ALFUSIN Tablets (Alfuzosin hydrochloride)

Composition

Each film-coated extended-release tablet contains:
Alfuzosin hydrochloride Ph.Eur ..... 10 mg

Dosage Form

Extended-release tablet

Pharmacology

Pharmacodynamics

Mechanism of action
Alfuzosin is a selective antagonist of post-synaptic alpha$_1$-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

Alfuzosin exhibits selectivity for alpha adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH.

Cardiac Electrophysiology
The effect of 10 mg and 40 mg alfuzosin on QT interval was evaluated in a double-blind, randomized, placebo and active-controlled (moxifloxacin 400 mg), 4-way crossover single dose study in 45 healthy white male subjects aged 19 to 45 years. The QT interval was measured at the time of peak alfuzosin plasma concentrations. The 40 mg dose of alfuzosin was chosen because this dose achieves higher blood levels than those achieved with the co-administration of alfuzosin and ketoconazole 400 mg. Table 3 summarizes the effect on uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia, population-specific and subject-specific correction methods) at the time of peak alfuzosin plasma concentrations. No single one of these correction methodologies is known to be more valid. The mean change of heart rate associated with a 10 mg dose of alfuzosin in this study was 5.2 beats/minute and 5.8 beats/minute with 40 mg alfuzosin. The change in heart rate with moxifloxacin was 2.8 beats/minute.

Table 3. Mean QT and QTc changes in msec (95% CI) from baseline at T_{max} (relative to placebo) with different methodologies to correct for effect of heart rate.

Drug/Dose	QT	Fridericia method	Population-specific method	Subject-specific method
Alfuzosin 10 mg	-5.8 (-10.2, -1.4)	4.9 (0.9, 8.8)	1.8 (-1.4, 5.0)	1.8 (-1.3, 5.0)
Alfuzosin 40 mg	-4.2 (-8.5, 0.2)	7.7 (1.9, 13.5)	4.2 (-0.6, 9.0)	4.3 (-0.5, 9.2)

Moxifloxacin* 400 mg	6.9 (2.3, 11.5)	12.7 (8.6, 16.8)	11.0 (7.0, 15.0)	11.1 (7.2, 15.0)

*Active control

The QT effect appeared greater for 40 mg compared to 10 mg alfuzosin. The effect of the highest alfuzosin dose (four times the therapeutic dose) studied did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. There has been no signal of Torsade de Pointes in the extensive post-marketing experience with alfuzosin outside the United States. A separate post-marketing QT study evaluated the effect of the co-administration of 10 mg alfuzosin with a drug of similar QT effect size. In this study, the mean placebo-subtracted QTcF increase of alfuzosin 10 mg alone was 1.9 msec (upperbound 95% CI, 5.5 msec). The concomitant administration of the two drugs showed an increased QT effect when compared with either drug alone. This QTcF increase [5.9 msec (UB 95% CI, 9.4 msec)] was not more than additive. Although this study was not designed to make direct statistical comparisons between drugs, the QT increase with both drugs given together appeared to be lower than the QTcF increase seen with the positive control moxifloxacin 400 mg [10.2 msec (UB 95% CI, 13.8 msec)]. The clinical impact of these QTc changes is unknown.

Pharmacokinetics

The pharmacokinetics of alfuzosin have been evaluated in adult healthy male volunteers after single and/or multiple administration with daily doses ranging from 7.5 mg to 30 mg, and in patients with BPH at doses from 7.5 mg to 15 mg.

Absorption

The absolute bioavailability of alfuzosin hydrochloride 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg alfuzosin hydrochloride under fed conditions, the time to maximum concentration was 8 hours. The C_{max} and AUC_{0-24} were 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng.h/mL, respectively. Alfuzosin hydrochloride exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of alfuzosin hydrochloride administration. Steady-state alfuzosin hydrochloride plasma concentrations are 1.2- to 1.6-fold higher than those observed after a single administration.

Effect of Food

The extent of absorption is 50% lower under fasting conditions. Therefore, alfuzosin hydrochloride should be taken with food and with the same meal each day.

Distribution

The volume of distribution following intravenous administration in healthy male middle-aged volunteers was 3.2 L/kg. Results of *in vitro* studies indicate that alfuzosin hydrochloride is moderately bound to human plasma proteins (82-90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

Metabolism

Alfuzosin hydrochloride undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin hydrochloride is metabolized by three metabolic pathways: oxidation, O-demethylation and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion
Following oral administration of ^{14}C-labelled alfuzosin hydrochloride solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in the faeces and 24% in the urine. Following oral administration of 10 mg alfuzosin hydrochloride, the apparent elimination half-life is 10 hours.

Pharmacokinetics in Special Populations
Renal Impairment: The Pharmacokinetic profiles of alfuzosin 10 mg tablets in subjects with normal renal function (CLCR>80 mL/min), mild impairment (CLCR 60 to 80 mL/min), moderate impairment (CLCR 30 to 59 mL/min), and severe impairment (CLCR max and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment.

Hepatic Impairment: The pharmacokinetics of alfuzosin have not been studied in patients with mild hepatic impairment. In patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), the plasma apparent clearance (CL/F) was reduced to approximately one-third to one-fourth that observed in healthy subjects. This reduction in clearance results in three to four-fold higher plasma concentrations of alfuzosin in these patients compared to healthy subjects. Therefore, alfuzosin is contraindicated in patients with moderate to severe hepatic impairment

Pediatric Use: Alfuzosin tablets are not indicated for use in the pediatric population

Geriatric Use: In a pharmacokinetic assessment during phase 3 clinical studies in patients with BPH, there was no relationship between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentrations in subjects ≥75 years of age were approximately 35% greater than in those below 65 years of age.

Indications

ALFUSIN tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia.
ALFUSIN tablets are not indicated for the treatment of hypertension.
ALFUSIN tablets are not indicated for use in pediatric population

Dosage and Administration

The recommended dosage is one 10 mg **ALFUSIN** tablet once daily to be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

Contraindications

ALFUSIN tablets should not be used in patients with moderate or severe hepatic impairment (Childs-Pugh categories B and C) since alfuzosin hydrochloride blood levels are increased in these patients.

ALFUSIN tablets should not be co-administered with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir, since alfuzosin hydrochloride blood levels are increased.

ALFUSIN tablets are contraindicated in patients with known hypersensitivity, such as, urticaria and angioedema to alfuzosin hydrochloride or any component of **ALFUSIN** tablets.

Warnings and Precautions

General

Postural Hypotension
Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of **ALFUSIN** tablets. As with other alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope occur. There may be an increased risk of hypotension/postural hypotension and syncope when taking **ALFUSIN** tablets, concomitantly with antihypertensive medication and nitrates. Care should be taken when **ALFUSIN** tablets are administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

Prostatic Carcinoma
Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Therefore, patients thought to have BPH should be examined to rule out the presence of carcinoma of the prostate prior to starting therapy with **ALFUSIN** tablets.

Intraoperative Floppy Iris Syndrome (IFIS)
IFIS has been observed during cataract surgery in some patients on or previously treated with alpha-adrenergic antagonists. This variant of small-pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings or viscoelastic substances. There does not appear to be a benefit of stopping alpha-adrenergic antagonist therapy prior to cataract surgery.

Priapism
Rarely (probably less than 1 in 50,000), alfuzosin, like other alpha-adrenergic antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients should be advised about the seriousness of the condition.

Coronary Insufficiency
If symptoms of angina pectoris should newly appear or worsen, **ALFUSIN** tablets should be discontinued.

Patients with Congenital or Acquired QT Prolongation
Use with caution in patients with acquired or congenital QT prolongation or who are taking medications that prolong the QT interval.

Drug Interactions

Potent CYP3A4 Inhibitors
CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin hydrochloride. Repeated administration of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, increased the alfuzosin hydrochloride C_{max} by 2.3-fold and the AUClast by 3.2-fold following a single 10 mg dose of alfuzosin hydrochloride.

In another study, repeated oral administration of a lower (200 mg/day) dose of ketoconazole

increased the alfuzosin hydrochloride C_{max} by 2.1-fold and the AUClast by 2.5-fold, following a single 10 mg dose of alfuzosin.

Therefore, **ALFUSIN** tablets should not be co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or ritonavir) because of increased alfuzosin hydrochloride exposure.

Moderate CYP3A4 Inhibitors
Diltiazem: Repeated co-administration of 240 mg/day of diltiazem, a moderately-potent inhibitor of CYP3A4, with 7.5 mg/day (2.5 mg three times daily) alfuzosin hydrochloride increased the C_{max} and AUC0-24 of alfuzosin hydrochloride 1.5- and 1.3-fold, respectively. Alfuzosin hydrochloride increased the C_{max} and AUC_{0-12} of diltiazem 1.4-fold. Although no changes in blood pressure were observed in this study, diltiazem is an antihypertensive medication and the combination of alfuzosin hydrochloride and antihypertensive medications has the potential to cause hypotension in some patients. In human liver microsomes, at concentrations that are achieved at the therapeutic dose, alfuzosin did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6 or 3A4 isoenzymes. In primary culture of human hepatocytes, alfuzosin did not induce CYP1A, 2A6 or 3A4 isoenzymes.

Other alpha adrenergic antagonists
The pharmacokinetic and pharmacodynamic interactions between alfuzosin and other alpha adrenergic antagonists have not been determined. However, interactions may be expected, and alfuzosin should not be used in combination with other alpha adrenergic antagonists.

Phosphodiesterase-5 (PDE5) Inhibitors
PDE5-inhibitors are also vasodilators. Caution is advised for concomitant use of PDE5-inhibitors and alfuzosin, as this combination can potentially cause symptomatic hypotension

Antihypertensive Medication and Nitrates
There may be an increased risk of hypotension/postural hypotension and syncope when taking alfuzosin concomitantly with anti-hypertensive medication and nitrates.

Warfarin
Multiple dose administration of an immediate-release tablet formulation of alfuzosin hydrochloride 5 mg twice daily for 6 days to 6 healthy male volunteers did not affect the pharmacological response to a single 25 mg oral dose of warfarin.

Digoxin
Repeated co-administration of alfuzosin hydrochloride 10 mg and digoxin 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug.

Cimetidine
Repeated administration of 1 g/day cimetidine increased both the alfuzosin hydrochloride C_{max} and AUC values by 20%.

Atenolol
Single administration of 100 mg atenolol with a single dose of 2.5 mg of an immediate-release alfuzosin hydrochloride tablet in 8 healthy young male volunteers increased alfuzosin hydrochloride C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin hydrochloride increased atenolol C_{max} and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin hydrochloride with atenolol caused significant reductions in the mean blood pressure and in mean heart rate.

Hydrochlorothiazide
Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters

of alfuzosin hydrochloride. There was no evidence of pharmacodynamic interaction between alfuzosin hydrochloride and hydrochlorothiazide in the 8 patients in the study.

Information for Patients

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning **ALFUSIN** tablets, and they should be cautioned about driving, operating machinery, or performing hazardous tasks during this period. This is important for those with low blood pressure or who are taking antihypertensive medications or nitrates.

Patients should be instructed to tell their ophthalmologist about their use of **ALFUSIN** tablets before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking alfuzosin hydrochloride.

Patients should be advised about the possibility of priapism resulting from treatment with **ALFUSIN** tablets and medications in the same class. Although this reaction is extremely rare, if it is not brought to immediate medical attention, it can lead to permanent erectile dysfunction (impotence).

Renal Impairment

Caution should be exercised when alfuzosin hydrochloride tablets are administered in patients with severe renal impairment (creatinine clearance <30 mL/min). Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal impairment. In phase 3 studies, the safety profile of patients with mild (n=172) or moderate (n=56) renal impairment was similar to the patients with normal renal function in those studies. Safety data are available in only a limited number of patients (n=6) with creatinine clearance below 30 mL/min; therefore, caution should be exercised when alfuzosin is administered in patients with severe renal impairment

Hepatic Impairment

ALFUSIN tablets are contraindicated for use in patients with moderate or severe hepatic impairment. Although the pharmacokinetics of alfuzosin hydrochloride has not been studied in patients with mild hepatic impairment, caution should be exercised when alfuzosin hydrochloride tablets are administered to such patients.

Pregnancy

Pregnancy Category B
Alfuzosin hydrochloride is not indicated for use in women, and there are no studies of alfuzosin hydrochloride in pregnant women.

Lactation

ALFUSIN tablets are not indicated for use in women.

Paediatric Use

ALFUSIN tablets are not indicated for use in paediatric population.

Efficacy of alfuzosin hydrochloride was not demonstrated in a randomized, double-blind, placebo-controlled, efficacy and safety trial conducted in 172 patients ages 2 to 16 years with elevated

detrusor leak point pressure (LPP≥40 cm H_2O) of neurologic origin treated with alfuzosin hydrochloride using pediatric formulations. The trial included a 12-week efficacy phase followed by a 40-week safety extension period. No statistically significant difference in the proportion of patients achieving a detrusor leak point pressure of 20 was observed between the alfuzosin and placebo groups.

During the placebo-controlled trial, the adverse reactions reported in ≥2% of patients treated with alfuzosin and at a higher incidence than in the placebo group were: pyrexia, headache, respiratory tract infection, cough, epistaxis and diarrhea. The adverse reactions reported for the whole 12-month trial period, which included the open-label extension, were similar in type and frequency to the reactions observed during the 12-week period. Alfuzosin hydrochloride was not studied in patients below the age of 2.

Geriatric Use

Of the total number of subjects in clinical studies of alfuzosin hydrochloride, 48% were 65 years of age and over, whereas 11% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but the greater sensitivity of some older individuals cannot be ruled out.

Undesirable Effects

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The incidence of treatment-emergent adverse events has been ascertained from three placebo-controlled clinical trials involving 1,608 men where daily doses of 10 and 15 mg alfuzosin hydrochloride were evaluated. In these 3 trials, 473 men received alfuzosin Hydrochloride 10 mg extended-release tablets. In these trials, 4% of patients taking alfuzosin Hydrochloride 10 mg extended-release tablets withdrew from the trial due to adverse reactions, compared with 3% in the placebo group.

Table 1 summarizes adverse reactions that occurred in ≥2% of patients receiving alfuzosin, and at a higher incidence than that of the placebo group. In general, the adverse reactions seen in long-term use were similar in type and frequency to the events described below for the 3-month trials.

Table 1: Adverse Reactions Occurring in ≥2% of Alfuzosin Hydrochloride Treated Patients and More Frequently than with Placebo in 3-Month, Placebo-Controlled Clinical Trials

Adverse Reaction	Placebo (n=678)	Alfuzosin Hydrochloride (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Upper respiratory tract infection	4 (0.6%)	14 (3.0%)
Headache	12 (1.8%)	14 (3.0%)
Fatigue	12 (1.8%)	13 (2.7%)

The other adverse reactions, reported by between 1% and 2% of patients receiving alfuzosin hydrochloride and occurring more frequently than with placebo are listed alphabetically by body system and by decreasing frequency within body system:

Body as a whole: pain
Gastrointestinal system: abdominal pain, dyspepsia, constipation, nausea
Reproductive system: impotence
Respiratory system: bronchitis, sinusitis, pharyngitis

Signs and Symptoms of Orthostasis in Clinical Studies
The adverse events related to orthostasis that occurred in the double-blind Phase 3 trials with alfuzosin hydrochloride 10 mg are summarized in Table 2. Approximately 20-30% of patients in these studies were taking antihypertensive medication.

Table 2: Number (%) of Patients with Symptoms Possibly Associated with Orthostasis in 3-Month, Placebo-Controlled Clinical Trials

Symptoms	Placebo (n=678)	Alfuzosin Hydrochloride (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Hypotension or postural hypotension	0	2 (0.4%)
Syncope	0	1 (0.2%)

Testing for blood pressure changes or orthostatic hypotension was conducted in three controlled studies. Decreased systolic blood pressure (≤90 mmHg, with a decrease ≥20 mmHg from baseline) was observed in none of the 674 placebo patients and in 1 (0.2%) of the 469 alfuzosin hydrochloride patients. Decreased diastolic blood pressure (≤50 mmHg, with a decrease ≥15 mmHg from baseline) was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the alfuzosin hydrochloride patients. A positive orthostatic test (decrease in systolic blood pressure of ≥20 mmHg upon standing from the supine position) was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the alfuzosin hydrochloride patients.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of alfuzosin hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders: Oedema.

Cardiac disorders: Tachycardia, chest pain, angina pectoris in patients with pre-existing coronary artery disease, atrial fibrillation.

Gastrointestinal disorders: Diarrhoea.

Hepatobiliary disorders: Hepatocellular and cholestatic liver injury (including cases with jaundice leading to drug discontinuation).

Respiratory system disorders: Rhinitis.

Reproductive system disorders: Priapism.

Skin and subcutaneous tissue disorders: Rash, pruritus, urticaria, angioedema.

Vascular disorders: Flushing.

Blood and lymphatic system disorders: thrombocytopenia

Overdosage

In case an overdose of **ALFUSIN** tablets leads to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then the administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and the renal function should be monitored and supported as needed. Alfuzosin hydrochloride is 82-90% protein-bound; therefore, dialysis may not be of benefit.

Storage and Handling Instructions

Store in a cool dry place. Protect from light.

Packaging Information

ALFUSIN: Blister pack of 10 tablets

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