XATRAL ®

Alfuzosin

5mg Sustained Release Film-coated Tablet

[sanofi logo]

COMPOSITION

Each tablet contains 5mg Alfuzosin hydrochloride.

PHARMACEUTICAL FORM

A sustained release, pale yellow, biconvex, scored film-coated tablet.

CLINICAL PARTICULARS

Therapeutic indications

Treatment of functional symptoms of benign prostatic hyperplasia.

Dosage and method of administration

Oral use.

The tablet must be swallowed whole with a glass of water

(see Special warnings and special precautions for use).

Adults

One XATRAL SR 5 mg tablet morning and evening.

In elderly patients or patients treated for hypertension: as a systematic precaution, it is recommended that treatment be started with one XATRAL SR 5 mg tablet in the evening and that the dosage then be increased on the basis of the patient's individual response, without exceeding the maximum dosage of one XATRAL SR 5 mg tablet morning and evening.

Patients with impaired liver function: it is recommended that treatment be started with one XATRAL 2.5 mg tablet per day and that the dosage then be increased on the basis of the patient's individual response, without exceeding one XATRAL 2.5 mg tablet twice daily.

Contraindications

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

- hypersensitivity to alfuzosin and/or any of the other ingredients;
- postural hypotension;
- severe liver failure (class C in the Child-Pugh classification);
- 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 medications). 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.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.

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.

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.

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.

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

<u>Special precautions for use</u>
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.

Inadvisable combinations

+ Anti-hypertensive alpha-receptor blockers (prazosin, trimazosin, urapidil):

Enhanced hypotensive effect. Risk of severe postural hypotension.

+ Ketoconazole, itraconazole: 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.

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 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.

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	dizziness,, Faintness, headache, vertigo	drowsiness		cerebral ischemic disorders in patients with underlying cerebrovascular disturbances, syncope
Vision disorders		abnormal vision		Intraoperative floppy iris syndome
Cardiac disorders	postural hypotension	tachycardia, palpitations,	Angina pectoris in patients with a history of coronary artery disease (*see special warnings and precautions for use*)	atrial fibrillation, flushing
Respiratory, thoracic and mediastinal disorders				rhinitis
Gastrointestinal disorders	nausea, abdominal pain, diarrhea, dry mouth, vomiting			
Skin and subcutaneous tissue disorders		skin rashes, pruritus	urticaria, angioedema	
Systemic disorders	Asthenia, malaise	flushing, edema, chest pain *(see Special warnings and special precautions for use)*		
Hepatobiliary disorders:				hepatocellular injury, cholestatic hepatitis
Reproductive system and breast disorders:			priapism	

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.

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 ≤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.

Pharmacokinetic properties
- The peak plasma concentration is reached approximately 3 hours after administration.
- The plasma elimination half-life is 8 hours.
- The bioavailability is reduced by an average of approximately 15% relative to that of the immediate release 2.5-mg formula.

- The pharmacokinetic profile is not modified by the concomitant intake of food.

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%).
- In subjects over the age of 75 years, the absorption of alfuzosin is more rapid and the maximum concentrations are higher. The bioavailability may be

increased and a reduction in the distribution volume is observed in some patients. Then elimination half-life remains unchanged.
- In subjects with severely impaired liver function, the elimination half-life is prolonged. The bioavailability is increased in comparison with healthy volunteers.
- In subjects with impaired kidney function, requiring dialysis or otherwise, the distribution volume and clearance of alfuzosin increase due to an elevation in the free fraction. Dosage adjustment is not necessary in subjects with impaired kidney function with creatinine clearance > 30 ml/min.

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

Preclinical safety data
Not applicable.

PHARMACEUTICAL PARTICULARS

Shelf life
3 years

Nature and contents of container
Box of 56's

MANUFACTURER
SANOFI WINTHROP INDUSTRIE
30-36, avenue Gustave Eiffel
37100 Tours, FRANCE

Reference:
CCDS v13, July 2018