

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Xatral 10mg Prolonged Release Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg alfuzosin hydrochloride

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet, prolonged release.

*Product imported from France and Italy:*

Round biconvex three layer tablet; one white layer between two yellow layers.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Treatment of the functional symptoms of benign prostatic hypertrophy.

Adjunctive therapy with urethral catheterisation for Acute Urinary Retention related to BPH.

### 4.2 Posology and method of administration

Xatral 10mg Prolonged Release Tablets are for oral administration.

Xatral 10mg Prolonged Release Tablets should be swallowed whole.

BPH: The recommended dose is one 10mg tablet once daily to be taken after a meal.

AUR: One 10mg tablet daily after a meal to be taken from the first day of catheterisation.

Paediatric population:

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

### 4.3 Contraindications

Hypersensitivity to alfuzosin or any component. History of orthostatic hypotension. Combination with other  $\alpha$ -blockers. Hepatic insufficiency.

### 4.4 Special warnings and precautions for use

As with all  $\alpha_1$ -blockers in some subjects, in particular patients receiving antihypertensive medications or nitrates.

In some subjects postural hypotension may develop, with or without symptoms (dizziness, fatigue, sweating) within a few hours following administration. These effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. In such cases, the patient should lie down until the symptoms have completely disappeared. The patient should be warned of the possible occurrence of such events.

Care should be taken when alfuzosin is administered to patients who have had a pronounced hypotensive response to another alpha<sub>1</sub>-blocker. Blood pressure should be monitored regularly, especially at the beginning of treatment.

In patients with coronary insufficiency, specific therapy for coronary insufficiency should be continued. If angina pectoris reappears or worsens alfuzosin should be discontinued.

As with all alpha<sub>1</sub>-receptor blockers, alfuzosin should be used with caution in patients with acute cardiac failure.

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.

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.

Alfuzosin 10 mg prolonged release tablets contain hydrogenated castor oil which may cause stomach upset and diarrhoea.

As there are no clinical safety data available in patients with severe renal impairment (creatinine clearance < 30ml/min), alfuzosin 10 mg prolonged-release tablets should not be administered to this patient group.

Patients should be warned that the tablet should be swallowed whole. 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Combinations contra-indicated:

- Alpha1-receptor blockers (see section 4.3)

Combinations to be taken into account:

- Antihypertensive drugs (see section 4.4 Special Warnings and Precautions for Use).
- Nitrates(see section 4.4 Special Warnings and Precautions for Use)
- Potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and ritonavir since alfuzosin blood levels are increased (see section 5.2)

Concomitant use with other alpha1 -receptor blockers should be avoided and antihypertensive agents should be used with caution because of the risk of a hypotensive effect.

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

#### **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**

There are no data available on the effect on driving vehicles. Adverse reactions such as vertigo, dizziness and asthenia may occur. Some subjects particularly those on antihypertensive medication may experience postural hypotension, which may or may not result in symptoms such as dizziness and fatigue. This has to be taken into account when driving vehicles and operating machinery.

## 4.8 Undesirable effects

Classification of expected frequencies:

Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $<1/10$ ), uncommon ( $\geq 1/1000$  to  $<1/100$ ), rare ( $\geq 1/10000$  to  $<1/1000$ ), very rare ( $<1/10000$ ), not known (cannot be estimated from the available data)

	<b>Very Common (<math>\geq 1/10</math>)</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt;1/10</math>)</b>	<b>Uncommon (<math>\geq 1/1000</math> to <math>&lt;1/100</math>)</b>	<b>Rare (<math>\geq 1/10000</math> to <math>&lt;1/1000</math>)</b>	<b>Very rare (<math>&lt;1/10000</math>)</b>	<b>Not known (cannot be estimated from the available data)</b>
<b>Cardiac disorders</b>			Tachyardia		Angina pectoris in patients with pre-existing coronary artery disease	Atrial fibrillation
<b>Eye disorders</b>						Intraoperative floppy iris syndrome
<b>General disorders and administration site conditions</b>		Asthenia	Oedema, chest pain			
<b>Gastrointestinal disorders</b>		Nausea, abdominal pain,	Diarrhoea			Vomiting
<b>Hepatobiliary disorders</b>						hepatocellular injury, cholestatic liver disease
<b>Nervous system disorders</b>		Faintness/dizziness, headache	Syncope, vertigo			
<b>Reproductive system and breast disorders</b>						Priapism
<b>Respiratory, thoracic and mediastinal disorders</b>			Rhinitis			
<b>Skin and subcutaneous tissue disorders</b>			Rash, pruritus		Urticaria, angiodema	
<b>Vascular disorders</b>			Flushing, Hypotension (postural)			

<b>Blood and lymphatic system disorders</b>					Neutropenia	
---	--	--	--	--	-------------	--

## 4.9 Overdose

In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.

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

Alfuzosin is highly protein-bound; therefore, dialysis may not be of benefit.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Alfuzosin is an orally active quinazoline derivative. It is a selective, peripherally acting antagonist of postsynaptic alpha<sub>1</sub>-adrenoceptors.

*In vitro* pharmacological studies have documented the selectivity of alfuzosin for the alpha1-adrenoreceptors located in the prostate, bladder base and prostatic urethra.

Clinical manifestations of Benign Prostatic Hypertrophy are associated with infra vesical obstruction which is triggered by both anatomical (static) and functional (dynamic) factors. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by alpha1-adrenoceptors. Activation of alpha1-adrenoceptors stimulates smooth muscle contraction, thereby increasing the tone of the prostate, prostatic capsule, prostatic urethra and bladder base, and, consequently, increasing the resistance to bladder outflow. This in turn leads to outflow obstruction and possible secondary bladder instability.

Alpha-blockade decreases infra vesical obstruction via a direct action on prostatic smooth muscle.

*In vivo*, animal studies have shown that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin inhibits the hypertonic response of the urethra more readily than that of vascular muscle and shows functional uroselectivity in conscious normotensive rats by decreasing urethral pressure at doses that do not affect blood pressure.

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

In placebo controlled studies in BPH patients, alfuzosin:

- significantly increases peak flow rate (Q<sub>max</sub>) in patients with Q<sub>max</sub> ≤ 15ml/s by a mean of 30%. This improvement is observed from the first dose,
- significantly reduces the detrusor pressure and increases the volume producing a strong desire to void,
- significantly reduces the residual urine volume.

In addition, the efficacy on peak flow rate is maintained up to 24 hours after intake.

These favourable urodynamic effects lead to an improvement of lower urinary tract symptoms i.e. filling (irritative) as well as voiding (obstructive) symptoms.

Alfuzosin may cause moderate antihypertensive effects.

A lower frequency of acute urinary retention is observed in the alfuzosin treated patient than in the untreated patient. In addition, alfuzosin significantly increases the success rate of spontaneous voiding after catheter removal in men with an episode of AUR related to BPH.

#### 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 ( $LPP \geq 40$  cm H<sub>2</sub>O) 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

#### Prolonged-release formulation:

The mean value of the relative bioavailability is 104.4 % versus the immediate release formulation (2.5 mg tid) in middle-aged healthy volunteers and the maximum plasma concentration is being achieved 9 hours after administration compared to 1 hour for the immediate release formulation.

The apparent elimination half-life is 9.1 hours.

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

Under fed conditions, mean C<sub>max</sub> and C<sub>trough</sub> values are 13.6 (SD=5.6) and 3.2 (SD=1.6) ng/ml respectively. Mean AUC<sub>0-24</sub> is 194 (SD=75) ng.h/ml. A plateau of concentrations is observed from 3 to 14 hours with concentrations above 8.1ng/ml (C<sub>av</sub>) for 11 hours.

Compared to healthy middle aged volunteers, the pharmacokinetic parameters (C<sub>max</sub> and AUC) are not increased in elderly patients.

Compared to subjects with normal renal function, mean C<sub>max</sub> 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. Therefore, this does not necessitate a dosing adjustment.

The binding of alfuzosin to plasma proteins is about 90%. Alfuzosin undergoes extensive metabolism by the liver, with only 11 % of the parent compound being excreted unchanged in the urine. The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91 %).

The pharmacokinetic profile of alfuzosin is not affected by chronic cardiac insufficiency.

Metabolic interactions: CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin. Ketoconazole is a strong-potency inhibitor of CYP3A4. Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in an increased of the C<sub>max</sub> (2.11-fold) and AUC<sub>last</sub> (2.46-fold) of alfuzosin 10 mg OD under fed conditions. Other parameters such as t<sub>max</sub> and t<sub>1/2Z</sub> were not modified.

The 8-day repeated administration of ketoconazole 400 mg daily increased C<sub>max</sub> of alfuzosin by 2.3-fold, AUC<sub>last</sub> and AUC by 3.2 and 3.0, respectively (see section 4.5)

## 5.3 Preclinical safety data

No data of therapeutic relevance.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Ethylcellulose  
Hydrogenated Castor Oil  
Hypromellose  
Yellow Ferric Oxide (E172)  
Magnesium Stearate  
Microcrystalline Cellulose  
Povidone  
Silica, Colloidal Hydrated  
Mannitol (E421)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

The shelf-life expiry date of this product is the date shown on the blister strips and outer carton of the product on the market in the country of origin.

### **6.4 Special precautions for storage**

Do not store above 25°C.  
Store in the original package.

### **6.5 Nature and contents of container**

Boxes of 30 tablets in blister strips. Each pack contains 3 blister strips of 10 tablets in a cardboard outer carton.

### **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.

## **7 PARALLEL PRODUCT AUTHORISATION HOLDER**

Chemilines Healthcare (Ireland) Limited  
The Blackchurch  
St Mary's Place  
Dublin 7

## **8 PARALLEL PRODUCT AUTHORISATION NUMBER**

PPA 1915/8/1

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of First Authorisation: 26<sup>th</sup> September 2008

**10 DATE OF REVISION OF THE TEXT**

August 2013