Xatral®

Alfuzosin
10mg Prolonged-Release Tablet

[sanofi logo]

COMPOSITION:
Alfuzosin hydrochloride ..... 10 mg

PHARMACEUTICAL FORM
Prolonged-release tablet.

CLINICAL PARTICULARS
Therapeutic indications
Treatment of the functional symptoms of benign prostatic hypertrophy (BPH). Adjuvant treatment to a catheter in first episode of acute urinary retention (AUR) related to benign prostatic hypertrophy (BPH).

Posology and method of administration
Benign Prostatic Hypertrophy (BPH):
The recommended dosage is one 10-mg tablet per day, to be taken immediately after the evening meal.
Adjuvant treatment to a catheter in the first episode of acute urinary retention related to benign prostatic hypertrophy:
The recommended dosage is one 10-mg 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 1 day after it is removed.
The tablet must be swallowed whole with a glass of water (see Special warnings and special precautions for use).

Contraindications
This medicine 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 ritonavir
- Concomitant administration with potent CYP3A4 inhibitors

Special warnings and special precautions for use
Warnings
As with all alpha-1 blockers, some patients, and in particular those treated with antihypertensives may experience postural hypotension within a few hours following administration, possibly with symptoms (dizzy sensations, fatigue, sweating).

If this occurs, patient 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. 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). Patients should be warned of the possible occurrence of these events.
The risk of developing hypotension and related adverse reactions may be greater in elderly patients.

Treatment should be initiated gradually in patients with hypersensitivity to alpha-1 blockers. Xatral XL 10mg tablets should be administered carefully to patients being treated with antihypertensives. Blood pressure should be monitored regularly, especially at the beginning of the treatment.

Caution is recommended, particularly in the elderly.

Use with caution in patients with acquired or congenital QT prolongation or who are taking medications that prolong the QT interval.

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.

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 surgeons must be informed of any history of current use of alpha-1 blockers before the eye surgery.

This medicinal product contains castor oil, which can cause gastrointestinal disorders (mild laxative effect, diarrhea).

Special precautions for use
Care should be taken when alfuzosin is administered to patients who have experienced marked 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.

Patients must be informed that the tablets must be swallowed whole. The tablets must not be crunched, chewed, crushed or ground into a powder.
Doing so could lead to inappropriate release and absorption of the medicinal product consequently causing unwanted effects which may be of early onset.

Interactions with other medicinal products and other forms of interaction
Contraindicated combination
+ Potent CYP3A4 inhibitors such as ketoconazole, itraconazole and Ritonavir:
Risk of increased plasma alfuzosin concentrations and increased undesirable effects.

+ Clarithromycin, erythromycin
Risk of increased plasma alfuzosin concentrations and increased undesirable effects.

Combination requiring precautions for use

+ Phosphodiesterase type 5 inhibitors (sildenafil, tadalafil, vardenafil)

Risk of postural hypotension, particularly in elderly subjects.
Treatment should be initiated at the lowest recommended dose and adjusted gradually if necessary.

Combination 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 unknown.

Effects on Ability to Drive and Use Machines

Particular caution is required when driving vehicles or using machines due to the risks of postural hypotension, dizzy sensations, asthenia, visual disturbances, especially at the start of treatment with alfuzosin.

Overdose

In the event of overdose, the patient should be hospitalized and kept lying down. Standard treatment for hypotension should be instigated. Due to its high degree of protein binding, alfuzosin is not easily dialysable.

Undesirable effects

	FREQUENCY			
ORGAN SYSTEM	Common (≥1% - < 10%)	Uncommon (≥0.1% - <1%)	Very rare (<0.01%)	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders				thrombocytopenia
Nervous system disorders	lightheadedness, dizziness, faintness, headache	dizzy spells drowsiness, vertigo		cerebral ischemic disorders in patients with underlying cerebrovascular disturbances
Cardiac disorders		tachycardia, , postural hypotension, syncope	angina pectoris in patients with a history of coronary artery disease *(see special warnings and special precautions for use)*	atrial fibrillation
Eye disorder		Vision abnormal		Intraoperative floppy iris syndrome
Respiratory,thoracic and mediastinal		nasal congestion		

disorders				
Gastrointestinal disorders	nausea, abdominal pain, vomiting	diarrhea		
Skin and subcutaneous tissue disorders		skin rashes, pruritus	urticaria, angioedema	
Systemic disorders	asthenia	flushing, edema, chest pain *(see special warnings and special precautions for use)*		
Hepatobiliary disorders:				hepatocellular injury, cholestatic hepatitis
Reproductive system and breast disorders:			priapism	

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ALPHA-BLOCKERS
ATC code: G04CA01
(G: genitourinary system and sex hormones).
Alfuzosin is a quinazoline derivative, active by the oral route. It is a selective antagonist of post-synaptic alpha-1 adrenergic receptors. Pharmacological studies conducted in vitro have confirmed the selectivity of alfuzosin for alpha-1 adrenergic receptors located in the prostate, the trigone of the bladder and the urethra.
Due to a direct action on the smooth muscle of the prostatic tissue, alpha-blockers reduce lower urinary tract obstruction.
In vivo studies in animals have shown that alfuzosin reduces urethral pressure and hence resistance to urinary flow during voiding. A study in conscious rats reveals an effect on urethral pressure greater than that on blood pressure.
In placebo-controlled studies in patients with benign prostatic hypertrophy, alfuzosin:

- significantly increased urinary flow rate by a mean of 30% in patients with a flow rate $\geq$ 15 ml/s. This improvement is observed from the first dose,
- significantly reduced the detrusor pressure and increased the volume, producing a strong need to void,
- significantly reduced the residual urine volume.

These effects lead to an improvement in irritative and obstructive urinary symptoms. They have no detrimental effect on sexual function.
In the ALFAUR study, the effect of alfuzosin on return to voiding was assessed in 357 men over the age of 50 presenting a first painful episode of acute urinary retention (AUR) related to benign prostatic hypertrophy (BPH) with a residual urine volume of between 500 and 1500 ml following insertion of a catheter and for the first hour after catheterisation. In this multicentre, randomised, doubleblind study in two parallel groups comparing 10 mg/day alfuzosin LP with placebo, evaluation of return to voiding was conducted 24 hours after removal of the catheter, in the morning, after at least two days of alfuzosin treatment.Treatment with alfuzosin significantly increased ($p = 0.012$) the rate of return to voiding after catheter removal in patients having suffered a first episode of AUR, i.e. 146 returns to voiding (61.9%) in the alfuzosin group versus 58 (47.9%) in the placebo group.

Pharmacokinetic properties

Alfuzosin

Plasma protein binding of alfuzosin hydrochloride is approximately 90%. Alfuzosin undergoes marked metabolisation by the liver with excretion in the urine of only 11% of unchanged substance.

Most of the metabolites (which are inactive) are excreted in the faeces (75 to 90%).

The pharmacokinetic profile of alfuzosin is not modified in the event of chronic heart failure.

Prolonged-release formulation

The mean value for relative bioavailability is 104.4% after administration of the 10-mg dose, in comparison with that for the immediate-release formulation at a dosage of 7.5 mg (2.5 mg t.i.d.), in middle-aged healthy volunteers. The peak plasma concentration is reached 9 hours after administration as compared to 1 hour for the immediate 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 (Cmax and AUC) are not increased in the elderly as compared to middle-aged healthy volunteers.

The mean Cmax and AUC values are moderately increased in patients with moderately impaired kidney function (creatinine clearance > 30 ml/min), without any modification in elimination half-life, as compared to patients with normal kidney function.

Dosage adjustment is not, therefore, necessary in patients with impaired kidney function with a creatinine clearance >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.

Incompatibilities : Not applicable.

Shelf life : 3 years.

Special precautions for storage :

No special precautions for storage.

Nature and contents of container

28 tablets in blisters (PVC/Aluminium)
30 tablets in blisters (PVC/Aluminium)
50 tablets in blisters (PVC/Aluminium)
100 tablets in blisters (PVC/Aluminium)
*Not all pack size is available in the local market

Instructions for use and handling and disposal :

No special requirements.

MANUFACTURER

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Reference:
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