Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Raporsin 8mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 8 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 DH embossed on one side.

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 and elderly:
The standard dose is 4 mg doxazosin once daily. If necessary, the dose can be increased to 8 mg once daily. It may take up to four weeks to achieve an optimal effect.

Raporsin 8 mg can be used in combination with thiazide diuretics, beta-adrenoceptor blocking agents, calcium antagonists or ACE inhibitors.

Symptomatic treatment of prostatic hyperplasia
Adults and elderly
The standard dose is 4 mg doxazosin once daily. If necessary, the dose can be increased to 8 mg once daily.

Doxazosin can be used in both normotensive and hypertensive patients with benign prostatic hyperplasia. The fall in blood pressure in normotensive patients is generally insignificant. The patient must be closely monitored during the initial phase of the treatment due to the risk of postural side effects.

Dose response studies have not been performed for doxazosin prolonged-release tablets, which means that an increased effect has not yet been shown with an increased dose (up to 8 mg).

Patients with renal impairment
As there is no change in the pharmacokinetics of doxazosin in patients with impaired renal function, and as there are no signs that doxazosin aggravates existing renal impairment, normal dosage can be used in these patients.

Patients with hepatic impairment

Doxazosin should be administered with particular caution in patients with signs of hepatic impairment. As there is no clinical experience in patients with severe hepatic impairment, the use of doxazosin is not recommended in these patients (see section 4.4).

Paediatric population
The safety and efficacy of Raporsin 8 mg in children and adolescents have not been established.

Method of administration
Raporsin 8 mg 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 must not be chewed, divided or crushed.

4.3 Contraindications

Doxazosin is contraindicated in

- - Patients with a known hypersensitivity to the active substance, other quinazolines (e.g. prazosin, terazosin, doxazosin) 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 flow obstruction in the upper urinary tract, chronic urinary tract infection or bladder stones.
- - Patients with a history of gastrointestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract.
- - During lactation (see section 4.6). [1]
- - Patients with hypotension. [2]

Doxazosin is contraindicated as monotherapy in patients with overflow incontinence or anuria with or without progressive renal failure.

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.

In Raporsin 8 mg prolonged-release tablets 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 tablet-like remains in their stools.

Abnormally short transit times through the gastrointestinal tract (e.g. following surgical resection) may result in incomplete absorption. In view of the long half-life of doxazosin the clinical significance of this is unclear.

Initiation of therapy:
On account of the alpha-blocking properties of doxazosin, patients may experience postural hypotension evidenced by dizziness and weakness, or, in rare cases, loss of consciousness (syncope), particularly at the commencement of therapy. Therefore, it is prudent to monitor blood pressure on initiation of therapy to minimise the potential risk of postural effects. The lowest effective dose of doxazosin should be initiated and titrated as appropriate by the physician. The patient should be cautioned to avoid situations where injury could result should dizziness or weakness occur at the beginning 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 vasodilator anti-hypertensive agent it is prudent medical practice to exercise caution when administering doxazosin to patients with the following acute cardiac conditions:
- pulmonary oedema due to aortic or mitral stenosis
- heart failure with hyperkinetic circulation
- right-sided heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

Use in patients with impaired hepatic function:
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. 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 use of doxazosin with phosphodiesterase-5-inhibitors (PDE-5 inhibitors) (e.g. sildenafil, tadalafil, and vardenafil) as both medicines have vasodilating effects and may result in symptomatic hypotension in some patients. To reduce the risk of postural hypotension, the patient should be stable on alpha-blocker therapy before initiating treatment with PDE-5 inhibitors. It is also recommended that the treatment with PDE-5 inhibitors be initiated with the lowest possible dose and that a 6-hour time interval from intake of doxazosin be respected. No studies have been conducted with doxazosin prolonged-release formulations.

Use in patients undergoing cataract surgery:
During cataract surgery in some patients on or previously treated with tamsulosin it has been observed that the iris muscle has become diffuse in consistency during the operation (IFIS, "Intraoperative Floppy Iris Syndrome"). Isolated reports have also been noted for other alpha-1 blockers, and therefore the possibility of a class effect cannot be excluded. As IFIS may result in increased 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 administration of doxazosin with PDE-5 inhibitors (e.g. sildenafil, tadalafil, verdenafil) may result in symptomatic hypotension in some patients (see section 4.4).

Most (98 %) of plasma doxazosin is protein bound. In vitro data from human plasma indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin.

In clinical use, conventional doxazosin tablets have been administered without any adverse drug interaction with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, and anticoagulants. However, there are no data from formal interaction studies.

Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other anti-hypertensives.

In an open-label, randomised, 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, 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 or limited amount of data from the use of doxazosin 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 doses equivalent to approximately 300 times the maximum recommended human dose (see section 5.3).

Breastfeeding
Doxazosin is contraindicated during lactation (see section 4.3) as the drug active substance accumulates in milk of lactating rats and there is no information about the excretion of doxazosin/metabolites into the milk of lactating women.
Alternatively, mothers should stop breast-feeding when treatment with doxazosin is necessary.

Fertility
Animal studies revealed a reduction in fertility in male rats treated with doxazosin in concentrations exceeding many times the recommended human daily dose.. This effect was reversible two weeks after the withdrawal of the drug (see section 5.3). There are no records of any effects caused by doxazosin in male human fertility.

For the benign prostatic hyperplasia indication:
This section is not applicable.

4.7 Effects on ability to drive and use machines

Doxazosin may impair the ability to drive and use machines, especially when initiating therapy.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with doxazosin. Frequencies used are 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 frequency cannot be estimated from available data

System organ class	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Blood and lymphatic systemdisorders	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, hypoaesthesia, syncope, tremor
	Very rare	Postural dizziness, 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	Palpitations, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very rare	Bradycardia, cardiac arrhythmia

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
Hepatobiliary disorders	Uncommon	Abnormal liver function tests
	Very rare	Cholestasis, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Common	Pruritus
	Uncommon	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, increased miction frequency
	Very rare	Miction disorders, nocturia, polyuria, increased diuresis
Reproductive system and breast disorders	Uncommon	Impotence
	Very rare	Gynaecomastia, priapism
	Unknown	Retrograde ejaculation
General disorders and administration site conditions	Common	Asthenia, chest pain, flu-like symptoms, peripheral oedema
	Uncommon	Pain, facial oedema
	Very rare	Fatigue, malaise
Investigations	Uncommon	Weight gain

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: Antiadrenergic agents, peripherally acting;alpha-adrenoreceptor antagonists, ATC code: C02CA04

The active substance in Raporsin 8 mg is doxazosin and is a quinazoline derivative. Doxazosin has a vasodilator effect through selective and competitive blocking of post-synaptic alpha-1 receptors.

With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and for 24 hours after intake.

Tolerance development has not been observed during long-term therapy with conventional doxazosin tablets. An increase in plasma renin activity and tachycardia are rare during maintenance therapy.

Doxazosin has a beneficial effect on blood lipids, with a moderate increase of HDL/total cholesterol ratio (approximately 4-13% of the baseline value). The clinical significance of these findings remains to be seen.

Doxazosin improves insulin sensitivity in patients with impaired sensitivity. Treatment with conventional doxazosin tablets has been shown to result in the regression of left ventricular hypertrophy. No studies investigating the effect on mortality and morbidity have been completed.

Hypertension
Data from two dose-effect studies (with a total of 630 patients treated with doxazosin) have shown that patients treated with conventional tablets in dosages of 1 mg, 2 mg or 4 mg are equally well-controlled on treatment with 4 mg doxazosin prolonged-release tablets.

Interim analyses of the study 'Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial' (ALLHAT) have shown that patients with hypertension and at least one other clinical risk factor for coronary heart disease, being treated with doxazosin, are exposed to a doubled risk of chronic heart failure compared to patients treated with chlorthalidone. They also had a 25% higher risk of developing clinically significant cardiovascular disorders. The doxazosin arm of ALLHAT was discontinued as a result of these findings. There was no difference in mortality.

These results are difficult to interpret for different reasons, including differences in the effect on systolic blood pressure and the withdrawal of diuretics in the group treated with doxazosin before treatment was started. The results have not yet been fully evaluated.

Benign prostatic hyperplasia
Doxazosin has been shown to inhibit phenylephrine-induced prostatic contractions in the prostate. High levels of alpha-1 adrenoreceptors have been found in the smooth muscle in the prostate, the proximal part of the urethra and the base of the urinary bladder. These mediate the tonus in the smooth muscle in the prostatic part of the urethra. Blocking alpha-1 adrenoreceptors through doxazosin reduces the tonus of the muscle in the prostatic part of the urethra, facilitating the urinary flow. This is the pharmacological basis for the clinical use of doxazosin in the treatment of benign prostatic hypertrophy.

Efficacy and safety studies (with a total of 1,317 patients being treated with doxazosin) have only been conducted in patients with a baseline of I-PSS >12 and a maximum urinary flow of <15 ml/sec. Data from these studies indicate that patients that are well-controlled on conventional tablets of doxazosin in dosages of 1 mg, 2 mg or 4 mg are equally well-controlled on doxazosin 4 mg prolonged-release tablets.

5.2 Pharmacokinetic properties

Absorption/distribution
Following oral administration of therapeutic doses, doxazosin from prolonged-release tablets is well absorbed with peak blood levels gradually being reached 8 to 9 hours after dosing. Peak plasma levels are approximately one third of the levels achieved after the same dose of a conventional doxazosin tablet. However, trough levels at 24 hours are comparable for both formulations.

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

Biotransformation/elimination
Doxazosin is extensively metabolised with <5 % excreted as unchanged product. Doxazosin is primarily metabolised by

O-demethylation and hydroxylation.

The plasma elimination is biphasic with a terminal half-life of 22 hours, which provides the basis for once-daily dosing.

Elderly
Pharmacokinetic studies with doxazosin prolonged-release tablets among the elderly have not shown any significant changes compared to younger patients.

Renal impairment
Pharmacokinetic studies with doxazosin in patients with renal impairment did not show any significant changes compared to patients with normal renal function.

Liver impairment
There is only limited data from patients with hepatic impairment and on the effects of medicinal products that are known to influence hepatic metabolism (e.g. cimetidine). In a clinical study of twelve patients with moderate hepatic impairment, a single dose of doxazosin resulted in an increase in AUC of 43% and a decrease in oral clearance of 30%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

Carcinogenicity:
Chronic administration in the diet (for 24 months) of doxazosin at doses up to maximum tolerated did not cause increased incidence of tumours in rats. The highest dose evaluated in this study was associated with an AUC value (a measure of systemic exposure) around 8 times the human AUC. The drug also showed no carcinogenic activity in mice.

Mutagenicity:
In vitro and *in vivo* mutagenicity studies revealed no genotoxic potential.

Reproductive toxicity:
Studies with rats revealed a reduction in fertility in males treated with doxazosin at oral doses of 20 mg/kg/day (but not with doses of 5 or 10 mg/kg/day) with AUC approximately 4 times the human AUC receiving doses of 12 mg/day. This effect was reversible two weeks after the withdrawal of the drug.
There are no records of any effects caused by doxazosin in male human being fertility.
Doxazosin showed no teratogenic potential in rats or rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Polyethylene oxide (MW 200,000)
Polyethylene oxide (MW 900,000)
Microcrystalline cellulose
Povidone (K29-32)
Butylhydroxytoluene (E321)
all-rac-α-tocopherol
Colloidal anhydrous silica
Sodium stearyl fumarate

Tablet coating
Methacrylic acid - ethyl acrylate copolymer (1:1), dispersion 30%
Colloidal hydrated silica
Macrogol 1300-1600
Titanium dioxide (E171)

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/Alu blister.

Pack sizes:
7, 10, 14, 15, 28, 30, 50, 56, 60, 98, 100 tablets.
Calendar packs: 7, 14, 28, 56 and 98 tablets.
Single-dose pack: 50 x 1 tablet.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA2315/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th September 2011
Date of last renewal: 31st August 2014

10 DATE OF REVISION OF THE TEXT

March 2023