

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kamiren 4 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4mg doxazosin (as mesilate)

Excipient(s) with known effect: Lactose Monohydrate 74.27mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablets.

Kamiren 4mg prolonged-release tablets are white, round, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension:

Kamiren 4mg prolonged-release tablets are indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

In patients inadequately controlled on single antihypertensive therapy, Kamiren prolonged-release tablets may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

4.2 Posology and method of administration

Posology

The initial dose of Kamiren prolonged-release tablets is 4mg once daily. A significant number of patients will be controlled on this dose. If necessary, the dosage may be increased to 8 mg once daily according to patient response. The maximum recommended dose is 8 mg once daily.

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 the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual dosages may be used in these patients. Kamiren prolonged-release tablets are 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 metabolised wholly by the liver, Kamiren prolonged-release tablets 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 Kamiren in children and adolescents have not been established.

Method of administration

Kamiren prolonged-release tablets can be taken with or without food.

The tablets should be swallowed whole with a sufficient amount of liquid. They should not be cut, crushed or chewed (see section 4.4).

4.3 Contraindications

Kamiren prolonged-release tablets are contraindicated in

- Patients who are hypersensitive to the active substance, other types of 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 (see section 4.6)
- Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

4.4 Special warnings and precautions for useInformation to be given to the patient:

Patients should be informed that Kamiren prolonged-release tablets should be swallowed whole. Patients should not chew, divide or crush the tablets.

In Kamiren the active compound is surrounded by an inert a non-absorbable shell that has been specially designed to control the release of the drug over a prolonged period. After transit through the gastrointestinal tract, when this process is completed the empty tablet shell is excreted. Patients should be advised that they should not 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 - As with all alpha-blockers, a very small percentage of patients have experienced 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 Kamiren prolonged-release tablets therapy, such as driving or operating machinery.

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, Kamiren prolonged-release tablets 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 Kamiren prolonged-release tablets aggravates renal dysfunction. However, Kamiren prolonged-release tablets dosage introduction and adjustments should be carried out with great care.

Use with Phosphodiesterase Type-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 the 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 formulations.

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.

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.

As this formulation contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Phosphodiesterase Type-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil)

Concomitant administration of an alpha blocker with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4). No studies have been conducted with Kamiren prolonged-release tablets.

Doxazosin is highly bound to plasma proteins (98%). In vitro data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin). However, the theoretical potential for interaction with other protein bound drugs should be borne in mind.

Conventional doxazosin has been administered without any adverse drug interactions in clinical experience with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or 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 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 in pregnant women, the safety of Kamiren prolonged-release tablets during pregnancy has not yet been established. Accordingly, during pregnancy, Kamiren prolonged-release tablets 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.

Lactation

Doxazosin is contraindicated during lactation as animal studies have shown that doxazosin accumulates in milk of lactating rats, and there is no information about the excretion of the drug into the milk of lactating women. The clinical safety of doxazosin during lactation has not been established, consequently doxazosin is contra-indicated in nursing mothers.

Breastfeeding

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

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 Kamiren prolonged-release tablets were of a postural type (rarely associated with fainting) or non-specific.

The undesirable effects for doxazosin prolonged-release tablets are similar to those with immediate release doxazosin tablets.

The following undesirable effects have been observed and reported during treatment with doxazosin prolonged-release tablets with the following: 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 ($< 1/10,000$).

System Organ Class	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 ($< 1/10,000$)	Unknown
Infections and infestations	Respiratory tract infection, urinary tract infection				
Blood and the lymphatic system disorders				Leukopenia, thrombocytopenia	
Immune system disorders		Allergic drug reaction			

Metabolism and nutrition disorders		Anorexia, gout, increased appetite			
Psychiatric disorders		Anxiety, depression, insomnia		Agitation, nervousness	
Nervous system disorders	Dizziness, headache, somnolence	Cerebrovascular accident, hypoesthesia, syncope, tremor		Dizziness postural, paresthesia	
Eye disorders				Blurred vision	Introperative floppy iris syndrome (see Section 4.4)
Ear and labyrinth disorders	Vertigo	Tinnitus			
Cardiac disorders	Palpitation, tachycardia	Angina pectoris, myocardial infarction		Bradycardia, cardiac arrhythmias	
Vascular disorders	Hypotension, postural hypotension			Hot flushes	
Respiratory, thoracic and mediastinal disorders	Bronchitis, cough, dyspnea, rhinitis	Epistaxis		Bronchospasm	
Gastrointestinal disorders	Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, diarrhoea, flatulence, vomiting, gastroenteritis	Gastrointestinal obstruction		
Hepato-biliary disorders		Abnormal liver function tests		Cholestasis, hepatitis, jaundice	
Skin and subcutaneous tissue disorders	Pruritus	Skin rash		Alopecia, purpura, urticaria	
Musculoskeletal, connective tissue and bone disorders	Back pain, myalgia	Arthralgia		Muscle cramps, muscle weakness	
Renal and urinary disorders	Cystitis, urinary incontinence	Dysuria, hematuria, micturition frequency		Micturition disorder, nocturia, polyuria, increased diuresis	
Reproductive system and breast disorders		Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions	Asthenia, chest pain, influenza-like symptoms, peripheral edema	Pain, facial oedema		Fatigue, malaise	

Investigations		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 may be appropriate in individual cases. Since doxazosin is highly protein bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, alpha-adrenoceptor antagonists, ATC code: C02CA04

Mode of action

Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist.

Administration of Doxazosin prolonged-release tablets 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 at 24 hours post dose. The majority of patients are controlled on the initial dose. In patients with hypertension, blood pressure during treatment with Doxazosin prolonged-release tablets 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 4mg Doxazosin prolonged-release tablets.

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 and enhanced activity of tissue plasminogen activator. Additionally, doxazosin improves insulin sensitivity in patients with impairment.

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 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.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, Doxazosin prolonged-release tablets are 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 Doxazosin prolonged-release tablets will lead to a smoother plasma profile.

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

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

Pharmacokinetic studies with Doxazosin prolonged-release tablets in the elderly have shown no significant alterations compared to younger patients.

Biotransformation / Elimination

The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basis for once daily dosing. Doxazosin is extensively metabolised with <5% excreted as unchanged drug.

Pharmacokinetic studies with immediate release Doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

There are only limited data 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 moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 30%. (See section 4.4).

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

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

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 and carcinogenicity. For further information see section 4.6 Pregnancy and lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose

Calcium hydrogen phosphate anhydrous

Lactose monohydrate

Magnesium stearate

Coating:

Opadry white Y-1-7000 consists of:

Hypromellose

Titanium dioxide (E171)

Macrogol 400

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

Kamiren 4 mg prolonged-release tablets are available as pack of 28 tablets.

OPA/Alu/PVC film with Alu foil blister strips in a carton box.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Krka d.d

Novo mesto

Šmarješka cesta 6

8501 Novo mesto

Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/038/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd March 2006

Date of last renewal: 3rd March 2011

10 DATE OF REVISION OF THE TEXT

February 2017