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.
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$_1$-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.
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 elderly patients (see section 4.8). Caution should be exercised when prescribing Xatral to elderly patients. 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 alpha1-blocker. Blood pressure should be monitored regularly, especially at the beginning of treatment.

Care should be taken when Xatral is administered to patients with symptomatic orthostatic hypotension or in patients on anti-hypertensive medication or nitrates.

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 alpha1-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.

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.

Alfuzosin, like other alpha adrenergic antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients should be advised about the seriousness of the condition (See Section 4.8 Undesirable Effects).

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:

- 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 may be increased (see section 4.4)

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)

Concomitant use with other alpha$_1$-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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data)

	Very common (≥1/10)	Common (≥1/100 to <1/10	Uncommon (≥1/1000 to <1/100)	Rare (≥1/100 00 to <1/1000	Very rare (<1/10000)	Not known (cannot be estimated from the available data)
Cardiac disorders			Tachycardia		Angina pectoris in patients with pre-existing coronary artery disease	Atrial fibrillation

Eye disorders						Intraoperative floppy iris syndrome
General disorders and administration site conditions		Asthenia	Oedema, chest pain			
Gastrointestinal disorders		Nausea, abdominal pain,	Diarrhoea			Vomiting
Hepatobiliary disorders						hepatocellular injury, cholestatic liver disease
Nervous system disorders		Faintness/dizziness, headache	Syncope, vertigo			
Reproductive system and breast disorders						Priapism
Respiratory, thoracic and mediastinal disorders			Rhinitis			
Skin and subcutaneous tissue disorders			Rash, pruritus		Urticaria, angiodema	
Vascular disorders			Flushing, Hypotension (postural) (see section 4.4)			
Blood and lymphatic system disorders						Neutropenia ,thrombocytopenia

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

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$_1$-adrenoceptors.

In vitro pharmacological studies have documented the selectivity of alfuzosin for the alpha$_1$-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 alpha$_1$-adrenoceptors. Activation of alpha$_1$-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 (Qmax) in patients with Qmax ≤ 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≥40 cm H2O) 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 Cmax and Ctrough values are 13.6 (SD=5.6) and 3.2 (SD=1.6) ng/ml respectively. Mean AUC_{0-24} is 194 (SD=75) ng.h/ml. A plateau of concentrations is observed from 3 to 14 hours with concentrations above 8.1ng/ml (Cav) for 11 hours.

Compared to healthy middle aged volunteers, the pharmacokinetic parameters (Cmax and AUC) are not increased in elderly patients.

Compared to subjects with normal renal function, mean Cmax 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 increase of the Cmax (2.11-fold) and AUClast (2.46-fold) of alfuzosin 10 mg OD under fed conditions. Other parameters such as tmax and t1/2Z were not modified. The 8-day repeated administration of ketoconazole 400 mg daily increased Cmax of alfuzosin by 2.3-fold, AUClast 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
Magnesium stearate
Microcrystalline cellulose
Povidone
Silica colloidal hydrated
Mannitol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf-life
Blister strips: 3 years
Polyethylene containers: 2 years

6.4 Special precautions for storage
Do not store above 25ºC.
Store in the original package.

6.5 Nature and contents of container
Boxes with 10 or 30 tablets in PVC/foil blister strips or polyethylene containers.

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. MARKETING AUTHORISATION HOLDER
sanofi-aventis Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER
PA 540/162/3

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st July 2009

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February 2020