SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kamiren XL modified-release tablets 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each modified-release tablet contains 4 mg doxazosin as doxazosin mesylate.
The excipients are stated under item 6.1.

3. PHARMACEUTICAL FORM

Modified-release tablets: white, round, slightly convex tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The drug is recommended for the treatment of hypertension. Kamiren XL may be used alone or in combination with other antihypertensive drugs, such as thiazide diuretics, beta-antagonists, calcium channel blockers or angiotensin-converting enzyme inhibitors.
The drug is recommended in benign prostatic hyperplasia to improve the clinical symptoms and increase the urine flow. It may be used in both hypertensive and normotensive patients. In hypertensive patients, it simultaneously reduces blood pressure. In normotensive patients, the effect on blood pressure is clinically insignificant.

4.2 Posology and method of administration

Kamiren XL modified-release tablets should be ingested whole with some liquid. They should not be chewed, broken or crushed (see also Special warnings and special precautions for use). Patients may take the drug before, during or after a meal.
Hypertension and benign prostatic hyperplasia
The usual dose of Kamiren XL is 1 tablet (4 mg) daily. Its effect can be seen already on the first day but the full effect occurs after 4 weeks of treatment. A daily dose of 4 mg is effective in the majority of patients. If the effect after 4 weeks of treatment is inadequate and if the patient tolerates the drug well, a higher dose of the drug may be administered. The maximum recommended dose is 2 tablets (8 mg) once daily.
No dosage adjustments are required in elderly patients and patients with renal impairment.
In patients with liver impairment, caution should be used (see also Special warnings and special precautions for use).
Paediatric population
The safety and efficacy of Kamiren XL in children and adolescents have not been established.
If the patient has missed a dose, he should leave it out and go back to the regular dosing schedule.

4.3 Contraindications

Patients who are hypersensitive to doxazosin or other quinazoline derivatives (prazosin, terazosin) or to any of the excipients should not take the drug.

4.4 Special warnings and special precautions for use

Orthostatic hypotension may occur especially at the beginning of treatment. The patient should be warned about the possibility of orthostatic hypotension and advised to be careful when rising from a

sitting or lying position. At the beginning of treatment, the patient should avoid situations where injury could result from vertigo or nausea. This is particularly important for elderly patients and those concurrently taking other antihypertensives or diuretics.
Hepatic impairment: In patients with hepatic impairment, the metabolism of doxazosin is slower and caution is required with administration (see also Pharmacokinetic properties).
Accelerated passage through the gastrointestinal tract: If the passage through the gastrointestinal tract is highly accelerated, the absorption and efficacy of the drug may be altered.
Instructions for patients: Patients should be warned to swallow the tablets whole. They should not chew, break or crush them.
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.

4.5 Interaction with other medicinal products and other forms of interaction
Doxazosin is bound to plasma proteins. In *in vitro* tests, doxazosin had no influence on the binding of digoxin, warfarin, phenytoin or indomethacin to plasma proteins. No harmful interactions were observed in patients taking doxazosin together with thiazide diuretics, furosemide, beta-antagonists, nonsteroidal anti-inflammatory drugs, antibiotics, oral hypoglycemic drugs, uricosuric drugs and anticoagulants.

4.6 Pregnancy and lactation
Doxazosin was not teratogenic in animal studies. At doses 300 times the maximum recommended human dose, the fetal survival rate decreased. Doxazosin was accumulated in the milk of dams.
Safety for use in pregnancy has not been established.
The risk to the fetus cannot be excluded. Pregnant women may be given Kamiren XL only if it is clearly needed, when the potential benefit for the mother justifies the risk to the fetus.
Breastfeeding is not recommended during the treatment because safety for the infant has not been established.

4.7 Effects on ability to drive and use machines
Especially at the beginning of treatment with Kamiren XL, excessive hypotension may occur and the patient may become dizzy. Driving motor vehicles or operating machinery is not recommended at that time.

4.8 Undesirable effects
Like other alpha-adrenergic receptor antagonists, doxazosin may also cause orthostatic hypotension, particularly at the beginning of treatment. Kamiren XL modified-release tablets allow more uniform plasma doxazosin concentrations without a pronounced peak, so the risk for orthostatic hypotension and for some other undesirable effects is lower than with ordinary tablets. The difficulties usually resolve spontaneously; if they are prolonged or severe, the dose should be reduced or treatment discontinued.
Frequently reported undesirable effects of doxazosin (> 1%) are:
- Autonomic nervous system: dry mouth.
- Body as a whole: asthenia, back pain, chest pain, influenza-like symptoms.
- Cardiovascular system: peripheral edema, orthostatic hypotension, hypotension, tachycardia, palpitations.
- Central and peripheral nervous system: dizziness, headache, vertigo.
- Gastrointestinal tract: abdominal pain, nausea, dyspepsia.
- Bones and muscles: myalgia.
- Psychiatric disorders: somnolence.
- Respiratory tract: bronchitis, cough, respiratory tract infections, rhinitis.
- Skin: pruritus.

- Urinary tract: urinary tract infections, urinary incontinence.

The following undesirable effects have been reported very rarely:

- Body as a whole: hypersensitivity reactions, hot flushes, pain, increase in body weight.
- Cardiovascular system: hypotension, syncope, bradycardia, angina pectoris, myocardial infarction, cerebrovascular insult, arrhythmias.
- Central and peripheral nervous system: hypoesthesia, paresthesia, tremor.
- Endocrine glands: gynecomastia.
- Gastrointestinal tract: constipation, diarrhea, dyspepsia, flatulence, vomiting.
- Hematopoietic system: leukopenia, thrombocytopenia, purpura.
- Liver and gall bladder: pathologic liver tests, cholestasis, hepatitis, jaundice.
- Bones and muscles: arthralgia, muscle cramps, muscle weakness.
- Psychiatric disorders: agitation, worry, depression, excessive tension, insomnia, anorexia.
- Respiratory tract: exacerbation of bronchospasm, dyspnea, cough, epistaxis.
- Skin: alopecia, skin rash.
- Senses: blurred vision, tinnitus.
- Urogenital system: hematuria, miction disorders (dysuria, micturition frequency, nocturia), impotence, priapism.

There is no reliable causal relationship between the drug and the above undesirable effects. Some undesirable effects were reported only in patients with hypertension and were probably disease-related (e.g. bradycardia, tachycardia, other cardiac arrhythmias, palpitations, chest pain, angina pectoris, myocardial infarctions and cerebrovascular insults). In patients with benign prostatic hyperplasia, the incidence of undesirable effects is similar to that with placebo.
The incidence of undesirable effects in elderly patients is similar to that in younger patients.

4.9 Overdose

Too large doses mainly cause hypotension, dizziness and vertigo, possibly also syncope. In most cases a dose reduction or temporary discontinuation of treatment is sufficient.
Ingestion of a larger quantity of the drug may lead to hypotension.
Measures: The patient should be placed in a supine position with the head lowered and legs slightly elevated. Induction of vomiting is not recommended. Other measures to eliminate the unabsorbed drug from the gastrointestinal tract should be employed (gastric lavage, activated charcoal, laxative).
Treatment is symptomatic and with α-adrenoceptor agonists, e.g. noradrenaline.
Hemodialysis is ineffective in the removal of the drug because doxazosin is almost completely bound to plasma proteins.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxazosin is a selective, long-acting α_1-adrenoceptor antagonist.
It reduces blood pressure by preventing the contraction of the smooth muscles in peripheral vascular walls, thus reducing the total peripheral vascular resistance. Blood pressure reduction in the standing position is similar to that in the sitting position. Patients with hypertension who take ordinary Kamiren tablets may replace them with Kamiren XL modified-release tablets. The efficacy and safety of treatment do not change. The effects on heart function are insignificant and transient. Resistance to doxazosin does not develop even after prolonged treatment.
Doxazosin reduces total cholesterol, LDL-cholesterol, triglyceride fats and produces an increase in blood HDL-cholesterol, therefore it has a protective effect against the development of atherosclerosis and coronary heart disease. Doxazosin is suitable for patients with non-insulin-dependent diabetes mellitus because it has a neutral or even positive effect on blood sugar and insulin. It inhibits platelet aggregation. After prolonged administration, left ventricular mass is reduced. Doxazosin is a safe drug in patients with renal impairment, chronic obstructive pulmonary disease, peripheral arterial angiopathy and gout.

A doxazosin dose is effective for more than 24 hours. The full effect will be seen after several weeks of regular use. If the effect is unsatisfactory, the patients may be concurrently treated with other antihypertensives: beta-blockers, diuretics, calcium channel antagonists or angiotensin-converting enzyme inhibitors.
Doxazosin prevents contraction of the smooth muscles of the upper part of the urethra and prostatic muscles, which encircle and compress the urethra. Due to muscle relaxation, micturition is facilitated, which considerably relieves the bothersome symptoms seen in benign prostatic hyperplasia. A beneficial effect on these symptoms is already seen within the first two weeks of treatment and increases with further treatment. Compared to the ordinary doxazosin tablets, the modified-release tablets have improved ratio between the efficacy and safety.
The effect of the drug on normal blood pressure is negligible.
The existing sexual dysfunction may improve.

5.2 Pharmacokinetic properties

Kamiren XL modified-release tablets are well absorbed after oral administration. Doxazosin gradually achieves maximum plasma concentrations in 8 to 9 hours. The maximum plasma concentrations of modified-release tablets are only one third of the concentrations of the standard tablets while the lowest concentrations are similar in both forms of the drug. Therefore the plasma profile of doxazosin is more uniform and the ratio between the maximum and minimum plasma concentrations twice lower in this form of the drug compared to the standard tablets.
In the blood, doxazosin is almost completely bound to plasma proteins. It is metabolized in the liver and subsequently excreted in the feces, mostly as metabolites. Less than 5% of an administered dose remains unchanged. The elimination half-life is 22 hours.
The pharmacokinetic properties of doxazosin in the elderly and patients with renal impairment do not differ significantly from those in young patients with normal renal function.
In patients with hepatic impairment, doxazosin is excreted more slowly and the plasma concentrations and AUC are considerably increased.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose, calcium hydrogen phosphate, lactose monohydrate, magnesium stearate, titanium dioxide (E171), macrogol 400.

6.2 Incompatibilities

None known.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package.
Keep out of the reach of children.

6.5 Nature and contents of container

Blister pack (aluminium foil, OPA/Al/PVC foil):
90 modified-release tablets, in a folding box.

1.3.1	Doxazosin mesylate
SPC, Labeling and Package Leaflet	MY

6.6 Instructions for use and handling

No special instructions required.

7 MARKETING AUTHORIZATION HOLDER

PAHANG PHARMACY SDN. BHD., Lot 5979,Jalan Teratai, 5 ½ Mile Off Jalan Meru, 41050 Klang, Selangor, Malaysia

8 MARKETING AUTHORIZATION NUMBER

MAL 10100162A

9 MARKETING AUTHORIZATION DATE

28.10.2010

10 DATE OF THE LATEST REVISION OF THE SPC

March, 2019