SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alfuzosin Stada 5 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg alfuzosin hydrochloride.

Excipients with known effect:
Each tablet contains 55 mg Lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, bevelled-edge, uncoated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe functional 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.
The tablet should be taken immediately after the same meal each day.

Adults
1 prolonged-release tablet 5 mg twice daily – (morning and evening), not exceeding 10 mg/day. The first dose should be taken at bedtime.

Elderly (over 65 years)
1 prolonged-release tablet 5 mg once daily. The first dose should be taken at bedtime. The dose may be increased to 10 mg daily if it is well tolerated and if additional efficacy is required, given as 1 prolonged-release tablet 5 mg twice daily. Pharmacokinetic and clinical safety data demonstrate that no dose reduction is necessary to elderly patients.

Reduced renal function
Mild to moderate renal insufficiency:
1 prolonged-release tablet 5 mg daily. The first dose should be taken at bedtime.
The dose is to be adjusted according to clinical response.

Severe renal insufficiency:
Alfuzosin Stada 5 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 Stada given as 5 mg prolonged release tablets are contraindicated in patients with hepatic insufficiency. After careful medical consideration, a preparation containing a lower dose of alfuzosin hydrochloride might be considered appropriate. Refer to the corresponding product information for dosing instructions.

4.3 Contraindications

- Hypersensitivity to alfuzosin, other quinazolines (e.g. terazosin, doxazosin, prazosin) or to any of the excipients listed in section 6.1.
- Conditions with orthostatic hypotension.
- Hepatic insufficiency.
- Combination with other alpha-1 receptor blocking agents.

4.4 Special warnings and precautions for use

Alfuzosin should be given with caution to patients who are on antihypertensive medication or nitrates. Blood pressure should be monitored regularly, especially at the beginning of treatment.

In some patients postural hypotension may develop, with or without symptoms (dizziness, fatigue, asthenia, sweating) within a few hours of administration.
In such cases, the patient should lie down until the symptoms have totally disappeared.

These effects are usually temporary. They occur at the start of the treatment and normally do not prevent continuation the treatment. Patients should be warned about the possibility of these effects.

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.

There is a risk of cerebral ischemic disorders in patients with symptomatic or asymptomatic pre-existing cerebral circulatory disturbances, due to the fact that hypotension may develop following alfuzosin administration (see section 4.8).

Caution should be exercised when alfuzosin is administered to patients who have responded with pronounced hypotension to other alpha-1 receptor blockers.

Treatment should be initiated gradually in patients with hypersensitivity to other alpha-1 receptor blockers.

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

In cardiac patients the treatment of coronary insufficiency should continue taking into account that the concomitant administration of nitrates and alfuzosin may increase the risk of occurrence of hypotension. Alfuzosin should be discontinued if angina pectoris recurs or worsens.

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.

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

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 (see section 4.8).

Patients should be instructed to swallow the tablet whole. Other methods of administration such as crushing, powdering or chewing the tablet, should be avoided. Incorrect administration may lead to undesirable release and absorption of the active substance with a risk of early undesirable effects.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Contra-indicated combinations:
Alpha-1 receptor blocking agents (see section 4.3).

Combinations requiring caution:
- Alfuzosin blood levels are increased by potent CYP3A4 inhibitors like ketoconazole, itraconazole and ritonavir.
- Antihypertensive agents (see section 4.4).
- Nitrate preparations (see section 4.4).

Concomitant use with antihypertensive agents or nitrates increases the risk of hypotension. See also section 4.4.

Administration of an anaesthetic to a patient being treated with alfuzosin may lead to profound hypotension. It is recommended that the tablets be withdrawn 24 hours before surgery.

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

4.6 Fertility, pregnancy and lactation

Due to the type of indication this section is not applicable

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse reactions such as vertigo, dizziness or asthenia may occur, especially at the beginning of treatment. This should be taken into account when driving or using machines.

4.8 Undesirable effects

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

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. 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); frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Frequency not known: Neutropenia, thrombocytopenia.

Nervous system disorders
Common: tiredness, faintness/dizziness, headache, vertigo.
Uncommon: Drowsiness.
Frequency not known: Cerebral ischemic disorders in patients with underlying cerebrovascular disturbances (see section 4.4)

Eye disorders
Uncommon: Visual disturbances.
Frequency not known: Intraoperative floppy iris syndrome (IFIS) (see section 4.4).

Cardiac disorders
Uncommon: Tachycardia, palpitations, syncope (initially above all with too high a dose or if treatment is started again after a short interruption of therapy).
Very rare: Aggravation or recurrence of angina pectoris (see section 4.4), angina pectoris in patients with pre-existing coronary artery disease.
Frequency not known: Atrial fibrillation.

Respiratory, thoracic an mediastinal disorders
Uncommon: Rhinitis.

Gastrointestinal disorders
Common: abdominal pain, nausea, dyspepsia, diarrhoea, dry mouth.
Uncommon: Vomiting.

Hepato-biliary disorders
Very rare: Hepatotoxicity.
Frequency not known: Hepatocellular injury, cholestatic liver disease.

Skin and subcutaneous tissue disorders
Uncommon: Rash (urticaria, exanthema), pruritus.
Very rare: Angioedema.

Vascular disorders
Common: Postural hypotension (initially, primarily with too high a dose or if treatment is resumed after a short interruption of therapy) (see section 4.4).

Renal and urinary disorders
Uncommon: Urinary incontinence.
Very rare: Isolated cases of priapism were reported.

General disorders and administration site conditions
Common: Asthenia, malaise.
Uncommon: Oedema, flushes, chest pains.

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 [to be completed nationally].

4.9 Overdose

In case of overdose, the patient should be admitted to hospital and given normal support therapy for hypotension. The appropriate antidote is a vasoconstrictor that acts directly on the smooth muscle in the blood vessels such as noradrenaline.

Gastric lavage and/or administration of medicinal charcoal should be considered. Alfuzosin is difficult to dialyse, due to the high degree of protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists.
ATC code: G04C A01

Alfuzosin, which is a racemate, is an orally acting quinazoline derivative, which selectively blocks post-synaptic alpha-1 receptors. *In vitro* studies have confirmed the selectivity of Alfuzosin for alpha-1 receptors located in the prostate, the trigonum vesicae and the prostatic urethra. The clinical symptoms in BPH are not only related to the size of the prostate, but also to sympathomimetic nerve impulses, which by stimulating the post-synaptic alpha receptors increase the tension of the smooth muscle of the lower urinary tract. Treatment with alfuzosin relaxes this smooth muscle, thus improving the urinary flow.

Clinical evidence of uroselectivity has been demonstrated by clinical efficacy and a good safety profile in men treated with alfuzosin, including the elderly and patients with hypertension. Alfuzosin may cause moderate anti-hypertensive effects.

In humans, alfuzosin improves the voiding of water by reducing urethral muscle tone, with reduction in the resistance to outflow from the bladder, making it easier to empty the bladder

A lower frequency of acute urinary retention has been observed in patients treated with alfuzosin than in untreated patients.

In placebo-controlled studies of BPH patients, alfuzosin has:
- significantly increased maximum urinary flow (Q_{max}) in patients with Q_{max} <15 ml/s by an average 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.

These urodynamic effects lead to an improvement of Lower Urinary Tract Symptoms (LUTS), i.e. filling (irritative) as well as voiding (obstructive) symptoms, which has been clearly demonstrated.

5.2 Pharmacokinetic properties

Alfuzosin has linear pharmacokinetic properties within the therapeutic dose range. The peak plasma concentration is reached approx. 3 hours after administration. The kinetic profile is characterised by large interindividual fluctuations in plasma concentrations. Absorption is increased when the medication is administered after a meal.

Absorption
After the first dose (fed) the mean maximum plasma concentration was 8.71ng/ml. AUCinf was 93.5 ng x h/ml (fed), and tmax was 5.46 h (fed).Under steady state conditions (fed) the

mean AUC over the dosing interval (AUCτ) was 145 ng x h/ml, mean Cmax was 17.0 ng/ml and Cmin was 7.90 ng/ml.

Distribution
The binding rate to plasma protein is approx. 90%. Alfuzosin´s distribution is 2.5 l/kg in healthy volunteers. It has been shown to preferentially distribute in the prostate in comparison to plasma.

Elimination
The apparent elimination half-life is approx5 hours Alfuzosin is extensively metabolised in the liver (through various routes), metabolites are eliminated via renal excretion and probably also via biliary excretion. Of an oral dose, 75-91% is excreted in the faeces; 35% in unmodified form and the rest as metabolites, which indicates some degree of biliary excretion. About 10% of the dose is excreted in the urine in its unmodified form. None of the metabolites is pharmacologically active.

Renal or hepatic impairment
Volume of distribution and clearance increase with reduced renal function, possibly owing to a decreased degree of protein binding. The half-life, however, is unchanged. In patients with severe hepatic insufficiency the half-life is prolonged. The peak plasma concentration is doubled, and the bioavailability increases in relation to that in young, healthy volunteers.

Elderly patients
Oral absorption is more rapid, and AUC values are greater in elderly (> 75 years) than in younger subjects. The increase in plasma concentration may be explained by a reduction in the metabolic capacity of the elderly. Oral bioavailability is somewhat higher than in younger subjects. The elimination half-life remains unchanged.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or reproductive toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose (E 464)
Povidone K25
Magnesium stearate (E 470b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 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 blister.

10, 56, 60 and 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse. 2-18
61118 Bad Vilbel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

19365

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 April 2004/9 February 2009

10. DATE OF REVISION OF THE TEXT

2015-04-08