SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Besavar XL 10mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg alfuzosin hydrochloride in a sustained release formulation.
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged-release tablets.
Round, biconvex three layer tablets; one white layer between 2 yellow layers.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Besavar XL is indicated in the treatment of the functional symptoms of benign prostatic hypertrophy (BPH).

For information on use in acute urinary retention (AUR) related to BPH see sections 4.2 and 5.1.

4.2 Posology and method of administration

Besavar XL tablets should be swallowed whole.

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

AUR: In patients 65 years and older, one 10 mg 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 its removal. In this indication no benefit has been established in patients under 65 years of age or if treatment is extended beyond 4 days.

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 the paediatric population.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1).
- History of orthostatic hypotension.

- Combination with other -alpha-1 receptor blockers.
- Concomitant administration with ritonavir alone or in combination with ombitasvir/paritaprevir, lopinavir and nirmatrelvir (see Section 4.5).
- Hepatic insufficiency.

4.4 Special warnings and precautions for use

Warnings

As with all alpha-1 blockers in some subjects, in particular patients receiving antihypertensive medications or nitrates, postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases, the patient should lie down until the symptoms have completely disappeared.

These effects are transient, occur at 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, see section 4.8). The risk of developing hypotension and related adverse reactions may be greater in elderly patients. The patient should be warned of the possible occurrence of such events.

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

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

Treatment should be initiated gradually in patients with hypersensitivity to alpha-1-blockers. Besavar XL should be administered carefully to patients being treated with antihypertensive medication or nitrates (see section 4.5). Blood pressure should be monitored regularly, especially at the beginning of treatment.

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.

Prolonged erections and priapism have been reported with alpha-1 blockers including alfuzosin in post marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance (see section 4.8).

Precautions

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

As there are no clinical safety data available in patients with severe renal impairment (creatinine clearance < 30ml/min), Besavar XL 10mg tablets should not be administered to this patient group.

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.

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 alpha-1 blockers. Although the risk of this event with alfuzosin appears very low, ophthalmic surgeons should be informed in advance of cataract surgery of current or past use of alpha-1-blockers, as IFIS may lead to increased procedural complications. The ophthalmologists should be prepared for possible modifications to their surgical technique.

Excipients
Besavar XL 10mg tablets contain hydrogenated castor oil which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations contra-indicated:
- Alpha-1-receptor blockers (see section 4.3).

Concomitant use not recommended:
- Potent CYP3A4 inhibitors such as itraconazole, ketoconazole, protease inhibitors (e.g. ritonavir), 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).

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 when administered as a single dose under fed conditions (high fat meal). Other parameters such as t_{max} and $t_{1/2}$ were not modified.

C_{max} and AUC of alfuzosin 10 mg, when administered as a single dose under fed conditions, increased 2.3-fold and 3.0-fold, respectively following 8-day repeated 400 mg ketoconazole daily dosing (see section 5.2).

The administration of general anaesthetics to patients receiving Besavar XL 10mg Tablets could cause profound hypotension. It is recommended that the tablets be withdrawn 24 hours before surgery.

Other forms of interaction

No pharmacodynamic or pharmacokinetic interaction has been observed in healthy volunteers between alfuzosin and the following drugs: warfarin, digoxin, hydrochlorothiazide and atenolol.

4.6. Pregnancy and lactation

Due to the type of indication this section is not applicable.

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 and asthenia may occur essentially at the beginning of treatment. This has to be taken into account when driving vehicles and operating machinery.

4.8 Undesirable effects

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).

- **Cardiac disorders**

Uncommon: tachycardia, palpitations, hypotension (postural)
Very rare: new onset, aggravation or recurrence of angina pectoris in patients with pre-existing coronary artery disease (see section 4.4.)
Not known: atrial fibrillation

- **Eye disorders**

Uncommon: vision abnormal
Not known: intraoperative floppy iris syndrome (see section 4.4)

- **General disorders and administration site conditions**

Common: asthenia
Uncommon: flushes, oedema, chest pain

- **Gastro-intestinal disorders**

Common: nausea, abdominal pain
Uncommon: diarrhoea, dry mouth
Not known: vomiting

- **Hepatobiliary disorders**

Not known: hepatocellular injury, cholestatic liver disease

- **Nervous system disorders**

Common: faintness/dizziness, headache
Uncommon: syncope, vertigo, malaise, drowsiness

- **Reproductive system and breast disorders**

Not known: priapism

- **Respiratory, thoracic and mediastinal disorders**

Uncommon: rhinitis

- **Skin and subcutaneous tissue disorders**

Uncommon: rash, pruritus
Very rare: urticaria, angioedema

- **Vascular disorders**

Uncommon: hypotension (postural), flushing

- **Blood and lymphatic system disorders**

Not known: neutropenia, thrombocytopenia

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.

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

Alfuzosin is not dialysable because of its high degree of protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha-adrenoreceptor antagonists, ATC code: G04CA01

Alfuzosin is an orally active quinazoline derivative. It is a selective, peripherally acting antagonist of postsynaptic α_1-adrenoceptors.

In vitro pharmacological studies have documented the selectivity of alfuzosin for the alpha-1-adrenoreceptors located in the prostate, bladder base and prostatic urethra.

Clinical manifestations of Benign Prostatic Hypertrophy are associated with infra vesical obstruction which is triggered by both anatomical (static) and functional (dynamic) factors. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by alpha adrenoceptors. Activation of alpha-1-adrenoceptors stimulates smooth muscle contraction, thereby increasing the tone of the prostate, prostatic capsule, prostatic urethra and bladder base, and, consequently, increasing the resistance to bladder outflow. This in turn leads to outflow obstruction and possible secondary bladder instability.

Alpha-blockade decreases infra vesical 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.

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

In placebo controlled studies in BPH patients, alfuzosin:

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

These favourable urodynamic effects lead to an improvement of lower urinary tract symptoms ie. filling (irritative) as well as voiding (obstructive) symptoms.

Alfuzosin may cause moderate antihypertensive effects.

A lower frequency of acute urinary retention is observed in the alfuzosin treated patient than in the untreated patient.

AUR (related to BPH):
In the ALFAUR study, the effect of alfuzosin on the return of normal voiding was evaluated in 357 men over 50 years, presenting with a first episode of acute urinary retention (AUR), related to BPH. In this multicentre, randomised double blind parallel group study comparing alfuzosin 10mg/day and placebo, the evaluation of voiding was performed 24 hours after catheter removal, the morning after 2-3 days of treatment.

In men aged 65 years and over alfuzosin significantly increased the success rate of spontaneous voiding after catheter removal – see table. No benefit has been established in patients under 65 years of age or if treatment is extended beyond 4 days.

ALFAUR study: Percentage of patients (ITT population) successfully voiding post-catheter removal

Age	**Placebo N (%)**	**Alfuzosin N (%)**	**Relative difference vs placebo 95%CI**	**p value**
65 years and above	30 (35.7%)	88 (56.1%)	1.57 (1.14-2.16)	0.003
Below 65 years	28 (75.7%)	58 (73.4%)	0.97 (0.77-1.22)	0.80
All patients (50 years and above)	58 (47.8%)	146 (61.9%)	1.29 (1.04-1.60)	0.012

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≥40cm H_20) 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.

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 3.1 (SD=1.6) ng/ml respectively. Mean AUC_{0-24} is 194 (SD=75) ng.h/ml. A plateau of concentration is observed from 3 to 14 hours with concentrations above 8.1 ng/ml (Cav) for 11 hours.

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 renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore, this does not necessitate a dosing adjustment.

The binding of alfuzosin to plasma proteins is about 90%. Alfuzosin undergoes extensive metabolism by the liver, with only 11 % of the parent compound being excreted unchanged in the urine. The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91 %).

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

Metabolic interactions: CYP3A4 is the main hepatic enzyme isoform involved in the metabolism of alfuzosin (see section 4.5).

5.3. Preclinical safety data

No data of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ethylcellulose
Hydrogenated castor oil
Hypromellose
Yellow ferric oxide (E172)
Magnesium stearate
Microcrystalline cellulose
Povidone,
Colloidal hydrated silica
Mannitol.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.
Store in the original container.

6.5 Nature and contents of container

Boxes with 10, 30, 50, 100 and 500 tablets in pvc/foil blister strips.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
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United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 17780/0221

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