SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xatral SR 5 mg sustained-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is alfuzosin. Each tablet contains 5 mg alfuzosin hydrochloride.
Excipient with known effect: each tablet contains 19.6 mg hydrogenated castor oil.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale yellow biconvex film coated sustained release tablet for oral administration.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of certain functional symptoms of benign prostatic hypertrophy, particularly if surgery has to be delayed for some reason

4.2. Posology and method of administration

Oral use
Xatral SR 5mg tablet must be swallowed whole with a glass of water.

The first dose of Xatral SR 5mg tablet should be given just before bedtime.

Adults:
The usual dose is one Xatral SR 5 mg tablet morning and evening

Elderly patients (over 65 years) 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 individual response, without exceeding the maximum dosage of one Xatral SR 5mg tablet morning and evening.

Some patients should receive a lower dose of XATRAL, in particular the following patient groups:
- Renal insufficiency
- Hepatic insufficiency

If lower dose is not optional, the physician should consider alternative therapies for these patients.

Paediatric population
The efficacy of Xatral in children aged 2 to 16 years has not been established (see section 5.1). Therefore Xatral is not indicated for use in paediatric patients.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Antecedents of orthostatic hypotension.
- Combination with other alpha-blockers.
- Hepatic insufficiency.
- Concomitant administration of ritonavir alone or in combination with ombitasvir/paritaprevir, lopinavir, nirmatrelvir.

4.4. Special warnings and precautions for use

Warnings

As with all α_1-blockers, orthostatic hypotension may occur during the first few hours after intake of medicinal product, especially at the beginning of the treatment, especially in individuals treated with antihypertensive medicinal products. This may or may not be accompanied by symptoms (sensation of vertigo, fatigue, and sweating).
In this case the patient should be placed in a supine position until the symptoms have disappeared completely. These symptoms are temporary and usually do not prevent further treatment.

During post-marketing surveillance, a marked decrease in blood pressure was reported in patients with pre-existing risk factors (such as underlying cardiac diseases and/or concomitant treatment with antihypertensive medicinal products).

Advanced age is a contributing risk factor for the development of severe hypotension.

The patient should be informed about the possibility of these incidents occurring.

Alfuzosin should be administered with caution to patients suffering from symptomatic orthostatic hypotension or treated with antihypertensive medicinal products or nitrate derivatives (see section 4.5). Blood pressure should be monitored regularly, especially at the beginning of the treatment.

Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or taking medicinal products known to prolong the QTc interval should be evaluated before and during administration of alfuzosin.

In patients with pre-existing symptomatic or asymptomatic cerebral circulatory disorders, there is a risk of cerebral ischaemia due to the fact that hypotension may occur following the administration of alfuzosin (see section 4.8).

Precautions for use

People with a history of hypersensitivity to alpha-1-blockers.

Alfuzosin should be administered with caution to patients who have previously shown a severe hypotensive reaction after taking another α-blocker (see section 4.5).

In coronary patients the specific treatment of coronary insufficiency should be monitored. If angina pectoris should recur or worsen, alfuzosin should be discontinued.

It is essential to rule out prostate cancer before starting the treatment, especially since its first symptoms are similar to those in the case of benign prostatic hypertrophy.

As with all alpha1-receptor blockers, alfuzosin should be administered with caution in patients with acute cardiac insufficiency.

Like other alpha-adrenergic antagonists, alfuzosin has been associated with priapism (persistent painful erection unrelated to sexual activity). As this condition may lead to permanent impotence if not treated properly, patients should be informed of the severity of the condition (see section 4.8).

Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) was observed during cataract surgery in some patients under treatment with some alpha-1 blockers or previously treated with them.
Although the risk of this phenomenon seems to be very low with Xatral, ophthalmic surgeons should be informed about the current or past use of alpha-1 blockers prior to cataract surgery, as IFIS may lead to an increased risk of complications during surgery. The ophthalmologists should be prepared to adjust their surgical techniques if necessary.

Concomitant use of alfuzosin and potent CYP3A4 blockers (such as itraconazole, ketoconazole, protease blockers, clarithromycin, telithromycin and nefazodone) should be avoided (see section 4.5). Alfuzosin should not be used concomitantly with CYP3A4 blockers that are known to prolong the QTc interval (e.g. itraconazole and clarithromycin); temporary discontinuation of alfuzosin treatment is recommended when initiating treatment with such medicinal products.

Concomitant use of phosphodiesterase-5 blockers (e.g., sildenafil, tadalafil, vardenafil) and Xatral may lead to symptomatic hypotension in some patients. To minimise the risk of developing postural hypotension, the patient should be stable under alpha-blocker treatment before initiating phosphodiesterase-5 blockers.

Patients should be informed that the tablet should be taken whole. Any other method of ingestion (chewing, crushing, biting, pulverising or grinding) should be avoided as it may lead to inappropriate release and thus absorption of the active substance. This may cause premature unwanted effects.

Xatral SR 5 mg sustained-release tablets contain hydrogenated castor oil, which may cause stomach upset and diarrhoea.

Elderly patients
Xatral should be prescribed with caution to the elderly.

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

Contraindicated combinations:
Other α_1-blockers (see section 4.3).
Ritonavir alone or in combination with “ombitasvir/paritaprevir, lopinavir and nirmatrelvir” (see section 4.3)

Combinations not recommended:
Potent CYP3A4 blockers such as itraconazole, ketoconazole, protease blockers, clarithromycin, telithromycin and nefazodone as alfuzosin blood levels may be elevated (see section 4.4).

Combinations to be taken into account:

- Antihypertensive medicinal products (see section 4.4).
- Nitrate derivatives (see section 4.4)
- General anaesthetics: the administration of a general anaesthetic to a patient treated with alfuzosin may result in unstable blood pressure.
- Concomitant use of phosphodiesterase-5 blockers (e.g., sildenafil, tadalafil, and vardenafil) and Xatral may lead to symptomatic hypotension in some patients (see section 4.4).
- Medicinal products known to prolong the QTc interval (see section 4.4).

4.6. Fertility, pregnancy and lactation

Not applicable.

4.7. Effects on the ability to drive and use machines

No information is known on the effect on the ability to drive and operation of machines.
Effects such as drowsiness, hypotension, vertigo, dizziness and asthenia may occur and especially at the start of treatment. These effects must be taken into account when driving vehicles and using machines.

4.8. Undesirable effects

Tabulated summary of undesirable effects

The undesirable effects are listed in the table below according to the MedDRA system/organ classes and frequency categories. The CIOMS frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System/Organ class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders					Neutropoenia Thrombocytopaenia
Nervous system disorders	Weakness; fatigue; sensation of vertigo; vertigo; headache; dizziness.	Sleepiness; Syncope.			Cerebral ischaemic disorders in patients with underlying cerebrovascular disorders (see section 4.4).
Eye disorders		Abnormal vision			Intraoperative floppy iris syndrome (see section 4.4)
Cardiac disorders		Tachycardia; palpitations		Angina pectoris in coronary patients (see section 4.4)	Atrial fibrillation
Vascular disorders	Hypotension (orthostatic)	Hot flushes			

System/Organ class	Common	Uncommon	Rare	Very rare	Not known
	(see section 4.4)				
Respiratory system disorders		Rhinitis			
Gastrointestinal disorders	Nausea; abdominal pain; stomach pain; dry mouth; and diarrhoea	Vomiting			
Hepatobiliary disorders					Hepatocellular injury; cholestatic liver disease.
Skin and subcutaneous tissue disorders		Skin rash; itching		Urticaria; and angioedema	
Reproductive system and breast disorders					Priapism
General disorders	Asthenia; malaise	Chest pain; oedema.			

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il

4.9. Overdose

The main signs of overdose are hypotension and its possible complications.

In case of an overdose, the patient should be hospitalised, kept in a supine position and classical treatment for hypotension should be initiated (vascular filling and vasopressin)

In case of significant hypotension, the appropriate corrective treatment may consist of a vasoconstrictor acting directly on the vascular muscle fibres.

Alfuzosin is difficult to dialyse because of its high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: a drug used in cases of benign prostatic hypertrophy. ATC code: G04C A 01

Alfuzosin is a derivative of quinazoline, which is active via the oral route.

It is a selective antagonist of the postsynaptic alpha-1-adrenergic receptors. Pharmacological studies conducted in vitro confirmed the selectivity of alfuzosin for the alpha-1 receptors at the trigonum of the bladder, urethra and prostate.

Studies in vivo in animals indicate that alfuzosin reduces urethral pressure and thus the resistance to micturition.

In the case of benign hypertrophy of the prostate the occurrence and intensity of functional urinary symptoms are not only related to the volume of the prostate but also to the sympathetic (nervous) tone.

An alpha-adrenergic nerve was demonstrated in the smooth muscle of the prostate stroma. Alfuzosin exhibits selective tissue distribution in the prostate.

The hypertrophy of the stroma of the prostate concerns the smooth muscle tissues. Stimulation of postsynaptic alpha-1 receptors increases the muscle tone of the urinary tract, while blockage of these receptors by alfuzosin leads to relaxation of smooth muscle fibres.

Alfuzosin shows a certain degree of urological selectivity: inhibition of the hypertonic response of the urethra appears earlier than the effect on the vascular walls.

In humans alfuzosin improves evacuation parameters by reducing urethral tone and resistance at the bladder neck, thereby promoting emptying of bladder.
Clinical placebo-controlled studies in patients with benign prostatic hypertrophy showed that alfuzosin:

- the maximum flow rate (Qmax) increases significantly in patients where the Q max is ≤15 ml/s, by 30% on average. This improvement is observed from the first dose.
- significantly decreases the detrusor pressure and increases the volume, leading to a strong need to urinate.
- significantly reduces the residual volume.

These positive urea dynamic effects lead to a clearly demonstrated improvement in the lower urinary tract symptoms, both in terms of filling (irritation symptoms) and evacuation (obstructive symptoms).

In treated patients the frequency of acute urinary retention is decreased compared to patients who are not treated patients.

Paediatric population
Xatral is not indicated for use in paediatric patients (see section 4.2)
The efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 patients aged 2 to 16 years with increased detrusor leak point pressure (LPP ≥40 cm H2O) of a neurological nature. Patients were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day with adapted paediatric formulations.

5.2. Pharmacokinetic properties

Absorption
The average bioavailability is approximately 49%.
The maximum plasma concentration is reached approximately 3 hours after administration.

Distribution

Binding to plasma proteins is approximately 90%, 68.2% to serum albumin and 52.5% to serum alpha-1-glycoproteins.

Biotransformation
Alfuzosin is highly metabolised in the liver, while only 11% of the product is excreted unchanged in the urine.
CYP3A4 is the major hepatic isoenzyme involved in the metabolism of alfuzosin. Ketoconazole is a very potent CYP3A4 inhibitor. Repeated daily doses of 200 mg ketoconazole for 7 days resulted in a 2.11-fold increase in C_{max} and 2.46-fold increase in AUC_{load} after the administration of 10 mg alfuzosin after a meal. The other parameters, such as tmax and t1/2Z, had not changed. Repeated daily doses of 400 mg ketoconazole for 8 days increased the C_{max} of alfuzosin by 2.3 times, the AUC_{load} and the AUC by 3.2 and 3.0 times, respectively (see section 4.5).

Elimination
Most metabolites (without pharmacodynamic activity) are excreted in the faeces (75 to 91%).
The plasma half-life of alfusozin [*sic:* alfuzosin], calculated on the elimination rate, is 8 hours.

Renal insufficiency
In patients with renal impairment, with or without the need for dialysis, the volume of distribution and the clearance of alfuzosin are increased due to the increased free fraction.

Hepatic insufficiency
In patients with severe hepatic insufficiency the elimination half-life was prolonged, the values of Cmax doubled, and those of AUC tripled. Bioavailability is increased compared to healthy volunteers.

Elderly patients
In patients older than 75 years the reabsorption of alfuzosin is faster and the maximum concentrations are higher. Bioavailability may be increased and a reduction in the volume of distribution is seen in certain patients. The elimination half-life remains unchanged.

Chronic cardiac insufficiency
In the case of chronic cardiac insufficiency, the pharmacokinetic profile of alfuzosin is not affected.

5.3. Preclinical safety data

No available data.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

calcium hydrogen phosphate dihydrate, microcrystalline cellulose, hydrogenated castor oil, povidone, Hypromellose, magnesium stearate, titanium dioxide, propylene glycol, yellow iron oxide, red iron oxide.

6.2. Incompatibilities

There are no known significant incompatibilities.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

28 or 56 tablets in Blister. Not all package sizes may be marketed

6.6. Special precautions for disposal

There are no special precautions.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Sanofi Israel LTD
Greenwork Park, P.O box 47, Yakum

8. LICENSE NUMBER

110-16-29084

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