye disorders
Common: Accommodation disturbances
Uncommon: Abnormal tear flow, photophobia
Rare: Blurred vision
Not known: IFIS (intra-operative floppy iris syndrome, see section 4.4)

Ear and labyrinth disorders
Common: Vertigo
Uncommon: Tinnitus

Cardiac disorders
Common: Palpitations, tachycardia
Uncommon: Cardiac arrhythmia, angina pectoris, myocardial infarction
Very rare: Bradycardia

Vascular disorders
Common: Giddiness, hypotension, postural hypotension
Uncommon: Hot flushes, peripheral ischaemia

Postural hypotension and syncope can occur initially during treatment, especially at too high doses, but can also arise if therapy is restarted after a short break

Respiratory, thoracic and mediastinal disorders
Common: Bronchitis, nasal congestion, rhinitis, cough, dyspnoea
Uncommon: Epistaxis, bronchospasm, pharyngitis

Gastrointestinal disorders
Common: Diarrhoea, abdominal pain, nausea, constipation, dyspepsia, dry mouth
Uncommon: Vomiting, gastroenteritis, flatulence

Hepatobiliary disorders
Uncommon: Abnormal liver function test
Rare: Jaundice, increased liver enzymes
Very rare: Cholestasis, hepatitis

Skin and subcutaneous tissue disorders
Common: Pruritus
Uncommon: Alopecia, skin rash, purpura
Very rare: Urticaria

Musculoskeletal and connective tissue disorders
Common: Muscle cramps, myalgia, back pain
Uncommon: Arthralgia, muscle weakness, joint swelling

Renal and urinary disorders
Common: Incontinence, cystitis, increased urination/polyuria, frequent need to urinate
Uncommon: Urinary disturbances, dysuria, haematuria
Very rare: Increase in plasma of BUN and creatinine, nocturia

Reproductive system and breast disorders
Common: Ejaculation disorders (e.g. retrograde ejaculation)
Uncommon: Impotence
Very rare: Gynaecomastia, priapism

General disorders and administration site conditions
Common: Asthenia, chest pain, influenza like symptoms (e.g. fever/shivering), oedema (e.g. peripheral, facial, laryngeal oedema)
Uncommon: General pain, facial redness, paleness
Rare: Decreased body temperature in elderly
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
Website: www.hpra.ie

4.9 Overdose

Overdosage with doxazosin usually produces hypotension, which may give rise to syncope.

If a doxazosin overdose produces hypotension, cardiovascular support will be most important. Move the patient to the horizontal position for blood pressure and heart rate normalisation. In case of severe hypotension, administer plasma expanders and vasopressors. Kidney function should be monitored and, if necessary, supported. As doxazosin is highly protein bound, dialysis would not be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives
ATC code: C02CA04

Doxazosin selectively and competitively blocks postsynaptic alpha1-adrenergic receptors, thus producing peripheral vasodilatation.
In hypertensive patients doxazosin produces blood pressure reduction by reducing peripheral vascular resistance.
With single daily dosing, blood pressure response continues to be demonstrable as late as 24h post-dose. Gradual blood pressure reduction is observed after the start of therapy, and patients may experience orthostatic responses. Maximum reductions in blood pressure usually occur 2-6h after dosing. In hypertensive patients supine and standing blood pressures are similar during doxazosin therapy.
No tolerance development relative to antihypertensive effect has been observed during long-term doxazosin therapy. With continued use there have been occasional reports of increases in plasma renin activity and of tachycardia.

After an interim analysis of ALLHAT (Antihypertensive and lipid-lowering treatment to prevent heart attack trial) the doxazosin treatment arm based on comparisons with chlorthalidone was discontinued. There was a significantly higher (25%) incidence of combined cardiovascular disease events and in particular congestive heart failure (CHF) compared with the chlorthalidone group. The risk of CHF was almost doubled. There were also negative trends for stroke and for combined coronary heart disease (CHD) that is fatal CHD, non-fatal myocardial infarction, coronary revascularization procedures and hospitalized angina. The total mortality did not differ between the doxazosin and chlorthalidone arms.

5.2 Pharmacokinetic properties

Oral doxazosin is absorbed readily, and peak plasma concentrations occur at 2h. Plasma elimination is biphasic, with a terminal elimination half-life of 22h, allowing once-daily dosing.

Bioavailability: Absolute bioavailability is almost 63%.

98.3% of circulating doxazosin is bound to plasma proteins. Doxazosin is extensively metabolised (O-demethylation and hydroxylation), with the faeces being the predominant route of elimination (only 5% of the administered dose is eliminated as unchanged doxazosin in faeces). 6´-hydroxy-doxazosin is a potent and selective α-blocker and in man accounts for 5% of an oral dose. Therefore 6´-hydroxy-doxazosin contributes little to the antihypertensive activity of doxazosin.
Studies in elderly patients and patients with renal impairment have shown no significant differences in pharmacokinetics.

There are only limited data on the use of doxazosin in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients with mild hepatic insufficiency, the area under the plasma concentration-time curve (AUC) was increased by 43%, and clearance after single oral dosing was reduced by 30%.

As doxazosin is metabolised almost entirely in the liver, Doxatan should be titrated carefully in patients with hepatic impairment (see section 4.4).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenicity (see section 4.6).

Although animal studies have produced no evidence of a teratogenic effect, doses approximately 300 times the maximum recommended human therapeutic dose were associated with reduced foetal survival in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Magnesium stearate
Sodium laurilsulfate
Sodium starch glycolate (type A)
Colloidal anhydrous silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blisters made of PVC/PVDC and aluminium.
Pack sizes:10, 20, 28, 30, 40, 50, 56, 98, 100, 150, 200, 250, 300, 400, 500 or 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel, Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/202/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st January 2000
Date of last renewal: 9th August 2010

10 DATE OF REVISION OF THE TEXT

January 2022