Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alfu 10 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 10 mg alfuzosin hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white round (diameter 8.1 mm), biconvex, film-coated tablets debossed with 'X' on one side and '47' on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Adjunctive therapy with urethral catheterisation for Acute Urinary Retention related to BPH.

4.2 Posology and method of administration

Posology

Adults:
BPH: The recommended dose is one 10 mg prolonged-release tablet once daily to be taken after a meal.

Acute urinary retention:
One 10mg tablet daily after a meal to be taken from the first day of catheterisation. The treatment should be administered for 3-4 days, 2-3 days during catheterisation and 1 day after catheter removal. In this indication, No benefit on progression of acute urinary retention has been established in patients under 65 years of age or if treatment is extended beyond 4 days.

Elderly (over the age of 65 years)
The recommended dose is the same as that for adults. Pharmacokinetic and clinical safety studies have shown that dose adjustment is not necessary in the case of elderly patients.

Impaired renal function
Mild to moderate renal insufficiency (creatinine clearance > 30 ml/min): Dose reduction is usually not necessary (see section 5.2).

Severe renal insufficiency
Alfuzosin 10 mg should not be given to patients with severely impaired renal function (creatinine clearance < 30 ml/min) as there are no clinical safety data available for this patient group.

Hepatic insufficiency:
Alfuzosin, given as 10 mg prolonged-release tablets are contraindicated in patients with hepatic insufficiency (see section 4.3). 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 on children aged 2 to 16 years (see section 5.1). Therefore, alfuzosin is not indicated for use in paediatric population.

Method of administration
Oral Use

The prolonged-release tablet should be taken whole with sufficient amount of fluid (e.g. a glass of water). The prolonged-release tablets must not be crushed, chewed or divided (see section 4.4).

The first dose should be taken at bedtime. The prolonged-release tablet 10 mg should be taken immediately after the same meal each day.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinazolines (e.g. terazosine, doxazosine) or to any of the excipients listed in section 6.1
- Previous history of orthostatic hypotension
- Hepatic insufficiency
- Combination with other alpha 1- blockers (see section 4.5)
- Combination with dopamine receptor agonists (e.g. special antiparkinson drugs , see section 4.5)

4.4 Special warnings and precautions for use

Alfuzosin should be given with caution to patients with symptomatic orthostatic hypotension or 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. In such cases, the patient should lie down until the symptoms have completely disappeared.

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 elderly patients (see section 4.8). Caution should be exercised when prescribing alfuzosin to elderly patients. The patient should be warned of the possible occurrence of such events.

Precautions
Before the initiation of the treatment the possibility of malignancy must be eliminated (rectal check and PSA test).

Use with PDE5 inhibitors: concomitant administration of Alfu 10 mg tablets 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

Care should be taken when alfuzosin is administered to patients who have had a pronounced hypotensive response to another alpha1-blocker. Treatment should be initiated gradually in patients with hypersensitivity to alpha-1-blockers. Blood pressure should be monitored regularly, especially at the beginning of treatment.

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 'Interoperative 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. Although the risk of this event with alfuzosin appears very low, 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. The ophthalmologists should be prepared for possible modifications to their surgical technique.

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. It is recommended that the tablets be withdrawn 24 hours before surgery.

Combinations contra-indiacted

- Other alpha-1 receptor blockers as well as dopamine receptor agonists (see section 4.3)Increased hypotensive effect. Risk of severe orthostatic hypotension.

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)
- + Ombitasvir + paritaprevir + RitonavirIncrease in alfuzosin plasma concentrations by decreased hepatic metabolism with dual therapy.

Combinations to be taken into account

- Antihypertensive drugs (see section 4.4)
- Nitrates (see section 4.4)
- + Dapoxetine There is a risk of increased undesirable effects, particularly dizziness or syncope.
- + Blood-pressure lowering agents There is a risk of enhanced hypotension, particularly orthostatic.

Combinations requiring precautions for use

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

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 $C_{max,}$ $AUC_{(last)}$ and AUC following 8-days repeated 400 mg daily administration of ketoconazole was 2.3-fold, 3.2-fold and 3.0-fold, respectively (see section 5.2).

See also section 4.4.

4.6 Fertility, pregnancy and lactation

As Alfuzosin is not used in women, this section does not apply.

4.7 Effects on ability to drive and use machines

There are no data available on the effect on driving vehicles.
Adverse reactions such as vertigo, dizziness, asthenia and visual disturbances may occur essentially at the beginning of treatment. Some subjects particularly those on antihypertensive medication may experience postural hypotension, which may or may not result in symptoms such as dizziness and fatigue. This has to be taken into consideration when driving vehicles and operating machines. This applies in particular associated with alcohol.

4.8 Undesirable effects

Tabulated list of adverse reactions

Classification of expected frequencies:
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	**Frequency**			
	Common	**Uncommon**	**Very rare**	**Not Known**
Blood and lymphatic system disorders				Neutropenia, thrombocytopenia
Nervous system disorders	Dizziness, headache	Syncope, Vertigo, Drowsiness, Malaise		Stroke in patients with underlying cerebrovascular disorders
Eye disorders		Abnormal vision		Intraoperative floppy iris syndrome
Cardiac disorders		Tachycardia, Palpitations	New onset, aggravation or recurrence of angina pectoris in patients with pre-existing coronary artery disease (see section 4.4).	Atrial fibrillation
Vascular disorders		Hypotension (postural) (see section 4.4), flushing		
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal isorders	Nausea, abdominal	Diarrhoea , Dry mouth		Vomiting

	pain			
Hepatobiliary disorders			hepatotoxicity	Hepatocellular injury, cholestatic liver disease
Skin and subcutaneous tissue disorders		Rash, pruritus	Urticaria, angioedema	
Renal and urinary disorders		Urinary Incontinence		
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions	Asthenia	Oedema, chest pain		

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
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In case of overdosage, the patient should be hospitalized, kept in the supine position, and conventional treatment of hypotension should take place. Other supporting measures are suggested in individual cases, such as the careful administration of a volume expanders. In case of significant hypotension, the appropriate corrective treatment may be a vasoconstrictor that acts directly on vascular muscle fibres. Administration of activated charcoal should be considered.
Alfuzosin is highly protein-bound, therefore, dialysis may not be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha-adrenoreceptor antagonists. ATC code: G04C A01 Alfuzosin

Mechanism of action
Alfuzosin, a racemic compound, is an orally active quinazoline derivative that selectively blocks post-synaptic alpha-l-receptors. In vitro studies have shown that the substance acts selectively on alpha-1-receptors in the trigone of the urine bladder, the urethra and the prostate gland. The clinical symptoms of benign prostate hyperplasia are not only related to the size of the prostate but also to the sympathicomimetic nerve impulses which through stimulation of the postsynaptic alpha-receptors increase the tension of the smooth muscles of the lower urinary tract. Through treatment with alfuzosin the smooth muscles relax as a result of which the urine flow improves. This in turn leads to outflow obstruction and possible secondary bladder instability.

Alpha-blockade decreases infra vesicle obstruction via a direct action on prostatic smooth muscle.

In vivo, animal studies have shown that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin inhibits the hypertonic response of the urethra more readily than that of vascular muscle and shows functional uroselectivity in conscious normotensive rats by decreasing urethral pressure at doses that do not affect blood pressure.

The clinical evidence of the selective effect on the urinary tract is shown by the clinical efficacy and the good safety profile in men treated with alfuzosin, including elderly patients and patients with hypertension. Alfuzosin can result in moderate antihypertensive effects.

In men, alfuzosin improves the voiding of water by reducing urethral muscle tone and bladder outlet resistance, thereby facilitating bladder emptying.
In patients treated with alfuzosin a lower frequency of acute urine retention was observed than in untreated patients.

In placebo-controlled studies in patients with benign prostate hyperplasia alfuzosin:

- significantly increased maximum urine flow (Q_{max}) in patients with Q_{max}<15 ml/sec by an average of 30%. This improvement was observed from the first dose;
- a significantly reduced detrusor pressure and an increased volume, producing a strong desire to void,
- a significantly reduced the residual urine volume.

In addition, the efficacy of alfuzosin 10mg on peak flow rate and the limited effect on blood pressure have been demonstrated to be related to its pharmacokinetic profile. Moreover, the efficacy on peak flow rate is maintained up to 24 hours after intake.

These urodynamic effects result in an improvement in lower urinary tract symptoms (LUTS), i.e. symptoms relating to retention (irritating) and urine discharge (obstructive) which is clearly demonstrated.

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, multicentre study in two parallel groups comparing 10 mg/day prolonged-release alfuzosin 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.

Paediatric population

Alfuzosin 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 ≥ 40 cm H_2O) 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

Prolonged-release formulation:
The mean value of the relative bioavailability is 104.4% versus the immediate release formulation (2.5 mg tid) in middle-aged healthy volunteers and the maximum plasma concentration is being achieved 9 hours after administration compared to 1 hour for the immediate release formulation.

Alfuzosin has linear pharmacokinetics in the therapeutic dosage range. The kinetic profile is characterised by large inter-individual fluctuations in the plasma concentration.

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

After the first dose (following a meal) the mean maximum plasma concentration was 7.72 ng/ml and the AUC_{inf} 127 ng x h/ml (after a meal) and the t_{max} was 6.69 hours (after a meal).

Under fed conditions, mean C_{max} and $C_{\mathbf{trough}}$ 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. A plateau of concentrations is observed from 3 to 14 hours with concentrations above 8.1 ng/ml (C_{av}) for 11 hours.

Distribution
Plasma protein binding is approx. 90%. The distribution volume of alfuzosin in healthy test subjects is 2.5 l/kg. It has been shown that the substance is distributed more in the prostate than in the plasma.

Elimination
The apparent elimination half-life is 9.1 hours. Alfuzosin is largely metabolised in the liver by the isoenzyme CYP3A4 (see section 4.5) (various routes), the metabolites are eliminated by the kidneys and probably also via the bile, 75-91% of an oral dose is eliminated in the faeces, 35% in unmodified form and the rest as metabolites, which indicates that some excretion via the bile takes place. Around 11% of the dose is eliminated in unmodified form in the urine. None of the metabolites are pharmacologically active.

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

Renal or hepatic impairment
The volume of distribution and clearance increases with reduced renal function, possibly owing to a decreased degree of protein binding. The half-life, however, is unchanged. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore, this does not necessitate a dosing adjustment in patients with mild to moderate renal insufficiency (see sections 4.2 and 4.4).

The half-life is prolonged in patients with severe hepatic insufficiency. The peak plasma concentration is doubled and the bioavailability increases in relation to that in young, healthy volunteers. Alfuzosin 10 mg prolonged release tablets are contraindicated in hepatic insufficiency (see section 4.3).

Elderly
Compared to healthy middle-aged volunteers, the peak plasma concentration (C_{max}) and bioavailability (AUC) are not increased in elderly patients. The elimination half-life ($t_{½}$) remains unchanged.

5.3 Preclinical safety data

Pre-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity, carcinogenic potential or reproductive toxicity for males. *In vitro,* alfuzosin prolonged the action potential duration and QT interval duration at a clinically relevant concentration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Hypromellose (E464)
Hydrogenated vegetable oil
Povidone (K-30) (E1201)
Calcium hydrogen phosphate
Carbomer
Silica colloidal anhydrous (E551)
Magnesium stearate (E572)

Film-coating:
Hypromellose (E464)
Propylene glycol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Alfu tablets are available in clear PVC/PVdC Aluminium blister packs and white opaque round HDPE bottles containing silica gel.

Package sizes:
Blister pack: 30, 50, 90 & 100 tablets
HDPE bottle pack: 30, 500 & 1000 tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana
FRN 1913
Malta

8 MARKETING AUTHORISATION NUMBER

PA1445/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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