SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Alfuzosin Hydrochloride 2.5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5 mg alfuzosin hydrochloride

Excipient with known effect: lactose monohydrate (78.75mg)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Alfuzosin hydrochloride 2.5 mg film-coated tablets are white, round, slightly arched tablets debossed "LFN" on one side and "2.5" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of the functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Alfuzosin Hydrochloride tablets should be swallowed whole. The first dose should be given just before bedtime.

Adults
The usual dose is one tablet three times daily. The dose may be increased to a maximum of 4 tablets (10mg) per day depending on the clinical response.

Older people and treated hypertensive patients
As a routine precaution when prescribing alfuzosin to older patients (aged over 65 years) and the treated hypertensive patient, the initial dose should be 1 tablet in the morning and 1 tablet in the evening.

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.

Renal insufficiency
In patients with renal insufficiency, as a precaution, it is recommended that the dosing be started at alfuzosin hydrochloride 2.5 mg twice daily adjusted according to clinical response.

Hepatic insufficiency
In patients with mild to moderate hepatic insufficiency, it is recommended that the therapy should commence with a single dose of alfuzosin hydrochloride 2.5 mg/day to be increased to alfuzosin hydrochloride 2.5 mg twice daily according to clinical response.

Alfuzosin 2.5 mg tablets are contraindicated in patients with severe hepatic insufficiency (see section 4.3).

4.3 Contraindications

Hypersensitivity to the active substance, other quinazolines (e.g. terazosin, doxazosin) or to any of the excipients listed in section 6.1.
A medical history of orthostatic hypotension.
In combination with other α1-blockers and/or dopamine receptor agonists.
Severe hepatic insufficiency.

4.4 Special warnings and precautions for use

Alfuzosin should be administered with care to patients with a medical history of orthostatic hypertension or pronounced hypotension, patients who are on antihypertensive medication or nitrates and elderly patients. A reduction in blood pressure may arise in individual cases Blood pressure should be monitored at the start of treatment.

In cases of postural hypotension the patient should lie or sit down until the symptoms have disappeared. In some subjects postural hypotension may develop, with or without symptoms (dizziness, fatigue, sweating) within a few hours following administration. These effects are 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.

Care should be taken when alfuzosin is administered to patients who have had a pronounced hypotensive response to another alpha1-blocker.

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 alpha1-receptor blockers, alfuzosin should be used with caution in patients with acute cardiac failure (including high output cardiac failure cardiac failure due to pulmonary embolism or pericardial effusion and in the patients with lung oedema due to mitral or tricuspidal stenosis).

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.

The patient should be examined prior to treatment with alfuzosin to exclude other conditions, which may cause the same symptoms as benign prostatic hyperplasia. A digital rectal examination should be performed prior to treatment and regularly during treatment. A prostate specific antigen (PSA) test should also be carried out if required.

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. 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 opthalmic surgeon in advance of surgery.

Alfuzosin should not be used in patients suffering from incontinence due to overflow, anuria or prolonged renal insufficiency.

Excipent(s)

Lactose
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interactions with other medicinal products and other forms of interaction

Combinations contraindicated
- Alpha-1 receptor blocking agents and dopamine-receptor agonists

Combinations to be taken into account
- Antihypertensive drugs (see section 4.4)
- Nitrate preparations (see section 4.4)
- Potent CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir, clarithromycine, erythromycine) since alfuzosin blood levels are increased

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 pharmacokinetic interactions have been observed between alfuzosin and the following agents in healthy volunteers: warfarin and digoxin.

4.6 Fertility, pregnancy and lactation

Due to the indication area this section is not applicable.

4.7 Effects on ability to drive and use machines

There are no data available on the effect on ability to drive or use machines. Adverse reactions such as, vertigo, dizziness or asthenia may occur essentially at the beginning of treatment. This has to be taken into consideration when driving vehicles and operating machines.

4.8 Undesirable effects

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); very rare (≤1/10,000). not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	
Not known	neutropenia
Nervous system disorders	
Common	faintness/dizziness, headache, vertigo
Uncommon	syncope, drowsiness
Eye disorders	
Uncommon	vision abnormal
Not known	intraoperative floppy iris syndrome
Cardiac disorders	
Uncommon	tachycardia, palpitations
Very rare	angina pectoris in patients with pre-existing coronary artery disease
Not known	atrial fibrillation
Vascular disorders	
Common	hypotension (postural)* (see section 4.4)
Uncommon	flushing
Respiratory, thoracic and mediastinal disorders	
Uncommon	rhinitis
Gastrointestinal disorders	
Common	nausea, abdominal pain, diarrhea, dry mouth
Not known	vomiting
Hepatobiliary disorders	
Very rare	hepatotoxicity
Not known	hepatocellular injury, cholestatic liver disease
Skin and subcutaneous tissue disorders	
Uncommon	rash, pruritus
Very rare	urticaria, angioedema
Renal and urinary disorders	
Uncommon	incontinence
Reproductive system and breast disorders	
Not known	priapism
General disorders and administration site conditions	
Common	asthenia, malaise
Uncommon	oedema, chest pain

*initially, primarily with too high a dose or if treatment is resumed after a short interruption of therapy

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 hospitalized, kept in a 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 vascular muscle fibres.
Alfuzosin is highly protein bound, therefore, dialysis may not be of benefit. Gastric lavage is a possibility followed by administration of activated carbon and a laxative.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: alpha adrenoreceptor antagonist.
ATC code: G04CA01

Alfuzosin is an orally active quinazoline derivative. It is a selective, peripherally acting antagonist of post synaptic 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 α-adrenoceptors. Activation of α_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} 15ml/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.

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

Alfuzosin is absorbed well: the mean biological availability amounts to 64%. Maximum plasma concentrations are generally achieved in 0.5 – 6 hours. The kinetics are linear within the therapeutic dosage. The kinetic profile is characterised by large inter-individual variations in plasma concentrations. The half-life is 3 – 5 hours. The plasma-protein binding of alfuzosin is approximately 90%. Alfuzosin is metabolised by the liver and is primarily excreted in urine and faeces. None of the metabolites found in humans has a pharmacodynamic action. Theharmacokinetic profile is not influenced by concurrent ingestion of food.

Absorption
Absorption in patients older than 75 years is more rapid and plasma levels are higher. Biological availability may be higher, while for some patients the distribution volume is reduced. The elimination half-life remains unchanged.

Distribution
The distribution volume and metabolic clearance of alfuzosin is increased with renal insufficiency through an increase of the free fraction. Chronic renal insufficiency, even where this is severe (creatinine clearance between 15 and 40 ml/minute) is not negatively influenced by alfuzosin.

A twofold increase of C_{max} levels and a threefold increase in the AUC have been observed in patients with severe hepatic insufficiency. The biological availability is increased in comparison with healthy volunteers. The pharmacokinetic profile of alfuzosin is not influenced by chronic cardiac insufficiency.

Biotransformation
CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin (see section 4.5)

5.3 Preclinical safety data

In vitro, alfuzosin prolonged the action potential duration and QT interval duration at a clinically relevant concentration.

No other data of therapeutic relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose monohydrate
Povidone
Sodium starch glycolate
Cellulose, microcrystalline
Magnesium stearate

Tablet coating:

Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Macrogol
Glycerol triacetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

PVC/PVDC/Aluminium blisters available in packs containing 30, 50, 60, 90, 100 tablets.
Also available as hospital packs of 50 x 1 tablet

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No specific requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1120

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