Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Raporsin 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 with bossing "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:
Adults: Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily.
It may take up to 4 weeks to reach optimal effect.

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

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

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. Raporsin is not dialysable.

Patients with 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 drug metabolized wholly by the liver, Raporsin should be used with care in patients with significant existing hepatic dysfunction. (See section 4.4 and section 5.2).

Paediatric population: The safety and efficacy of Raporsin prolonged-release tablets in children and adolescents have not been established.

Method of administration

Oral use
Raporsin, 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.

4.3 Contraindications

Doxazosin is contraindicated in

- Patients with a known hypersensitivity to the active substance, to other 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 stones.
- Patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract (For patients taking the sustained release tablets only)
- During lactation (For the hypertension indication only, please see section 4.6)
- Patients with hypotension (For benign prostatic hyperplasia indication only)

Doxazosin is contraindicated as monotherapy in patients with benign prostatic hyperplasia causing overflow bladder, anuria or progressive renal insufficiency.

4.4 Special warnings and precautions for use

Doxazosin is not appropriate for first-line treatment for essential hypertension. It may be used as monotheraphy in patients who have failed to respond to or have contraindications to other agents. Alternatively, use should be limited to second- or third-line treatment in combination with others antihypertensives.

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 specially 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.

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.

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.

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 (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 Raporsin aggravates renal dysfunction. However Raporsin dosage introduction and adjustments should be carreid out with great care.

Use with PDE-5 inhibitors:
Concomitant administration of doxazosin 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 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 formulation.

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 with BPH symptoms.

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of Phosphodiesterase-5-inhubitors (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. 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 with 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)

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

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 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.

Breastfeeding

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 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.

The following undesirable effects have been observed and reported during treatment with Raporsin 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 (cannot be estimated from the available data).

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
	Not known	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 flushes
Respiratory, thoracic and mediastinal disorders	Common	Bronchitis, cough, dyspnoea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Bronchospasm
Gastrointestinal disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea
	Uncommon	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis
	Rare	Gastrointestinal obstruction
	Not known	Taste disturbances
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, haematuria, micturition frequency
	Very Rare	Micturition disorder, nocturia, polyuria, increased diuresis
Reproductive system and breast disorders	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Not known	Retrograde ejaculation
General disorders and administration site conditions	Common	Asthenia, chest pain, influenza-like symptoms, peripheral oedema
	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 Website: www.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-adrenoreceptor antagonists, ATC code: C02CA04 (Hypertension)

Mode of action
Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist

Hypertension:
Administration of Raporsin prolonged-release tablets 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-adrenoreceptors 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 Raporsin prolonged-release tablets. In patients with hypertension, the decrease in blood pressure during treatment with Raporsin prolonged-release tablets was similar in both the sitting and standing position.

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 Raporsin.

Administration of Raporsin prolonged-release tablets 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.

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 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.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to Raporsin 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 a significant increase of HDL/total cholesterol ratio (app. 4-13% of base line values), and trends to a favourable reduction in total glycerides and total cholesterol. 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. The clinical relevance of these findings is still unknown.

Benign prostatic hyperplasia:
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 accounts for the action in BPH patients.

Raporsin has demonstrated sustained efficacy and safety in the long-term treatment of BPH.
Raporsin given in the recommended dosage regimen has little or no effect on blood pressure in normotensive patients.

In a controlled clinical BPH trial, treatment with doxazosin in patients with sexual dysfunction was associated with improvement in sexual function.

5.2 Pharmacokinetic properties

Absorption
After oral administration of therapeutic doses, doxazosin in Raporsin 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 Raporsin will lead to a smoother plasma profile.

Peak/trough ratio of Raporsin prolonged-release tablets is less than half that of immediate release doxazosin tablets.

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

Elderly:
Pharmacokinetic studies with doxazosin in the elderly have shown no significant alterations compared to younger patients.

Distribution
Approximately 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

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.).

Doxazosin is extensively metabolised in the liver. In vitro studies suggest that the primary pathway for elimination is via CYP 3A4; however, CYP 2D6 and DYP 2C9 metabolic pathways are also involved for elimination, but to a lesser extent.

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.

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. 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 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

For further information, see section 4.6.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 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 blister.

Pack sizes: 10,28, 30, 50, 90, 98 and 100 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/005/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd May 2009
Date of last renewal: 12th February 2014

10 DATE OF REVISION OF THE TEXT

June 2024