Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xatger 10mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg alfuzosin hydrochloride

Excipient with known effect:
Each tablet contains 7.6 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White, round, bevelled-edge, uncoated prolonged-release tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH)including adjunctive therapy with urethral catheterization for acute urinary retention (AUR) related to BPH and management following catheter removal.

4.2 Posology and method of administration

Posology

Adults

BPH: One prolonged-release tablet 10 mg dailyto be taken after an evening meal.

AUR: One 10 mg tablet daily after a meal to be taken from the first day of catheterization and
continued beyond catheter removal unless there is a relapse of acute urinary retention or disease progression.

Elderly (over 65 years) and patients with renal insufficiency

Based on pharmacokinetic and clinical safety data, elderly and patients with renal insufficiency
(creatinine clearance ≥30 ml/min) can be treated with the usual dose. Due to lacking clinical safety data alfuzosin should not be given to patients with severe renal impairment (creatinine
clearance <30 ml/min, see section 4.4).

Patients with hepatic insufficiency

Xatger prolonged-release tablet 10 mg is contraindicated in patients with hepatic insufficiency (see section 4.3).

Paediatric population
Efficacy of alfuzosin has not been demonstrated in children aged 2 to 16 years (see section 5.1). Therefore, alfuzosin is not indicated for use in paediatric population.

Method of administration
For oral use.

The prolonged-release tablet should be swallowed whole with a sufficient amount of fluid . Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.

The tablet should be taken after a meal.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinazolines (e.g. terazosin, doxazosin) or to any of the excipients listed in section 6.1.
- Conditions with orthostatic hypotension.
- Liver insufficiency.
- Combination with other alpha$_1$-receptor blockers.

4.4 Special warnings and precautions for use

Patients with severe renal impairment
Alfuzosin should not be given to patients with severe renal impairment (creatinine clearance < 30ml/min) in view of the lack of clinical safety data in this group of patients (see sections 4.2 and 5.2).

Risk of hypotension
Xatger should be given with caution to patients who are on antihypertensive medication or nitrates. Blood pressure should be monitored regularly, especially at the beginning of treatment (see section 4.5).

In some subjects postural hypotension may develop, with or without symptoms (dizziness, fatigue, asthenia, sweating) within a few hours following administration (see section 4.8). In such cases, the patient should lie down until the symptoms have totally disappeared.

These effects are usually transient, occur in the beginning of treatment and do not usually prevent the continuation of treatment.

Pronounced drop in blood pressure has been reported in post-marketing surveillance in patients with pre-existing risk factors (such as underlying cardiac diseases and/or concomitant treatment with anti-hypertensive medication). The risk of developing hypotension and related adverse reactions may be greater in older people. Patients should be warned about the possibility of these effects.

Care should be taken when alfuzosin is administered to patients who have had a pronounced hypotensive response to another alpha$_1$-receptor blocker.

In coronary patients, the specific treatment for coronary insufficiency should be continued. If angina pectoris reappears or worsens, alfuzosin should be discontinued.
Concomitant administration of specific treatment for coronary insufficiency such as nitrates and alfuzosin may increase the risk of occurrence of hypotension (see section 4.5)

Cardiac failure
As with all alpha$_1$-receptor blockers, alfuzosin should be used with caution in patients with acute cardiac failure.

QTc prolongation

Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or who are taking drugs known to increase the QTc interval should be evaluated before and during the administration of alfuzosin.

Cerebral ischaemia
There is a risk of cerebral ischaemic disorders in patients with symptomatic or asymptomatic pre-existing cerebral circulatory disturbances, due to the fact that hypotension may develop following alfuzosin administration (see section 4.8).

Previous history of hypersensitivity to other alpha$_1$-receptor blockers
Treatment should be initiated gradually in patients with hypersensitivity to other alpha$_1$-receptor blockers.

Concomitant use with other potent CYP3A4 inhibitors
Concomitant use of alfuzosin and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone) should be avoided (see section 4.5). Alfuzosin should not be used concomitantly with CYP3A4 inhibitors that are known to increase the QTc interval (e.g. itraconazole and clarithromycin) and a temporary interruption of alfuzosin treatment is recommended if treatment with such medicinal products is initiated.

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$_1$-receptor 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-receptor-blockers should be made known to the ophthalmic surgeon in advance of surgery.

Priapism
Alfuzosin, like other alpha adrenergic antagonist, has been associated with priapism (persistent painful penile erection unrelated to sexual activity; see section 4.8). Because this condition can lead to permanent impotence if not properly treated, patients should be advised to seek immediate assistance in the event of an erection that persists longer than 4 hours.

Lactose
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

Administration of general anaesthetics to a patient treated with alfuzosin may lead to blood pressure instability. It is recommended that the tablets be withdrawn 24 hours before surgery.

No pharmacodynamic or pharmacokinetic interactions have been observed in studies with healthy volunteers between alfuzosin and the following active substances: warfarin, digoxin, hydrochlorothiazide and atenolol.

Combinations contra-indicated:

- Alpha$_1$-receptor blockers (see section 4.3).

Concomitant use not recommended:

- Potent CYP3A4 inhibitors such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone since alfuzosin blood levels are increased (see section 4.4).

Ketoconazole

Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in a 2.1-fold increase in C_{max} and a 2.5-fold increase in exposure of alfuzosin 10 mg prolonged-release tablets when administered under fed conditions. Other parameters such as t_{max} and $t_{1/2}$ were not modified.

The increase in alfuzosin C_{max} and $AUC_{(last)}$ following repeated 400 mg daily administration of ketoconazole was 2.3-fold and 3.2-fold respectively (see section 5.2).

Combinations to be taken into account:

- Antihypertensive drugs (see section 4.4).
- Nitrates (see section 4.4)

- Patients being treated with alfuzosin must be haemodynamically stable before treatment with a phosphodiesterase-5 inhibitor (sildenafil, tadalafil, vardenafil) is initiated.

See also section 4.4**.**

4.6 Fertility, pregnancy and lactation

Not relevant.

4.7 Effects on ability to drive and use machines

There are no data available on reduced reaction ability.
Adverse reactions such as vertigo, dizziness and asthenia may occur, essentially at the beginning of treatment. This has to be taken into consideration when driving vehicles and operating machines.

4.8 Undesirable effects

Classification of expected frequencies:
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 (cannot be estimated from the available data)

The most commonly reported event is dizziness, which occurs in approximately 5% of treated patients.

MedDRA system organ class	Common	Uncommon	Rare	Very rare	Not known:
Blood and lymphatic system disorders					Neutropenia, thrombocytopenia
Nervous system disorders	Faintness /dizziness, headache, tiredness	Vertigo, drowsiness, syncope*			Cerebral ischaemic disorders in patients with underlying cerebrovascular disturbances (see section 4.4)
Eye disorders		Visual disturbances			Intraoperative floppy iris syndrome (see section 4.4)
Cardiac				Angina pectoris predominantly in patients with	Atrial fibrillation

disorders		tachycardia, palpitations		pre-existing coronary artery disease; aggravation or recurrence of angina pectoris (see section 4.4)	
Vascular disorders		Flushing, postural hypotension*			
Respiratory, thoracic and mediastinal disorders		Rhinitis			
Gastrointestinal disorders	Abdominal pain, nausea, dyspepsia,	Vomiting diarrhoea, dry mouth			
Hepatobiliary disorders					Hepatocellular injury, cholestatic liver disease
Skin and subcutaneous tissue disorders		Rash (urticaria, exanthema), pruritus		Angioedema,	
Renal and urinary disorders		Urinary incontinence			
Reproductive system and breast disorders					Priapism
General disorders and administration site conditions	Asthenia, malaise	Chest pain, oedema, hot flushes, sweating			

*at start of treatment, with too high a dose or after short interruption of treatment

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

Symptoms
Hypotension, reflex tachycardia.

Management
In case of overdose, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension such as addition of fluids and vasopressor drugs should take place.

In case of significant hypotension, the appropriate corrective treatment may be a vasoconstrictor that acts directly on vascular muscle fibres.

Administration of medicinal charcoal should be considered. Alfuzosin is highly protein-bound, therefore, dialysis may not be of benefit

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy, alpha-adrenoreceptor antagonists, ATC code: G04CA01

Mechanism of action
Alfuzosin, which is a racemate, is an oral quinazoline derivative which selectively blocks post-synaptic alpha$_1$-receptors.

Pharmacodynamic effects
In vitro studies have confirmed the selectivity of alfuzosin for alpha$_1$-adrenoreceptors located in the prostate, the trigonum of the urinary bladder and the prostatic urethra.

Clinical efficacy and safety

Benign Prostatic Hypertrophy (BPH)
The clinical symptoms in BPH are not only related to the size of the prostate, but also to the sympathomimetic nerve impulse, which by stimulating the post-synaptic alpha receptors increase the tension of the smooth muscles of the lower urinary tract. Treatment with alfuzosin relaxes these smooth muscles, thus improving the urinary flow.

Clinical evidence of uroselectivity has been demonstrated by clinical efficacy and a good safety profile in men treated with alfuzosin, including the elderly and hypertensive men.

However, alfuzosin may cause moderate anti-hypertensive effects.

In man, alfuzosin improves voiding by reducing urethral muscle tone, and bladder outlet resistance, and facilitateses bladder emptying.

In placebo-controlled studies in BPH patients, alfuzosin:

- significantly increasedpeak flow rate (Q_{max}) in patients with Q_{max} <15 ml/s by a mean of 30%. This improvement was observed from the first dose,

- significantly reduced the detrusor pressure and increased the volume producing a strong desire to void,
- significantly reduced the residual urine volume.

The efficacy on peak flow rate is observed up to 24 hours after intake.

These urodynamic effects lead to an improvement of Lower Urinary Tract Symptoms (LUTS), i.e. filling (irritative) as well as voiding (obstructive) symptoms, which was clearly demonstrated.

Acute urinary retention (AUR) related to BPH
A lower frequency of acute urinary retention (AUR) was observed in alfuzosin treated patients than in untreated patients. Alfuzosin has been shown to increase the chances of successful spontaneous urination at first episode of acute urinary retention (AUR) related to BPH and in the following six months after this episode, reducing the requirement for surgery.

In a double-blind placebo-controlled study including 357 patients, alfuzosin 10 mg daily increased the success rate of spontaneous urination after catheter removal in men over 65 years.

88 patients (56.1%) in alfuzosin group had successful urination, while 30 patients (35.7%) in the placebo treatment had successful urination (p = 0.003).

165 patients who achieved successful urination during the first phase were included in the second phase and were re-examined: alfuzosin reduced the risk of surgery (both emergency surgery due to recurrence of AUR or as non-emergency) compared to placebo with a risk reduction of respectively 61%, 52%, and 29% at 1, 3 and 6 months of treatment with alfuzosin.

Paediatric population
Alfuzosin is not indicated for use in the paediatric population (see section 4.2).

Efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 patients 2 to 16 years of age with elevated detrusor leak point pressure (LPP≥40 cm H_2O) of neurologic origin. Patients were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day using adapted paediatric formulations.

5.2 Pharmacokinetic properties

Absorption
The maximal plasma concentration is achieved 9 hours after administration.

Studies have shown that consistent pharmacokinetic profiles are obtained when the product is administered after a meal.

After the first dose (fed) the mean maximum plasma concentration was 7.72 ng/ml, AUC_{inf} was 127 ng x h/ml (fed), and t_{max} was 6.69 h (fed). Under steady state conditions (fed) the mean AUC over the dosing interval (AUC_{τ}) was 194 (SD = 75) ng x h/ml, mean C_{max} was 13.6 (SD = 5.6) ng/ml and C_{min} was 3.1 (SD = 1.6) ng/ml.

Distribution
The binding rate to plasma protein is approx. 90%. Alfuzosin's distribution volume is 2.5 l/kg in healthy volunteers. It has been shown to preferentially distribute in the prostate in comparison to plasma.

Biotransformation
Alfuzosin is extensively metabolised in the liver (through various routes). None of the metabolites are pharmacologically active.

Metabolic interactions: CYP3A4 isoform is the principal hepatic enzyme involved in the metabolism of alfuzosin (see section 4.5).

Elimination
The apparent elimination half-life is approx. 9.1 hours.

Alfuzosin metabolites are eliminated via renal excretion and probably also via biliary excretion.

Of an oral dose, 75-91% is excreted in the faeces, 35% in unmodified form and the rest as metabolites, which indicates some degree of biliary excretion. About 10% of the dose is excreted in the urine in its unmodified form.

Linearity/non-linearity
Alfuzosin has linear pharmacokinetic properties within the therapeutic dose range.

Renal or hepatic impairment
Compared to subjects with normal renal function, mean C_{max} and AUC values are moderately increased in patients with renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant with creatinine clearance >30ml/min.

In patients with severe hepatic insufficiency the half-life is prolonged. The peak plasma concentration is doubled and the bioavailability increases in relation to that in young, healthy volunteers.

Elderly patients
C_{max} and AUC are not increased in elderly patients compared to healthy middle-aged volunteers.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose
Povidone K25
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister.

10, 20, 30, 30x1, 50, 60, 60 x 1, 90, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
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8 MARKETING AUTHORISATION NUMBER

PA0577/079/002

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