SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vasran XL 10 mg prolonged-release tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alfuzosin hydrochloride.

Excipients with known effect: lactose anhydrous
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white, round, uncoated, biconvex tablets with flattened edges, debossed with ‘RY 10’ on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

As an adjunct therapy in connection with catheterisation in acute urinary retention (AUR) related to BPH.

4.2 Posology and method of administration

Posology

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

AUR: One 10 mg tablet daily after a meal to be taken from the first day of catheterisation and continued beyond catheter removal unless there is a relapse of acute urinary retention or disease progression.

Elderly (over 65 years) and patients with renal impairment
Based on pharmacokinetic and clinical safety data, older people and patients with renal insufficiency (creatinine clearance ≥30 ml/min) can be treated with the usual dose.
Due to lacking clinical safety data.
Alfuzosin 10 mg should not be given to patients with severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4).

Hepatic insufficiency:
Alfuzosin, given as 10 mg prolonged-release tablets are contraindicated in patients with hepatic insufficiency. 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.

Method of administration

For oral use.
The tablet should be swallowed 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).

4.3 Contraindications

- Hypersensitivity to the active substance or to any one of the excipients listed in section 6.1
- History of orthostatic hypotension
- Combination with other alpha-1 receptor blockers
- Hepatic insufficiency.

4.4 Special warnings and precautions for use

The patient should be examined before commencement of therapy with alfuzosin to exclude the presence of other conditions that can produce similar symptoms to those of BPH. Before starting and regularly during treatment, examination with rectal touch and, if necessary, prostate specific antigen (PSA) should take place.

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

Alfuzosin should be given with caution to patients who are being treated with antihypertensive medications or nitrates.
Blood pressure should be monitored at the start 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). Elderly patients (especially the patient over 75 years of age) and patients receiving medication for cardiovascular disease are at the greatest risk of (orthostatic) hypotension. Blood pressure should be carefully monitored in these patients. In some subjects postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases the patient should rest lying down until the symptoms have completely disappeared. These effects are transient, occur at the start of the treatment and usually do not require the treatment to be stopped. The patient should be warned that these symptoms may possibly occur.

In coronary patients the specific treatment for coronary insufficiency should be continued. If angina pectoris recurs the treatment with alfuzosin should be discontinued.
As with all alpha-1-receptor 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 CYP3A 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.

Like other alpha-1-receptor blockers, alfuzosin is associated with priapism. If not treated properly, this side effect may lead to permanent tissue damage (including necrosis and/or gangrene) and impotence. If priapism occurs, the patient should seek immediate medical assistance to determine the severity of the side effect and the need for observation and/or treatment.

Use with PDE-5 inhibitors: Concomitant use of alfuzosin with a phosphodiesterase-5 inhibitor (e.g. sildenafil, tadalfil and vardenafil) may cause symptomatic hypotension in some patients (see section 4.5).
To reduce the risk of developing orthostatic hypotension, patients should be stabilized on alpha-blocker therapy before initiating therapy with a phosphodiesterase-5 inhibitor. In addition, it is recommended to start treatment with a phosphodiesterase-5 inhibitor at the lowest possible dose.

Patients should be warned that the tablet should be swallowed whole. Other methods of administration such as crunching, crushing, grinding, pounding to powder or chewing the tablets should be prohibited. These actions may lead to inappropriate release and absorption of the drug with the risk of early side effects.

As there are no clinical safety data available in patients with severe renal impairment (creatinine

clearance < 30ml/min), Alfuzosin 10 mg prolonged-release tablets should not be administered to this patient group.

This product contains lactose. Patients with rare hereditary conditions such as galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

General anaesthetics: administration of general anaesthetics to a patient using alfuzosin may lead to profound hypotension. It is recommended that the tablets be withdrawn 24 hours before surgery.

Combinations contra-indicated:

- Concomitant use with alpha-1-receptor blockers (see section 4.3

  Contraindications)

Concomitant use not recommended:

- potent CYP3A4 inhibitors such as itraconazole, ketoconazole, voriconazole, posaconazole, protese inhibitors (such as bocéprévir, nelfinavir, ritonavir and telaprevir), clarithromycin, erythromycin,telithromycin, cobicistat and nefazodone since alfuzosin blood levels may be increased (see section 4.4).

Combinations subject to precautions for use:

- patients being treated with alfuzosin must be haemodynamically stable before treatment with a phosphodiesterase-5 inhibitor (sildenafil, tadalafil, vardenafil) is initiated.

Combinations to be taken into account:

- Antihypertensive drugs (see Section 4.4 Special warnings and precautions for use)
- nitrates (see Section 4.4 Special warnings and precautions for use)
- dapoxetine (due to the increase of undesirable effects, such as dizziness or syncope).

The dose recommendation should be taken into account due to the possibility of hypotension (See section 4.4).

Repeated 200 mg daily dosing of the potent CYP3A4 inhibitor ketoconazole, for 7 days resulted in an increase in C_{max} (2.11-fold) and AUC_{last} (2.46-fold) of alfuzosin when administered as a single dose under fed conditions. Other parameters such as t_{max} and $t_{1/2}$ were not modified.

Repeated 400mg daily dosing of Ketoconazole for 8 days increased the Cmax of alfuzosin by 2.3-fold and AUC_{last} and AUC of alfuzosin by 3.2-fold and 3.0-fold respectively (see Section 5.2).

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 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on the ability to drive and use machines

There are no data available on the effect on driving vehicles or using machines.
Undesirable effects such as vertigo, dizziness and asthenia can occur particularly at the start of the treatment. This should be taken into account when driving vehicles or using machines.

4.8 Undesirable effects

The frequency of the adverse reactions listed below are defined using the following classification:
very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1000 to ≤1/100); rare (>1/10 000 to ≤1/1000); very rare (≤1/10 000), not known (cannot be estimated from the available data)

System Organ Class	Frequency			
	Common	Uncommon	Very rare	Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders				Neutropenia, Thrombocytopenia
Nervous system disorders	Weakness, malaise, headache, faintness/dizziness	Drowsiness, vertigo		
Eye disorders		Vision abnormal		Intraoperative floppy iris syndrome (See section 4.4)

System Organ Class	Frequency			
	Common	Uncommon	Very rare	Not Known (cannot be estimated from the available data)
Cardiac disorders		Tachycardia, palpitations, syncope	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), flushing		
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Gastrointestinal disorders	Nausea, abdominal pain, dry mouth	Diarrhoea		Vomiting
Hepatobiliary disorders			Hepatotoxicity	Hepatocellular injury, cholestatic liver disease.
Skin and subcutaneous tissue disorders		rash, pruritus	Urticaria, angio-oedema	
Reproductive system and breast disorders				Priapism
General disorders and administration site conditions	Asthenia	Oedema, chest pain (see section 4.4)		

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.

4.9 Overdose

In case of overdose, the patient should be admitted to hospital, kept in supine position, and conventional treatment for hypotension should take place.
In case of significant hypotension, the appropriate corrective treatment may be

a vasoconstrictor that acts directly on the vascular muscle fibres.
Alfuzosin is not easily dialysed due to the strong degree of protein binding.

Gastric flushing is possible, followed by administration of activated charcoal and a laxative.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

In benign prostate hyperplasia, in addition to the size of the prostate, the sympathetic nervous system also plays an important role in the development of symptoms. Histologically, benign prostatic hyperplasia is characterized in particular by a hyperplasia of the stromal component. This stroma consists for about 30% of smooth muscle tissue. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by alpha-1-receptors. Stimulation of these alpha-receptors results in increasing the tension of the smooth muscles of the trigone of the urine bladder, the urethra and the prostate gland, consequently, increasing the resistance of the urine flow.

Alfuzosin is an orally active quinazoline derivative. It is a selective antagonist of postsynaptic alpha-l-receptors. *In vitro* studies have shown that the alfuzosin acts selectively on alpha-1-receptors in the trigone of the urine bladder, the urethra and the prostate gland.

In vivo, animal studies have shown that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition. Moreover, alfuzosin has shown to have a functional uroselectivity. Clinical research has shown that symptoms of the lower urinary tract related to obstruction due to prostatic hyperplasia are improved. Alfuzosin can cause a mild drop in blood pressure. An improvement in the urine flow can be expected after 1 to 2 days.

Urodynamic studies (short-term) have shown that alfuzosin improves the bladder outlet resistance; there is an increase in urine flow with a simultaneous decrease in bladder pressure.

In placebo-controlled studies, where the peak flow rate (PFR) was measured 10-24 hours after intake, indicates that PFR in the alfuzosin-treated patient group increases from 9.4 (SD 1.9) to 11.7 (3.9) ml / s. In the placebo group there is an increase from 9.2 (2.0) to 10.6 (3.3) ml / s ($p = 0.03$). From this it is concluded that the efficacy on the urine flow continues for up to 24 hours after intake.

Alfuzosin may cause moderate antihypertensive effects.

In the ALFAUR study, the effect of alfuzosin on resumption of voiding was evaluated in 357 men aged over 50 years, with a first painful episode of acute urinary retention (AUR) linked to benign hypertrophy of the prostate (BPH) with a voiding residue of between 500 and 1500 ml when the catheter is placed and during the first hour after it. In this multicenter, randomized, double-blind, study in two parallel groups, comparing 10 mg / day of alfuzosin LP with a placebo, the evaluation of the resumption of voiding was carried out 24 hours after the withdrawal of the catheter, in

the morning, after at least two days of treatment with alfuzosin. Treatment with alfuzosin significantly increased (p = 0.012) the rate of resumption of voiding after catheter removal, in patients who had a first episode of AUR, i.e. 146 repetitions of voiding (61.9%) in the alfuzosin group versus 58 (47.9%) in the placebo group.

Paediatric population
There is no indication for the use of alfuzosin in children from 2 - 16 years old (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 H_2O) of neurologic origin. The dose in these patients was 0.1 mg/kg/day or 0.2 mg/kg/day. Adapted paediatric formulations were used.

5.2 Pharmacokinetic properties

Prolonged-release formulation:

The mean value of the relative bioavailability (AUC) is 104.4 % versus the immediate release formulation 2.5 mg (three times a day) in middle-aged healthy volunteers. The maximum plasma concentration (C_{max}) 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 the optimal pharmacokinetic profile is obtained when Alfuzosin 10 mg Prolonged-release tablets 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 following administration with concentrations above 8.1 ng/ml (C_{av}) for 11 hours.
Compared to healthy middle aged volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly patients.
Compared to subjects with normal renal function, mean C_{max} and AUC values are moderately increased in patients with renal impairment. The apparent elimination half-life is unchanged. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore, this does not necessitate a dosing adjustment.

Alfuzosin is well absorbed. The binding of alfuzosin to plasma proteins is about 90%.
Alfuzosin undergoes extensive metabolism by the liver.
Only 11% is excreted unchanged in the urine. The majority of the inactive metabolites 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

Lactose anhydrous
Colloidal anhydrous silica (E551)
Povidone (E1201)
Talc (E553B)
Magnesium stearate (E572)
Hypromellose (E464)
Hydroxypropyl cellulose (E463)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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-aluminium blister.

Pack sizes: 10, 30 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy (UK) Limited
5th floor, Hyde Park, Hayes 3
11 Millington Road
Hayes, UB3 4AZ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0567

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/11/2008

10 DATE OF REVISION OF THE TEXT

26/09/2022