

1. NAME OF THE MEDICINAL PRODUCT

Xatral 2.5mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5mg alfuzosin hydrochloride.

Excipients: Also contains 61mg Lactose Monohydrate.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Film-coated Tablet.

White round, film coated tablet engraved on one side with 'Xatral 2.5'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the functional symptoms of benign prostatic hypertrophy.

4.2 Posology and method of administration

Xatral 2.5mg Film-coated tablets are for oral administration

Xatral 2.5mg Film-coated tablets should be swallowed whole. The first dose should be given just before bedtime.

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.

Adults

The usual dose is one tablet three times daily. The dose may be increased to a maximum of 4 tablets (10mg) per day depending on the clinical response.

Elderly (over 65 years) and treated hypertensive patients

As a routine precaution when prescribing alfuzosin to elderly patients (aged over 65 years) and treated hypertensive patients, the initial dose should be 1 tablet in the morning and 1 tablet in the evening.

Renal insufficiency

In patients with renal insufficiency, as a precaution, it is recommended that the dosing be started at Xatral 2.5mg twice daily adjusted according to clinical response.

Hepatic insufficiency

In patients with mild to moderate hepatic insufficiency, it is recommended that therapy should commence with a single dose of Xatral 2.5mg per day to be increased to Xatral 2.5mg twice daily according to clinical response.

4.3 Contraindications

- Hypersensitivity to the alfuzosin or any component.
- History of orthostatic hypotension.
- Combination with other α_1 - blockers.
- Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Alfuzosin should be given with caution to patients who are on antihypertensive medication or nitrates.

In some patients postural hypotension may develop, with or without symptoms (dizziness, fatigue, sweating) within a few hours following administration. These effects are transient, occur in 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 α_1 -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. .

There is a risk of cerebral ischemic disorders in patients with symptomatic or asymptomatic pre-existing cerebral circulatory disturbances, due to the fact that hypotension may develop following alfuzosin administration.

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 α_1 -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.

Alfuzosin, like other α 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).

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.

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 some α_1 -blockers. Although the risk of this event with alfuzosin appears very low, ophthalmic surgeons should be informed in advance of cataract surgery of current or past use of α_1 -blockers, as IFIS may lead to increased procedural complications.

Alfuzosin 2.5mg film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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:

- α_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 α_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 Xatral 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 essentially at the beginning of the treatment. 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)

| | 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) |
|--|--------------------------------|--|---|---|---|--|
| Cardiac disorders | | | Tachycardia palpitations | | Angina pectoris in patients with pre- existing coronary artery disease | Atrial fibrillation |
| Eye disorders | | | Vision abnormal | | | Intraoperativ e floppy iris syndrome |
| General disorders and administratio n site conditions | | Asthenia, malaise | Oedema, chest pain | | | |
| Gastrointesti nal disorders | | Nausea, abdominal pain, diarrhoea, dry mouth | | | | Vomiting |
| Hepatobiliary disorders | | | | | | hepatocellul ar injury, cholestatic liver disease |
| Nervous system disorders | | Faintness/diz ziness, headache, | Syncope, drowsiness | | | Cerebral ischemic disorders in |

| | | | | | | |
|---|--|--|----------------|--|----------------------|---|
| | | vertigo | | | | patients with underlying cerebrovascular disturbances |
| Reproductive system and breast disorders | | | | | | Priapism |
| Respiratory, thoracic and mediastinal disorders | | | Rhinitis | | | |
| Skin and subcutaneous tissue disorders | | | Rash, pruritus | | Urticaria, angiodema | |
| Vascular disorders | | Hypotension (postural) (see section 4.4) | Flushing | | | |
| 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 Overdosage

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 α_1 -adrenoceptors.

In vitro pharmacological studies have documented the selectivity of alfuzosin for the α_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 α_1 -adrenoceptors. Activation of α_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 (Q_{max}) in patients with $Q_{max} \leq 15\text{ml/s}$ 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.

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.

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 ($LPP \geq 40\text{ cm H}_2\text{O}$) 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

Xatral is well absorbed with a mean bioavailability of 64%, peak plasma levels are generally reached in 0.5-3 hours. Kinetics within the therapeutic range are linear. The kinetic profile is characterised by large interindividual fluctuations in plasma concentrations. The terminal half-life is 3-5 hours. Alfuzosin is 90% protein bound in plasma, 68.2% to human serum albumin and 52.5% to human serum alpha-glycoprotein. It is partially metabolised and excreted mainly in the bile and faeces.

None of the metabolites found in man has any pharmacodynamic activity. The pharmacokinetic profile is not affected by taking Xatral with food.

In subjects over 75 years, absorption is more rapid and peak plasma levels are higher. Bioavailability may be increased and in some patients the volume of distribution is reduced. The elimination half-life does not change.

The volume of distribution and clearance of alfuzosin are increased in renal insufficiency, with or without dialysis, owing to an increase in the free fraction. Chronic renal insufficiency even when severe (creatinine clearance between 15 and 40 mls/min) is not adversely affected by alfuzosin.

In patients with severe hepatic insufficiency, the elimination half-life is prolonged. A two-fold increase in C_{max} values and a three-fold increase in the AUC is observed. Bioavailability is increased compared with healthy volunteers.

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 C_{max} (2.11-fold) and AUC_{last} (2.46-fold) of alfuzosin 10 mg OD under fed conditions. Other parameters such as t_{max} and t_{1/2Z} were not modified. The 8-day repeated administration of ketoconazole 400 mg daily increased C_{max} of alfuzosin by 2.3-fold, AUC_{last} 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

Tablet core

Microcrystalline cellulose
Lactose monohydrate
Povidone
Sodium starch glycollate
Magnesium stearate.

Coating

Hypromellose

Macrogol 400

Titanium dioxide suspension (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

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 with 30, 60 or 90 tablets in PVC/foil blister strips.

Not all packs may be marketed.

**6.6 Special precaution s for disposal of a used medicinal product or waste materials
derived from such medicinal product and other handling of that product**

No special requirements.

7. MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Limited. T/A SANOFI

Citywest Business Campus,

Dublin 24,

Ireland.

8. MARKETING AUTHORISATION NUMBER

PA 540/162/1

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AUTHORISATION**

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Date of last renewal: 1st July 2009

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February 2020