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: 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.

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: 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.

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.

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. 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 doxazosin with phospodiesterase-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 phospodiesterase-5-inhibitors only if the patient is hemodynamically stabilized on alpha-blocker therapy. Furthermore, it is recommended to initiate phospodiesterase-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: 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.

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.

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 high doses (see Section 5.3: Preclinical Safety Data).

Breastfeeding

Alternatively, mothers should stop breast-feeding when treatment with doxazosin is necessary (Please see section 5.3).

Lactation

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.

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 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	Introperative 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	Flush
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
	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, 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 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-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 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.

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 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 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.

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, Raporsin, prolonged-release tablets have 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 Raporsin prolonged-release tablets 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 Raporsin prolonged-release tablets lead to a minor variation in plasma levels. 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.

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 (Cmax 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

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.
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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

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10 DATE OF REVISION OF THE TEXT