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

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

***Hypertension:***

Kamiren 4 mg 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 4 mg 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).
- 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 use**

Information 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 'introoperative 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**4.5 Interaction with other medicinal products and other forms of interactions**

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.

*In vitro* studies suggest that doxazosin is a substrate of cytochrome P450 3A4 (CYP 3A4). Caution should be exercised when 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 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*
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.

**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 (≥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).

| **System Organ Class** | **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)** | **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 | Intraoperative floppy iris syndrome (see Section 4.4) |

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|---|---|---|---|---|---|
| **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 4 mg 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 lipoproteinHDL/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 4 mg dose and 59% at the 8 mg 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.

Doxazosin is extensively metabolized in the liver. *In vitro* studies suggest that the primary pathway for elimination is via CYP 3A4; however, CYP 2D6 and CYP 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 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
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**

August 2021