SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alfuzosin Sandoz 10 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg alfuzosin hydrochloride.

Excipients with known effect:
Each tablet contains 8 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, approximately 10 mm in diameter .

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.

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

Older people (over 65 years)
As adults. Pharmacokinetic and clinical safety data demonstrate that dose reduction is usually not necessary to elderly patients.

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

Severe renal insufficiency (creatinine clearance < 30ml/min):
Alfuzosin Sandoz 10 mg should not be given to patients with severely impaired renal function as there are no clinical safety data available for this patient group (see section 4.4).

Hepatic insufficiency
Alfuzosin Sandoz given as 10 mg prolonged release tablets are contraindicated in patients with hepatic insufficiency. Preparations containing a low dose 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 the paediatric population.

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 Sandoz 10 mg 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. Alfuzosin Sandoz should be given with caution to patients treated with antihypertensive medicinal products 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, sweating) within a few hours of administration. This effect is transient, occurs at the beginning of treatment, and does not usually prevent the continuation of treatment. The patient should be warned of the possible occurrence of such events. In such cases, the patient should lie down until the symptoms have completely disappeared.

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.

Caution should be exercised when alfuzosin is administered to patients who have responded with pronounced hypotension to other alpha$_1$-blockers.

Treatment should be initiated gradually in patients with hypersensitivity to other α_1-receptor blockers.

As with all α_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. If angina pectoris recurs or worsens, treatment with alfuzosin should be discontinued.

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.

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.

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 α_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 α_1-blockers, as IFIS may lead to increased procedural complications.

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.

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

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).
- Nitrates (see section 4.4).

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

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

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

Ketoconazole: Repeated 200 mg daily dosing of ketoconazole, for seven days resulted in a 2.1 fold increase in C_{max}. The increase in alfuzosin C_{max} and $AUC_{(last)}$ following repeated 400 mg daily administration of ketoconazole was 2.3-fold, and 3.2-fold, respectively.
A 2.5 fold increase in exposure of alfuzosin was seen when administered under fed conditions. (see section 5.2).

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

There are no data available on the effect on driving vehicles.

Adverse reactions such as vertigo, dizziness and asthenia may occur, especially 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.

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 (> 1/1000 to < 1/100); rare (> 1/10 000 to < 1/1000); very rare (< 1/10 000); not known (cannot be estimated from the available data)

Blood and lymphatic system disorders
Not known: Neutropenia, thrombocytopenia

Nervous system disorders
Common: Headache, faintness/dizziness.
Uncommon: Vertigo, drowsiness.

Eye disorders
Not known: Intraoperative Floppy Iris Syndrome (see section 4.4)

Cardiac disorders
Uncommon: Syncope (initially above all with too high a dose or if treatment is started again after a short interruption of therapy), postural hypotension (see section 4.4) (initially above all with too high a dose or if treatment is started again after a short interruption of therapy), tachycardia.
Very rare: Angina pectoris predominantly in patients with pre-existing coronary artery disease (see section 4.4).
Not known: Atrial fibrillation

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis.

Gastrointestinal disorders
Common: Nausea, abdominal pain, dyspepsia.
Uncommon: Diarrhoea, dry mouth, vomitting.

Hepatobiliary disorders
Not known: Hepatocellular injury, cholestatic liver disease.

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

Reproductive system and breast disorders
Not known: Priapism

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

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 overdosage, the patient should be hospitalized, kept in the supine position, and conventional treatment of hypotension such as addition of fluids and vasopressor drugs 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 highly protein-bound, therefore, dialysis may not be of benefit.

Active charcoal should be administered following possible gastric lavage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in benign prostate hypertrophy, alpha-adrenoreceptor antagonists.
ATC code: G04C A01

Mechanism of action
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 the substance on alpha-1 receptors in the trigone of the urine bladder, the urethra and the prostate gland. 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 efficacy and safety
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 man, alfuzosin improves the voiding parameters by reducing urethral tone and bladder outlet resistance, and thus facilitates bladder emptying.

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.

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 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 shows linear pharmacokinetics in the therapeutic dosage range. The kinetic profile is characterised by large interindividual fluctuations in plasma concentrations.

Absorption

The mean relative bioavailability of Alfuzosin Sandoz compared to the immediate release formulation is 104% in healthy volunteers. The maximum plasma concentration is achieved 9 hours after the administration. The apparent elimination half-life is 9 hours. Studies have shown consistent pharmacokinetics when the product is administered after a meal. Under fed conditions, mean C_{max} and C_{min} values are 14 (5.6) and 3 (1.6) ng/ml respectively. Mean AUC_{0-24} is 194 (75) ng * h/ml.

Distribution
Plasma protein binding is approximately 90 %. The volume of distribution of alfuzosin in healthy volunteers is 2.5 l/kg. It has been shown to preferentially distribute in the prostate in comparison to plasma.

Elimination
The kinetic profile is characterised by large inter-individual fluctuations (sevenfold) in plasma concentrations. Mean plasma half-life of alfuzosin is approximately 5 hours (1-10 hours). Alfuzosin is extensively metabolised in the liver (several 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 % as unchanged substance and the rest as metabolites, indicating some degree of biliary excretion. About 10 % of the dose is excreted in urine as unchanged substance. None of the metabolites has any pharmacological activity.

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. 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. Due to a lack of clinical safety data for patients with severe renal insufficiency, Alfuzosin Sandoz 10 mg prolonged-release tablets should not be administered to this patient group (see sections 4.2 and 4.4). 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. Alfuzosin Sandoz 10 mg prolonged-release tablets are contraindicated in hepatic insufficiency (see section 4.3).

Elderly patients
Immediate-release tablets: Oral absorption is more rapid, and bioavailability (AUC) is greater in elderly (>75 years) than in younger subjects.
Prolonged-release tablets: Compared to healthy middle-aged volunteers, the peak plasma concentration (Cmax) and bioavailability (AUC) are not increased in elderly patients.
The elimination half-life (t½) remains unchanged.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotxicity, carcinogenic potential, toxicity to reproduction.

Published nonclinical studies on cardiovascular safety pharmacology showed that alfuzosin increases plateau potential and prolongs action potential duration (rabbit purkinje fiber) and QT interval (isolated rabbit heart) at clinically relevant concentrations.
Increase in sodium current ($hNa_v1.5$) by alfuzosin was proposed to be the mechanism of the altered cardiac electrophysiology.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Hypromellose Povidone K25

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PVC/PVDC-aluminium blister.

10, 20, 30, 50, 60, 60x1, 90, 100 and 180 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

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

2016-11-25