

1. NAME OF MEDICINAL PRODUCT

Alfuzosin Hydrochloride 2.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 2.5 mg alfuzosin hydrochloride

Excipients: lactose monohydrate (78.75mg)

For a 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.

Elderly and treated hypertensive patients

As a routine precaution when prescribing alfuzosin to elderly 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.

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.

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

4.3 Contraindications

Hypersensitivity to alfuzosin, other quinazolines (e.g. terazosin, doxazosin) or any of the excipients;

A medical history of orthostatic hypotension.

In combination with other α 1-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 hypotension or pronounced hypotension during use of other alpha₁ receptor blockers. Dosage advice should be taken into consideration for specific groups of patients (elderly patients, concurrent administration with other anti-hypertensives or nitrates). Blood pressure should be monitored at the start of treatment. A reduction in blood pressure may arise in individual cases. In cases of orthostatic hypotension the patient should lie or sit down until the symptoms have disappeared. These symptoms are usually transient in nature and may arise at the start of treatment. In general, these symptoms do not interfere with the continuation of treatment. The patient should be informed of the occurrence of symptoms such as these. Treatment of coronary insufficiency should be continued. Treatment with alfuzosin should be discontinued if the angina pectoris returns or worsens.

As with all alpha blocking medicines alfuzosin should be administered with care in patients with the following acute cardiac signs and symptoms:

- lung oedema due to mitral or tricuspidal stenosis,
- high output cardiac failure,
- cardiac failure due to pulmonary embolism or pericardial effusion

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 ophthalmic surgeon in advance of surgery.

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

This medicinal 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 Interactions with other medicinal products and other forms of interaction

Combinations not recommended

- Alpha-1 receptor blocking agents and dopamine-receptor agonists
Increased hypotensive effect. Risk of severe orthostatic hypotension.
- Potent CYP3A4 inhibitors (Ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin)

Combinations to be taken into account

- Antihypertensive drugs
antihypertensive effect and risk of increased hypotension (cumulative effect).
- Nitrate preparations

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 Pregnancy and lactation

This section is not applicable given the therapeutic indications.

4.7 Effects on ability to drive and use machines

No data are available concerning the effect on ability to drive or use machines. Side-effects such as, vertigo, dizziness or asthenia may occur, in particular, at the start of treatment. This should be taken into consideration when driving vehicles or using 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 ($\geq 1/10$); common ($>1/100$ to $<1/10$); uncommon ($>1/10000$ to $\leq 1/1000$); very rare ($\leq 1/10000$).

	Frequency		
	Common	Uncommon	Very rare
Nervous system disorders	Dizziness/tiredness, headache vertigo	Drowsiness,	
Eye disorders		Visual disturbances	
Cardiac disorders	Postural hypotension (initially, primarily with too high a dose or if treatment is resumed after a short interruption of therapy).	tachycardia, palpitations, syncope (in particular at the beginning of the treatment),	New onset, aggravation or recurrence of angina pectoris (see section 4.4)
Respiratory, thoracic and medicinal disorders		rhinitis	
Gastrointestinal disorders	nausea, abdominal pain, diarrhoea, dry mouth		
Skin and subcutaneous tissue disorders		Skin rashes, pruritus, urticaria,	angioneurotic oedema
General disorders and administration site conditions	Asthenia, malaise	flushes, oedema, chest pains (see section 4.4)	
Renal and urinary disorders		Incontinence	

Although only reported in isolated cases with alfuzosin, occurrence of priapism can not be excluded as it is generally accepted as being attributable to all other alpha adrenoreceptor blockers.

4.9 Overdose

In cases of an overdose the patient should be maintained in a lying position whilst conventional treatment for hypotension is administered. Alfuzosin is not readily dialysed as a result of the high

protein binding. 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 α_1 -adrenoceptors 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 (Qmax) in patients with Qmax 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.

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. The pharmacokinetic profile is not influenced by concurrent ingestion of food.

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.

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.

Metabolic interactions: 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, Brampton Road, Hampden Park, Eastbourne, East Sussex, BN22 9AG

8. MARKETING AUTHORISATION NUMBER

PL 00289/1120

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION **23rd April 2008**

10. DATE OF REVISION OF THE SUMMARY

23/04/2008