Xatral XL 10mg
alfuzosin

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged release tablet contains Alfuzosin hydrochloride 10mg

PHARMACEUTICAL FORM

Round, biconvex 3-layer tablets: one white layer between two yellow layers

CLINICAL PARTICULARS

Therapeutic indications

- Treatment of the functional symptoms of benign prostatic hypertrophy
- Adjuvant treatment to a catheter in acute urinary retention related to benign prostatic hypertrophy

POSOLOGY AND METHOD OF ADMINISTRATION

Oral use

The tablet must be swallowed whole with a glass of water (see Special warnings and precautions for use). The recommended dosage is one 10mg tablet per day, to be taken immediately after the evening meal

Adjuvant treatment to a catheter in acute urinary retention related to benign prostatic hypertrophy:

The recommended dosage is one 10mg tablet per day, to be taken after a meal, from the first day of catheterization onwards. The treatment is administered for 3 to 4 days, i.e. 2 to 3 days while the catheter is in place and one day after it is removed

CONTRAINDICATIONS

This medicinal product must not be administered in the following situations:

- hypersensitivity to alfuzosin and/or any of the other ingredients
- postural hypotension
- liver failure
- severe kidney failure (creatinine clearance < 30 ml/min)
- in combination with potent CYP3A4 inhibitors (See Section Interactions)
- in combination with ombitasvir and paritaprevir (See Section Interactions)

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Special warnings

This medicinal product must be used with caution in patients treated with antihypertensives or nitrate derivatives. Use of this medicinal product is not recommended with antihypertensive alpha-blockers.

Some patients may experience postural hypotension within a few hours following administration, possibly with symptoms (dizzy spells, fatigue, sweating). If this occurs, patients should remain lying down until the symptoms have completely subsided.

These effects are usually transient, occur at the beginning of treatment and do not generally prevent continued treatment.

A marked drop in blood pressure has been reported in post-marketing surveillance in patients with preexisting risk factors (such as underlying cardiac disease and/or concomitant treatment with anti-hypertensive medication).

There is a risk of stroke, particularly in elderly patients with pre-existing asymptomatic or symptomatic disorders of cerebral circulation (such as cardiac arrhythmia, atrial fibrillation or a history of transient ischemic attack) due to the onset of hypotension following administration of alfuzosin.

Patients should be warned of the possible occurrence of these events.

Caution is recommended, particularly in the elderly.

As with alpha-1 blockers, this medicine should be used with caution in patients with acute heart failure.
Rarely, alfuzosin, like other alpha-1 blockers, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Rapid patient management (sometimes involving surgery) is essential. Priapism may lead to permanent impotence if not properly treated.

Patient with congenital prolonged QTc interval, or a history of prolonged QTc interval or who are being treated with medicines that increase the QTc interval should be monitored before and during treatment.

Intraoperative Floppy Iris Syndrome (IFIS, a small pupil syndrome variant) has been observed during cataract surgery in some patients previously or currently treated with tamsulosin. Isolated cases have also been reported with other alpha-1 blockers, therefore a possible class effect cannot be ruled out. Considering that IFIS can be the cause of additional technical difficulties during cataract operations, the surgeon must be informed of any history or current use of alpha-1 blockers before the eye surgery. Given the lack of data on safety in patients with severe kidney failure (creatinine clearance < 30ml/min), Xatral XL 10mg, prolonged-realease tablets should not be administered to this patients. This medicinal product contains castor oil, which can cause gastrointestinal disorders (mild laxative effect, diarrhea)

Precautions for use

Care should be taken when alfuzosin is administered to patients who have experienced severe hypotension following administration of another alpha-1 blocker. In patients with coronary disease, alfuzosin should not be prescribed alone. The specific coronary insufficiency treatment should be continued. If angina pectoris recurs or worsens, alfuzosin treatment should be discontinued. Use with PDE5 inhibitors: concomitant administration of Xatral LP 10 mg with a phosphodiesterase type 5 inhibitor (e.g. sildenafil, tadalafil or vardenafil) can cause symptomatic hypotension in certain patients (see Section 4.5). To reduce the risk of postural hypotension, patients must be stabilized under alpha-blocker treatment before initiating treatment with a phosphodiesterase type 5 inhibitor. In addition, treatment with the phosphodiesterase type 5 inhibitor should be started at the lowest possible dose.

Patients must be informed that the tablets must be swallowed whole and not crushed, ground into a powder or chewed. An incorrect method of administration could lead to inappropriate release and absorption of the medicinal product, causing undesirable effects with an early onset.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Contraindicated combinations

+ Potent CYP3A4 inhibitors (boceprevir, clarithromycin, cobicistat, erythromycin, itraconazole, ketoconazole, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, voriconazole)

There is a risk of increased plasma alfuzosin concentrations and increased undesirable effects

+ **Ombitasvir + paritaprevir**

The combined therapy causes an increase in plasma alfuzosin concentrations due to decreased alfuzosin liver metabolism.

Inadvisable combinations

+ Anti-hypertensive alpha-receptor blockers:

Enhanced hypotensive effect. Risk of severe postural hypotension

+ Ketoconazole, itraconazole:

Enhanced hypotensive effect. Risk of severe postural hypotension

+ Clarithromycin, erythromycin

Risk of increased plasma alfuzosin concentrations and increased undesirable effects

+ Vardenafil:

Risk of postural hypotension, particularly in elderly subject

Combination requiring precautions for use

+ Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil)

Risk of postural hypotension, particularly in elderly subjects. Treatment should be initiated at the lowest recommended dose and adjusted gradually if necessary. Administration of general anesthetics in patients treated with alfusozin may contribute to blood pressure instability.

Combinations to be taken into consideration

+ Antihypertensives except alpha-receptor blockers

Enhanced hypotensive effect. Higher risk of postural hypotension.

+ Nitrates, nitrites and related drugs (isosorbide dinitrate, isosorbide, linsidomine, molsidomine, nicorandil, nitroglycerin)

Increased risk of hypotension, particularly postural.

PREGNANCY AND LACTATION

The therapeutic indication does not apply to women. The safety of alfuzosin during pregnancy and its passage into breast milk are not known.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no available data on the effect of alfusozin on the ability to drive vehicles. Special caution must be exercised by patients who drive and use machines due to the risk of postural hypotension, dizziness, asthenia and visual disturbances, particularly at the beginning of treatment

UNDESIRABLE EFFECTS

Undesirable effects are classified by incidence based on the following convention: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, <1/100); rare (≥1/10 000, <1/1 000); very rare

(<1/10000); incidence unknown (cannot be estimated based on available data).

	INCIDENCE			
SYSTEM ORGAN	Common (≥1%-< 10%)	Uncommon (≥0.1%-< 10%)	Very rare (0.1%)	Unknown
Cardiac disorder		Tachycardia, palpitations	Angina pectoris in patients with a history of coronary artery disease	Atrial fibrillation
Eye disorders				Intraoperative floppy iris syndrome
General disorder and administration site conditions	Asthenia, malaise	Edema, chest pain		
Gastrointestinal disorders	Nausea, abdominal pain	Diarrhea, dry mouth, vomiting		
Hepatobilliary disorder				Hepatocellular injury, hepatic cholestasis
Nervous system disorder	Dizzy spells, lightheadedness, headache	Syncope, dizziness, drowsiness		Stroke in patients with underlying cerebrovascular disorders
Reproductive system and breast disorder				Priapism
Respiratory, thoracic and mediastinal disorders		Nasal congestion		
Skin and subcutaneous tissue disorders		Skin rash, pruritus	Urticarial, angioedema	
Vascular disorders		Postural hypotension, flushing		
Blood and lymphatic system disorders				Neutropenia, thrombocytopenia

OVERDOSE

If overdose occurs, the patient should be hospitalized and kept in the supine position. Conventional treatment of hypotension should be instituted. If severe hypotension occurs, a vasoconstrictor agent that acts directly on the vascular muscle fibers can be used. Alfuzosin is highly protein-bound and is therefore not

easily dialyzable.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ALPHA-BLOCKER. ATC code: G04CA01
(G: genitourinary system and sex hormones)

Alfuzosin is an orally active quinazoline derivative. It is a selective antagonist of post-synaptic alpha-1 adrenoreceptors. Pharmacological studies conducted in vitro have confirmed the selectivity of alfuzosin for alpha -1 adrenoreceptors located in the prostate, bladder trigone and urethra.

Alpha-blockers decrease infravesical obstruction via direct action on prostatic smooth muscle. In vivo studies in animals have shown that alfuzosin reduces urethral pressure thereby lowering resistance to urine flow during micturition. A study in conscious rats showed a greater effect on urethral pressure than the effect on blood pressure.

Placebo-controlled studies in patients with benign prostatic hypertrophy showed that alfuzosin:

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

These effects lead to an improvement in irritative and obstructive urinary symptoms, with no negative effect on sexual function.

Furthermore, maximum urinary flow rate remains significantly increased 24 hours after dosing. In the ALFAUR study, the effect of alfuzosin on the return of normal voiding was evaluated in 357 men over the age of 50 with a first painful episode of acute urinary retention (AUR) associated with benign prostatic hypertrophy (BPH), and a residual urine volume of between 500 and 1500 ml during catheter insertion and for the first hour following catheterization. In this double-blind, randomized, multicenter study in two parallel groups comparing 10mg/day alfuzosin prolonged-release with placebo, evaluation of the return to normal voiding was conducted 24 hours after catheter removal, in the morning, after at least two days of alfuzosin treatment.

Treatment with alfuzosin significantly increased ($p = 0.012$) the rate of successful voiding post-catheter removal in patients with a first episode of AUR, i.e. 146 patients with successful voiding (61.9%) in the alfuzosin group versus 58 (47.9%) in the placebo group.

Pharmacokinetic properties

Alfuzosin:

Alfuzosin hydrochloride is approximately 90% plasma protein bound. Alfuzosin is extensively metabolized in the liver with only 11% of the parent drug excreted in urine. Most of the metabolites (which are inactive) are excreted in faeces (75 to 90%). The pharmacokinetic profile of alfuzosin is unchanged in patients with chronic heart failure.

Prolonged release formulation

The mean value of the relative bioavailability is 104.4% after administration of the 10mg dose, in comparison with that of the immediate-release formulation at a dosage of 7.5mg (2.5mg three times daily), in middle-aged healthy volunteers. The peak plasma concentration is reached 9 hours after administration as compared to 1

hour for the immediate-release formulation.

The apparent elimination half-life is 9.1 hours.

Studies have shown that the bioavailability is increased when the drug is administered after a meal (see Posology and method of administration).

The pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly when compared to middle-aged healthy volunteers. The mean C_{max} and AUC values are moderately increased in patients with moderately impaired kidney function (creatinine clearance > 30 ml/min), with no change in elimination half-life, compared with patients with normal kidney function. Dosage adjustment is, therefore, not necessary in patients with impaired kidney function with a creatinine clearance of > 30 ml/min.

PHARMACEUTICAL PARTICULARS

List of excipients

Hypromellose, hydrogenated castor oil, ethylcellulose, yellow iron oxide, colloidal hydrated silica, magnesium stearate, mannitol, povidone, microcrystalline cellulose.

Shelf-life: 3 years

Special precautions for storage:

Store below 30ºC.

Nature and content of container:

Thermoformed blister packs (PVC/aluminium)

Presentation: 30 tablets

Manufacturer

Sanofi Winthrop Industrie,30-36,
Avenue Gustave Eiffel,
37100 Tours, France.

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