SANOFI

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xatral LP 10 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Alfuzosin Hydrochloride ..... 10 mg
For one prolonged-release tablet.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of the functional symptoms of benign prostatic hypertrophy.
- Adjunctive treatment for vesical catheterization in acute urinary retention associated with benign prostatic hypertrophy.

4.2. Posology and method of administration

Oral use.

The tablet must be swallowed whole with a glass of water (see Section 4.4).

The recommended dosage is one 10 mg tablet daily, to be taken immediately after the evening meal.

Adjunctive treatment for vesical catheterization in acute urinary retention associated with benign prostatic hypertrophy:

The recommended dosage is one 10 mg tablet daily, to be taken after a meal, starting on the day of insertion of the urethral catheter.

The treatment is administered for 3 to 4 days including 2 to 3 days during catheterization and 1 day following catheter removal.

Pediatric patients:

Since the efficacy of alfuzosin has not been demonstrated in children aged between 2 and 16 years (see Section 5.1), it should not be used in pediatric patients.

4.3. 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 4.5);

4.4. 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 (see Section 4.5).

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 pre-existing risk factors (such as underlying cardiac disease and/or concomitant treatment with antihypertensive 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 (see Section 4.6).

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

Caution is recommended, particularly in the elderly. The risk of hypotension and related symptoms may be higher in elderly patients.

As with all alpha-1 blockers, this medicine should be used with caution in patients with acute heart failure.

Patients 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, even if the risk of IFIS occurring with alfuzosin is low.

Given the lack of data on safety in patients with severe kidney failure (creatinine clearance < 30 ml/min), Xatral LP 10 mg, prolonged-release tablets should not be administered to these 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 marked hypotension following administration of another alpha-1 blocker.

In patients with coronary disease, alfuzosin should not be prescribed alone. 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 should be informed that the tablets must be swallowed whole. They 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 undesirable effects which may be of early onset.

4.5. Interaction with other medicinal products and other forms of interaction

Contraindicated combinations

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

Risk of increased plasma alfuzosin concentrations and increased undesirable effects.

Inadvisable combinations

+ Anti-hypertensive alpha-blockers (doxazosin, prazosin, urapidil)

Enhanced hypotensive effect. Risk of severe postural hypotension.

Combinations requiring precautions for use

+ Phosphodiesterase type 5 inhibitors (avanafil, 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-blockers

Enhanced hypotensive effect. Higher risk of severe postural hypotension.

+ Dapoxetine

Risk of enhanced undesirable effects, particularly dizziness or syncope.

+ Blood pressure-lowering drugs

Increased risk of hypotension, particularly postural.

4.6. Pregnancy and lactation

The therapeutic indication does not apply to women.

It is not known whether alfuzosin is safe during pregnancy nor whether it is excreted in breast milk.

4.7. Effects on ability to drive and use machines

There are no available data on the effect of alfuzosin 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, dizzy spells, asthenia and visual disturbances, particularly at the beginning of treatment.

4.8. 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 (<1/10 000); incidence unknown (cannot be estimated based on available data).

	INCIDENCE			
SYSTEM ORGAN	**Common (≥ 1% - < 10%)**	**Uncommon (≥ 0.1% - < 1%)**	**Very rare (< 0.1%)**	**Unknown**
Cardiac disorders		tachycardia, palpitations	angina pectoris in patients with a history of coronary artery disorders	atrial fibrillation
Eye disorders				intraoperative floppy iris syndrome
General disorders and administration site conditions	asthenia, malaise	edema, chest pain		
Gastrointestinal disorders	nausea, abdominal pain	diarrhea, dry mouth		vomiting

Hepatobiliary disorders				hepatocellular injury, hepatic cholestasis
Nervous system disorders	dizzy spells, lightheadedness, headache	syncope, dizziness, drowsiness		stroke in patients with underlying cerebrovascular disorders
Reproductive system and breast disorders				priapism
Respiratory, thoracic and mediastinal disorders		nasal congestion		
Skin and subcutaneous tissue disorders		skin rash, pruritus	urticaria, angioedema	
Vascular disorders		postural hypotension (see Section 4.4), flushing		
Blood and lymphatic system disorders				neutropenia, thrombocytopenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 the national reporting system, i.e. the French Agency for Medicinal and Health Products Safety (ANSM) and the Regional Pharmacovigilance Centers network via website www.ansm.sante.fr.

4.9. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ALPHA-BLOCKER, ATC Code: G04CA01 (G: genito-urinary system and sex hormones)

Alfuzosin is an orally active quinazoline derivative. It is a selective antagonist of post-synaptic alpha-1adrenergic receptors. *In vitro* pharmacological studies have confirmed that alfuzosin is selective for alpha-1-adrenergic receptors located in the prostate, bladder base and urethra.

Alpha-blockers decrease infravesical obstruction via direct action on prostatic smooth muscle. *In vivo* animal studies have shown that alfuzosin reduces urethral pressure, thereby lowering resistance to

urine flow during micturition. A study in alert rats showed a greater effect of alfuzosin on urethral pressure than on blood pressure.

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

- significantly increases urine flow 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 to 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 10 mg/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.

Pediatric patients

Alfuzosin should not be used in pediatric patients (see Section 4.2).

The efficacy of alfuzosin hydrochloride was not demonstrated in 2 studies conducted in 197 patients aged between 2 and 16 years with increased detrusor pressure (≥ 40 cm H_2O) caused by a neurological disorder. Patients were treated with 0.1 mg/kg/day or 0.2 mg/kg/day of alfuzosin hydrochloride using adapted pediatric formulations.

5.2. Pharmacokinetic properties

Alfuzosin

Alfuzosin hydrochloride is approximately 90 % plasma protein bound.

Alfuzosin is extensively metabolized in the liver, with only 11 % of the parent compound excreted unchanged in the urine.

The majority of the metabolites (which are inactive) are excreted in the feces (75 to 90%).

The pharmacokinetic pattern of alfuzosin is unchanged in patients with chronic heart failure.

Prolonged-release formulation

The mean value of the relative bioavailability is 104.4% following administration of a 10 mg dose *versus* the immediate-release formulation at a dose of 7.5 mg (2.5 mg three times daily) in middleaged healthy volunteers. Peak plasma concentrations are reached 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 bioavailability is increased when the medicinal product is administered after a meal (see Section 4.2).

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 moderate renal impairment (creatinine clearance > 30 ml/min), with no change in elimination half-life.

Dose adjustment is, therefore, not necessary in patients with renal failure with a creatinine clearance of > 30 ml/min.

5.3 Preclinical safety data

Not applicable.

6 . PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

Tablets in (PVC/aluminum) blister packs.

6.6. Special precautions for disposal and other handling

No special precautions.

7. APPLICANT

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