

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. 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).

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.

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 and 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 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 (For patients taking the sustained release tablets only).
- During lactation (see section 4.6). (For the hypertension indication only)
- Patients with hypotension (For benign prostatic hyperplasia indication only)

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 (see section 4.2).

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

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, 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. 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 at the beginning 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 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 at high output
- 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 (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 carried out with great care.

Use with PDE-5 inhibitors:

Concomitant use of doxazosin with phosphodiesterase-5-inhibitors (PDE-5 inhibitors) (e.g. sildenafil, tadalafil, and vardenafil) should be done with caution as both medicines have vasodilating effects and may result in symptomatic hypotension in some patients. To reduce the risk of orthostatic 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:

Intraoperative Floppy Iris Syndrome

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.

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.

Excipient 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 administration of doxazosin with PDE-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) may result in 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 from human plasma indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. 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)

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 when, in the opinion of the physician, the potential benefit outweighs the potential 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

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.

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

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 doxazosin. Frequencies used are as follows:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ to $< 1/1,000$

Very rare $< 1/10,000$

Not known frequency cannot be estimated from available data

System organ class	Frequency	Undesirable Effects
<i>Infections and infestations</i>	Common	Respiratory tract infection, urinary tract infection
<i>Blood and lymphatic system disorders</i>	Very rare	Leukopenia, thrombocytopenia
<i>Immune system disorders</i>	Uncommon	Allergic drug reaction

<i>Metabolism and nutrition disorders</i>	Uncommon	Anorexia, gout, increased appetite
<i>Psychiatric disorders</i>	Uncommon	Anxiety, depression, insomnia
	Very rare	Agitation, nervousness
<i>Nervous system disorders</i>	Common	Dizziness, headache, somnolence
	Uncommon	Cerebrovascular accident, hypoaesthesia, syncope, tremor
	Very rare	Postural dizziness, paraesthesia
<i>Eye disorders</i>	Very rare	Blurred vision
	Not known	Intraoperative floppy iris syndrome (see section 4.4)
<i>Ear and labyrinth disorders</i>	Common	Vertigo
	Uncommon	Tinnitus
<i>Cardiac disorders</i>	Common	Palpitations, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very rare	Bradycardia, cardiac arrhythmia
<i>Vascular disorders</i>	Common	Hypotension, postural hypotension
	Very rare	Hot flushes
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	Bronchitis, cough, dyspnoea, rhinitis
	Uncommon	Epistaxis
	Very rare	Bronchospasm
<i>Gastrointestinal disorders</i>	Common	Abdominal pain, dyspepsia, dry mouth, nausea
	Uncommon	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis
	Rare	Gastrointestinal obstruction
<i>Hepatobiliary disorders</i>	Uncommon	Abnormal liver function tests
	Very rare	Cholestasis, hepatitis, jaundice
<i>Skin and subcutaneous tissue disorders</i>	Common	Pruritus
	Uncommon	Skin rash
	Very rare	Alopecia, purpura, urticaria
<i>Musculoskeletal and connective tissue disorders</i>	Common	Back pain, myalgia
	Uncommon	Arthralgia
	Very rare	Muscle cramps, muscle weakness
<i>Renal and urinary disorders</i>	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, haematuria, micturition frequency
	Very rare	Micturition disorder, nocturia, polyuria, increased diuresis
<i>Reproductive system and breast disorders</i>	Uncommon	Impotence
	Very rare	Gynaecomastia, priapism
	Unknown	Retrograde ejaculation
<i>General disorders and administration site conditions</i>	Common	Asthenia, chest pain, flu-like symptoms, peripheral oedema
	Uncommon	Pain, facial oedema
	Very rare	Fatigue, malaise
<i>Investigations</i>	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: Antiadrenergic agents, peripherally acting; alpha-adrenoreceptor antagonists, ATC code: C02CA04 (Hypertension)

Mode of action

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.

Administration of Doxazosin to 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 for 24 hours after intake. The majority of patients are controlled on the initial dose. In patients with hypertension, blood pressure during treatment with Doxazosin was similar in both the supine 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 to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the alpha adrenoreceptors located in the muscular stroma and capsule of the prostate and in the bladder neck.

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. Additionally, doxazosin improves insulin sensitivity in patients with impairment.

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 produces favourable effects on blood lipids, with a significant increase in the high-density lipoprotein HDL/total cholesterol ratio and trends to a favourable reduction in total triglycerides. It therefore confers an advantage over diuretics and beta-adrenoreceptor 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.

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

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.

The pharmacokinetic characteristics of Raporsin will lead to a smoother plasma profile.

Peak/trough ratio of Raporsin is less than half that of intermediate 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.

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

Distribution:

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%. 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.

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 1 mg/kg of [2-14C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

For further information see section 4.6.

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

September 2024