Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xatger 5mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg alfuzosin hydrochloride

Excipients:
Each tablets contains 52.3mg of lactose as lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

White, round, bevelled-edge, uncoated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of moderate to severe functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

The prolonged-release tablet should be swallowed whole with a sufficient amount of fluid.
The tablet can be taken with or without food.

Adults
1 prolonged-release tablet 5 mg twice daily (morning and evening), not exceeding 10 mg/day. The first dose should be taken at bedtime.

Elderly (over 65 years)
Pharmacokinetic and clinical safety data demonstrate that no dose reduction is necessary for elderly patients. A lower initial dose may, however, be considered for patients with increased risk of undesirable effects.

Reduced renal function
Mild to moderate renal insufficiency
1 prolonged-release tablet 5 mg daily. The first dose should be taken at bedtime. The dose may be adjusted according to clinical response.

Severe renal insufficiency
Xatger 5 mg should not be given to patients with severely impaired renal function (creatinine clearance < 30 ml/min) as there are no clinical safety data available for this patient group (see section 4.4).

Hepatic insufficiency
Xatger given as 5mg prolonged release tablets is contraindicated in patients with hepatic insufficiency. An immediate-release preparation containing a low dose alfuzosin hydrochloride may be used in patients with mild to moderate hepatic insufficiency. See the corresponding product information for dosing instructions.

4.3 Contraindications

- Hypersensitivity to Xatger, other quinazolines (e.g. terazosin, doxazosin) or to any of the excipients.
- Conditions with orthostatic hypotension.
- Hepatic insufficiency.
- Combination with other alpha$_1$-receptor blocking agents.

4.4 Special warnings and precautions for use

- Xatger 5 mg should not be administered to patients with severely impaired renal function (creatinine clearance < 30 ml/min) as there are no clinical safety data available for this patient group.
- Xatger should be given with caution to patients treated with antihypertensive medicinal products. Blood pressure should be monitored regularly, especially at the beginning of treatment.
- In some patients postural hypotension may develop, with or without symptoms (dizziness, asthenia, sweating) within a few hours of administration. In such cases, the patient should lie down until the symptoms have totally disappeared. These effects are usually temporary. They occur at the start of the treatment and normally do not prevent continuation of the treatment. Patients should be warned about the possibility of these effects.
- Caution should be exercised when Xatger is administered to patients who have responded with pronounced hypotension to other alpha$_1$-blockers.
- Treatment should be initiated gradually in patients with hypersensitivity to other α_1-receptor blockers.
- As with all α_1-receptor blockers, Xatger should be used with caution in patients with acute cardiac failure.
- In cardiac patients the treatment of coronary insufficiency should continue taking into account that the concomitant administration of nitrates and Xatger may increase the risk of occurrence of hypotension. Xatger should be discontinued if angina pectoris recurs or worsens.
- Patients should be instructed to swallow the tablets whole. Other methods of administration such as crushing, powdering or chewing the tablet, should be avoided. Incorrect administration may lead to undesirable release and absorption of the active substance, with a risk of early undesirable effects.
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
- 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.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations:
- Alpha$_1$-receptor blocking agents (see section 4.3).

Combinations requiring caution:
- Xatger blood levels are increased by potent CYP3A4 inhibitors like ketoconazole, itraconazole and ritonavir.
- Antihypertensive agents (see section 4.4).
- Nitrate preparations.

Concomitant use with antihypertensive agents or nitrates increases the risk of hypotension. See also section 4.4.

Administration of an anaesthetic to a patient being treated with Xatger may lead to profound hypotension. 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 Xatger and the following active substances: warfarin, digoxin and hydrochlorothiazide.

4.6 Fertility, pregnancy and lactation

Due to the type of indication this section is not applicable.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Adverse reactions such as vertigo, dizziness or asthenia may occur, especially at the beginning of treatment. This should be taken into account when driving or using machines.

4.8 Undesirable effects

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

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1000 to ≤1/100); rare (>1/10 000 to ≤1/1000); very rare (≤1/10 000).

Nervous system disorders:
Common: tiredness/dizziness, headache, vertigo
Uncommon: drowsiness

Eye disorders:
Uncommon: visual disturbances

Cardiac and vascular disorders:
Common: postural hypotension (initially, primarily with too high a dose or if treatment is resumed after a short interruption of therapy
Uncommon: tachycardia, syncope (in particular at the beginning of treatment), palpitations
Very rare: aggravation or recurrence of angina pectoris (see section 4.4)

Respiratory, thoracic and mediastinal disorders:
Uncommon: rhinitis

Gastrointestinal disorders:
Common: abdominal pain, nausea, dyspepsia, diarrhoea, dry mouth
Uncommon: vomiting

Hepato-biliary disorders:
Very rare: hepatotoxicity

Skin and subcutaneous tissue disorders:
Uncommon: rash (urticaria, exanthema), pruritus
Very rare: angioedema

Renal and urinary disorders:
Uncommon: urinary incontinence.
Very rare: isolated cases of priapism were reported

General disorders and administration site conditions:
Common: asthenia, malaise
Uncommon: oedema, flushes, chest pains

4.9 Overdose

In case of overdose, the patient should be admitted to hospital and given normal support therapy for hypotension. The appropriate antidote is a vasoconstrictor that acts directly on the smooth muscle in the blood vessels such as noradrenaline.

Gastric lavage and/or administration of medicinal charcoal should be considered. Xatger is difficult to dialyse, due to the high degree of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists
ATC code: G 04 CA 01

Xatger, which is a racemate, is an orally acting quinazolin derivative which selectively blocks post-synaptic alpha$_1$-receptors.

In vitro studies have confirmed the selectivity of Xatger for alpha$_1$-adrenoreceptors located in the prostate, the trigonum vesicae and the prostatic urethra.
The clinical symptoms in BPH are not only related to the size of the prostate, but also to sympathomimetic nerve impulses, which by stimulating the post-synaptic alpha receptors increase the tension of the smooth muscle of the lower urinary tract. Treatment with Xatger relaxes this smooth muscle, thus improving the urinary flow.

Clinical evidence of uroselectivity has been demonstrated by clinical efficacy and a good safety profile in men treated with Xatger, including the elderly and patients with hypertension. Xatger may cause moderate anti-hypertensive effects.
In humans, Xatger improves the voiding of water by reducing the urethral muscle tone, with reduction in the resistance to outflow from the bladder, making it easier to empty the bladder.
A lower frequency of acute urinary retention has been observed in patients treated with Xatger than in untreated patients.

In placebo-controlled studies of BPH patients Xatger has:
- significantly increased maximum urinary flow (Q_{max}) in patients with Q_{max} <15 ml/s by an average 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.

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

5.2 Pharmacokinetic properties

Xatger shows linear pharmacokinetic properties within the therapeutic dose range. The kinetic profile is characterised by large inter-individual fluctuations in plasma concentrations.

Absorption
Prolonged release formulation: mean maximum plasma concentrations are following single dose administration was 8.71 ng/ml, AUC_{inf} was 93.5 ng/ x h ml (fasted) and tmax was 5.46 h (fasted). The mean terminal half-life was found to be 5.23 hours. Under steady state conditions (fasted) mean Cmax was 17.0 ng/ml and Cmin was 7.90 ng/ml. The pharmacokinetic profile is not affected if Xatger is taken with food.

Distribution
Plasma protein binding is approx. 90%. Xatger'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.

Elimination
Mean plasma half-life of Xatger is approximately 5 hours. Xatger is extensively metabolised in the liver, (through various routes), metabolites are eliminated via renal excretion and probably also via biliary excretion.

Of an oral dose, 75-91% is excreted in the faeces; 35% as unchanged substance and the rest as metabolites, indicating some degree of biliary excretion.
About 10% of the dose is excreted in the urine in its unmodified form. None of the metabolites is pharmacologically active.

Renal or hepatic impairment
Volume of distribution and clearance increase with reduced renal function, possibly owing to a decreased degree of protein binding. The elimination half-life, however, is unchanged. 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 (E464)
Povidone K25
Magnesium stearate (E470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

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-aluminium blister.

20, 28, 30, 50, 56, 60, 60 x l, 90, 100, 180, 500 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

Mc Dermott Laboratories Limited
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8 MARKETING AUTHORISATION NUMBER

PA 577/79/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 5th September 2010

10 DATE OF REVISION OF THE TEXT

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