

SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfuzosin Orion 10 mg prolonged-release tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains alfuzosin hydrochloride 10 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white round, biconvex, film-coated tablets debossed with 'X' on one side and '47' on other side. Diameter of the tablet is 8.1 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

The prolonged-release tablet should be swallowed whole with a sufficient amount of fluid.

Posology

Adults

1 prolonged-release tablet 10 mg daily to be taken after an evening meal.

Elderly and patients with renal insufficiency

Based on pharmacokinetic and clinical safety data, elderly and patients with renal insufficiency (creatinine clearance ≥ 30 ml/min) can be treated with the usual dose. Due to lacking clinical safety data Alfuzosin Orion should not be given to patients with severe renal impairment (creatinine clearance < 30 ml/min see section 4.4).

Hepatic impairment

Alfuzosin Orion 10 mg is contraindicated in patients with hepatic impairment. Preparations containing a low dose of alfuzosin hydrochloride might be used in patients with mild to moderate hepatic insufficiency as instructed in the corresponding product information.

Paediatric population

Efficacy of alfuzosin has not been demonstrated in children aged 2 to 16 years (see section 5.1). Therefore, alfuzosin is not indicated for use in paediatric population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Conditions with orthostatic hypotension.

- Hepatic insufficiency.
- Combination with other alpha-1-receptor blockers.

4.4 Special warnings and precautions for use

Alfuzosin Orion should not be given to patients with severe renal impairment (creatinine clearance <30 ml/min) in view of the lack of clinical safety data in this group of patients.

Alfuzosin Orion should be given with caution to patients who are on antihypertensive medication or nitrates.

In some subjects postural hypotension may develop, with or without symptoms (dizziness, fatigue, sweating) within a few hours following administration. These effects are usually transient, occur in the beginning of treatment and do not usually prevent the continuation of 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). The risk of developing hypotension and related adverse reactions may be greater in older people.

Care should be taken when alfuzosin is administered to patients who have had a pronounced hypotensive response to another-alpha-1-blockers.

In coronary patients, the specific treatment for coronary insufficiency should be continued. If angina pectoris reappears or worsens, alfuzosin should be discontinued.

As with all alpha-1-blockers, alfuzosin should be used with caution in patients with acute cardiac failure.

Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or who are taking drugs known to increase the QTc interval should be evaluated before and during the administration of alfuzosin.

Concomitant use of alfuzosin and potent CYP3A4 inhibitors (such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone) should be avoided (see section 4.5). Alfuzosin should not be used concomitantly with CYP3A4 inhibitors that are known to increase the QTc interval (e.g. itraconazole and clarithromycin) and a temporary interruption of alfuzosin treatment is recommended if treatment with such medicinal products is initiated.

The “Intraoperative Floppy Iris Syndrome” (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports have also been received with other alpha-1-blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1-blockers should be made known to the ophthalmic surgeon in advance of surgery.

Alfuzosin, like other alpha adrenergic antagonist, has been associated with priapism (persistent painful penile erection unrelated to sexual activity; see section 4.8). Because this condition can lead to permanent impotence if not properly treated, patients should be advised to seek immediate assistance in the event of an erection that persists longer than 4 hours.

Patients should be warned that the tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacodynamic or pharmacokinetic interactions have been observed in studies with healthy volunteers between alfuzosin and the following drugs: warfarin, digoxin, hydrochlorothiazide and atenolol.

Administration of general anaesthetics to a patient treated with alfuzosin may lead to blood pressure instability.

Combinations contra-indicated:

- Alpha-1-receptor blockers (see section 4.3)

Concomitant use not recommended:

- Potent CYP3A4 inhibitors such as itraconazole, ketoconazole, protease inhibitors, clarithromycin, telithromycin and nefazodone since alfuzosin blood levels may be increased (see section 4.4).

Combinations to be taken into account:

- Antihypertensive drugs (see section 4.4)
- Nitrates (see section 4.4)

Ketoconazole: Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in a 2.1 fold increase in C_{\max} and a 2.5 fold increase in exposure of alfuzosin 10 mg OD when administered under fed conditions. Other parameters such as t_{\max} and $t_{1/2}$ were not modified.

The increase in alfuzosin C_{\max} and $AUC_{(\text{last})}$ following repeated 400 mg daily administration of ketoconazole was 2.3-fold, and 3.2-fold, respectively (see section 5.2).

See also section 4.4.

4.6 Fertility, pregnancy and lactation

Not relevant.

4.7 Effects on ability to drive and use machines

There are no data available on reduced reaction ability.

Adverse reactions such as dizziness and weakness may occur essentially at the beginning of treatment. This has to be taken into consideration when driving vehicles and operating machines.

4.8 Undesirable effects

The most commonly reported event is dizziness, which occurs in approximately 5% of treated patients.

Classification of expected frequencies:

Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1\,000$ to $< 1/100$), rare ($\geq 1/10\,000$ to $< 1/1\,000$), very rare ($< 1/10\,000$), not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

MedDRA system organ class	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1\,000$ to $< 1/100$	Very rare $< 1/10\,000$	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Neutropenia, thrombocytopenia

MedDRA system organ class	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1\ 000$ to $< 1/100$	Very rare $< 1/10\ 000$	Not known (cannot be estimated from the available data)
Nervous system disorders	Dizziness, headache	Vertigo, drowsiness		
Eye disorders				Intraoperative floppy iris syndrome*
Cardiac disorders		Syncope (initially or if treatment is started again after a short interruption of therapy), postural hypotension* (initially above all with too high a dose or if treatment is started again after a short interruption of therapy), tachycardia	Angina pectoris predominantly in patients with pre-existing coronary heart disease*	Atrial fibrillation
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal disorders	Abdominal pain, nausea, dyspepsia	Vomiting, diarrhoea, dryness of the mouth		
Hepatobiliary disorders				Hepatocellular injury, cholestatic liver disease
Skin and subcutaneous tissue disorders		Rash (urticaria, exanthema), pruritus	Angioedema	
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions	Asthenia	Chest pain, oedema, hot flushes		

* For more information, see section 4.4.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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. Healthcare

professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

4.9 Overdose

In case of overdose, conventional treatment such as addition of fluids and vasopressor drugs should take place in a hospital. The patient should be kept in the supine position.

In case of significant hypotension, the appropriate corrective treatment may be a vasoconstrictor that acts directly on vascular muscle fibers.

Alfuzosin is not easily dialysable because of its high degree of protein binding. Active charcoal should be administered following possible gastric lavage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in benign prostatic hypertrophy. ATC code: G04CA01

Alfuzosin, which is a racemate, is an oral quinazoline derivative, which selectively blocks post synaptic alpha-1-receptors. *In vitro* studies have confirmed the selectivity of the substance on alpha-1-receptors in the trigone of the urine bladder, urethra and prostate. The clinical symptoms in benign prostatic hyperplasia are not only related to the size of the prostate, but also to the sympathomimetic nerve impulse, which by stimulating the post synaptic alpha receptors increase the tension of the smooth muscles of the lower urinary tract. During treatment with alfuzosin, smooth muscles are relaxed and thus urine flow is improved.

Clinical evidence of uroselectivity has been demonstrated by clinical efficacy and good safety profile in men treated with alfuzosin, including older people and hypertensive men.

In man, alfuzosin improves voiding by reducing urethral tone and bladder outlet resistance, and facilitates bladder emptying.

In placebo controlled studies in BPH patients, alfuzosin:

- significantly increased peak flow rate (Q_{\max}) in patients with $Q_{\max} < 15$ ml/s by a mean of 30%. This improvement was observed from the first dose.
- significantly reduced the detrusor pressure and increased the volume producing a strong desire to void.
- significantly reduced the residual urine volume.

The efficacy on peak flow rate is observed up to 24 hours after intake.

These urodynamic effects lead to an improvement of lower urinary tract symptoms (LUTS) i.e. filling (irritative) as well as voiding (obstructive) symptoms which was clearly demonstrated.

A lower frequency of acute urinary retention (AUR) was observed in alfuzosin treated patients than in untreated patients. In addition, alfuzosin significantly increased the success rate of spontaneous voiding after catheter removal in men with a first episode of AUR related to BPH and, in comparison with placebo, reduced the need of surgery for AUR relapse for up to 3 to 6 months.

Paediatric population

Alfuzosin Orion is not indicated for use in the paediatric population (see section 4.2).

Efficacy of alfuzosin hydrochloride was not demonstrated in the two studies conducted in 197 patients 2 to 16 years of age with elevated detrusor leak point pressure ($LPP \geq 40$ cm H₂O) of neurologic origin. Patients were treated with alfuzosin hydrochloride 0.1 mg/kg/day or 0.2 mg/kg/day using adapted paediatric formulations.

5.2 Pharmacokinetic properties

Alfuzosin:

Alfuzosin shows linear kinetics in the therapeutic dosage area. Bioavailability is 64%, when administered as an immediate release formulation (2.5 mg). Maximal plasma concentration is reached within 0.5-6 hours after administered dose. The kinetic profile is characterised by large inter-individual fluctuations (sevenfold) in plasma concentrations. Plasma half-life is approximately 5 hours (1-10 hours). The pharmacokinetic profile is not altered when alfuzosin is administered with food.

Plasma protein binding is about 90%. Alfuzosin is eliminated by metabolism, renal excretion and probably also biliar excretion. After extensive metabolism by the liver the majority of the metabolites are recovered in faeces (75% to 91%). CYP3A4 is the main hepatic enzyme isoform involved in the metabolism of alfuzosin (see section 4.5). None of the metabolites has any pharmacological activity.

Volume of distribution and clearance is increased in reduced renal function, possibly due to decreased protein binding capacity. Half-life is however unchanged. In patients with severe hepatic insufficiency, the elimination half-life is prolonged. A two-fold increased in C_{max} and three-fold increase in AUC is observed. Bioavailability is increased in comparison to that in healthy volunteers.

Older people have higher bioavailability, which leads to higher maximum plasma concentrations but unchanged half-life.

Prolonged-release tablets 10 mg:

The mean value of the relative bioavailability is 104.4% versus the immediate release formulation (2.5 mg tid) in middle aged healthy volunteers. The maximal plasma concentration is being achieved 9 hours after the administration compared to 1.0 hour for the immediate release formulation.

The apparent elimination half-life is 9.1 hours.

Studies have shown that consistent pharmacokinetic profiles are obtained when the product is administered after a meal.

Under fed conditions, mean C_{max} and C_{trough} values are 13.6 (SD=5.6) and 3.2 (SD=1.6) ng/ml respectively. Mean AUC_{0-24} is 194 (SD=75) ng · h/ml.

Compared to healthy middle aged volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in older people.

Compared to subjects with normal renal function, mean C_{max} and AUC values are moderately increased in patients with renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant for patients with creatinine clearance >30 ml/min.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Hypromellose

Hydrogenated vegetable oil

Povidone (K-30)

Calcium hydrogen phosphate

Carbomers

Silica, colloidal anhydrous

Magnesium stearate

Film-coating:

Hypromellose

Propylene glycol

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC / PVdC- Aluminium foil blister: 10, 20, 30, 50, 60 and 90 tablets.

HDPE container with polypropylene screw cap: 30 and 90 tablets.

The container contains a silica gel desiccant.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation

Orionintie 1

FI-02200 Espoo

Finland

8 MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10 DATE OF REVISION OF THE TEXT

07/03/2023