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For the use only of a Urologist

FLOTRAL

(Alfuzosin Hydrochloride Modified Release Tablets)

COMPOSITION

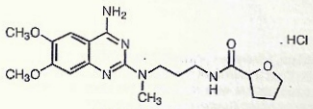
FLOTRAL

Each Modified Release Tablet contains:

Alfuzosin Hydrochloride Ph. Eur. .....10 mg

DESCRIPTION

FLOTRAL TABLETS contain alfuzosin hydrochloride, which is a selective antagonist of post-synaptic alpha1-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Alfuzosin hydrochloride is designated as (RS)-*N*-[3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)(methyl)amino]propyl]tetrahydrofuran-2-carboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is $C_{19}H_{28}ClN_5O_4$ and its molecular weight is 425.9.



STRUCTURAL FORMULA

PHARMACOLOGY[1,2]

- **Mechanism of action**

The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to the prostate size. Prostate size alone does not correlate with symptom severity. The dynamic component is a function of the smooth muscle tone in the prostate and its capsule, the bladder neck, and the bladder base as well as the prostatic urethra. The smooth muscle tone is regulated by alpha-adrenergic receptors. Alfuzosin Hydrochloride is a selective antagonist of post-synaptic alpha1-adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. 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.

- **Pharmacokinetics**

The pharmacokinetics of alfuzosin hydrochloride 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.

The absolute bioavailability of alfuzosin hydrochloride 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg alfuzosin hydrochloride tablets under fed conditions, the time to maximum concentration is 8 hours. Cmax and AUC0-24 are 13.6 (SD = 5.6) ng/Ml and 194 (SD = 75) ng.h/mL, respectively. Alfuzosin hydrochloride 10 mg tablet exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached by with the second dose of alfuzosin hydrochloride 10 mg tablets administration. Steady-state alfuzosin plasma concentrations are 1.2- to 1.6-fold higher than those observed after a single administration.

The extent of absorption is 50% lower under fasting conditions. Therefore alfuzosin hydrochloride tablets should be taken immediately following a meal.

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 is moderately bound to human plasma proteins (82% to 90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin 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 its metabolism.

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

Pharmacokinetics in special population

Geriatrics: 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 subject's ≥75 years of age were approximately 35% greater than in those below 65 years of age.

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 <30 mL/min) were compared. These clearances were calculated by the Cockcroft-Gault formula. Relative to subjects with normal renal function, the mean Cmax and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment.

Hepatic Insufficiency: 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. The pharmacokinetics of alfuzosin has not been studied in patients with mild hepatic insufficiency.

INDICATIONS[1,2]

FLOTRAL (Alfuzosin hydrochloride prolonged release) Tablets is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

FLOTRAL Tablet is not indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION[1,2]

FLOTRAL Tablets should be swallowed whole.

The recommended dose is one **FLOTRAL** 10 mg Tablet to be taken once daily after a meal.

PRECAUTIONS[1,2]

- **General**

Prostatic Carcinoma: Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting therapy with alfuzosin to rule out the presence of carcinoma of the prostate.

Drug-Drug Interactions: The pharmacokinetic and pharmacodynamic interactions between alfuzosin and other alpha-blockers have not been determined. However, interactions may be expected, and alfuzosin should NOT be used in combination with other alphablockers.

Coronary Insufficiency: If symptoms of angina pectoris should newly appear or worsen, alfuzosin should be discontinued.

Hepatic Insufficiency: Alfuzosin should not be given to patients with moderate or severe hepatic insufficiency. The pharmacokinetics of alfuzosin has not been studied in patients with mild hepatic insufficiency.

Renal Insufficiency: Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal insufficiency phase 3 studies, the safety profile of patients with mild or moderate 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 with creatinine clearance below 30 mL/min; therefore, caution should be exercised when alfuzosin is administered in patients with severe renal insufficiency.

Patients with Congenital or Acquired QT Prolongation: In a study of QT effect in 45 healthy males the QT effect appeared less with alfuzosin 10 mg than with 40 mg, and the effect of alfuzosin 40 mg did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe alfuzosin for patients with a known history of QT prolongation or patients who are taking medications known to prolong QT, although there has been no signal of Torsades de Pointe in the extensive post marketing experience with alfuzosin. There are no known PK/PD studies of the effects of other alpha-blockers on cardiac repolarization.

- **Contraindications**

FLOTRAL (Alfuzosin hydrochloride prolonged release) Tablets should not be used in patients with moderate or severe hepatic insufficiency, (Childs-Pugh categories B and C) since alfuzosin blood levels are increased in these patient.

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

FLOTRAL is contraindicated in patients known to be hypersensitive to alfuzosin hydrochloride or any component of alfuzosin tablets.

- **Pediatric Use**

FLOTRAL is not indicated for use in children.

- **Geriatric Use**

Of the total number of subjects in clinical studies of alfuzosin, 48% were 65 years of age and over, whereas 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

- **Carcinogenecity /Mutagenecity /Impairment of Fertility**

There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100mg/kg/day alfuzosin for 98 weeks (13 and 15 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively. The highest dose tested in female mice may not have constituted a maximally tolerated dose.

Likewise, there was no evidence of a drug-related increase in the incidence of tumors in rats following dietary administration of 100mg/kg/day alfuzosin for 104 weeks (53 and 37 times the level of exposure to humans based on AUC of unbound drug) in females and males, respectively.

Alfuzosin showed no evidence of mutagenic effect in the Ames and mouse lymphoma assays, and was free of any clastogenic effects in the Chinese hamster ovary cell and *in vivo* mouse micronucleus assays. Alfuzosin treatment did not induce DNA repair in a human cell line.

There was no evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral (gavage) doses of up to 250 mg/kg/day for 26 weeks, which corresponds to levels of exposure several hundred times that in humans. No impairment of fertility was observed following oral (gavage) administration to male rats at doses of up to 125 mg/kg/day for 70 days. Estrous cycling was inhibited in rats and dogs at doses of 25 mg/kg and 20 mg/kg, respectively, corresponding to levels of systemic exposure (based on AUC of unbound drug) 12- and 18-fold higher, respectively, than in humans, although this did not result in impaired fertility in rats.

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- **Pregnancy**

Teratogenic Effects, Pregnancy and Lactation. Alfuzosin is not indicated for use in women. There was no evidence of teratogenicity or embryotoxicity in rats at maternal (oral gavage) doses up to 250 mg/kg/day, corresponding to systemic exposure levels 1,200-fold higher than in humans. In rabbits, up to the dose of 100 mg/kg/day (approximately 3 times the clinical dose by body surface area) given orally (via gavage), no evidence of fetal toxicity or teratogenicity was seen. Gestation was slightly prolonged in rats with a maternal dose >5 mg/kg/day (oral gavage), which corresponds to systemic exposure levels (based on AUC of unbound drug) 12 times higher than human exposure levels, but there were no difficulties with parturition.

- **Lactation**

Alfuzosin is not indicated for use in women.

- **Drug Interactions**

Metabolic interactions

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin.

Potent CYP3A4 inhibitors

Repeated administration of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, increased alfuzosin Cmax 2.3-fold and AUClast 3.2-fold following a single 10 mg dose of alfuzosin. Therefore, alfuzosin should not be co-administered with potent inhibitors of CYP3A4 because exposure is increased, (e.g., ketoconazole, itraconazole, or ritonavir).

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 (equivalent to the exposure with alfuzosin 10mg) increased the Cmax and AUC0-24 of alfuzosin 1.5- and 1.3-fold, respectively. Alfuzosin increased the Cmax and AUC0-12 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 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 interactions

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

Digoxin: Repeated co-administration of alfuzosin 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 alfuzosin Cmax 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 tablet in eight healthy young male volunteers increased alfuzosin Cmax and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol Cmax and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin with atenolol caused significant reductions in mean blood pressure and in mean heart rate.

Hydrochlorothiazide: Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters of alfuzosin. There was no evidence of pharmacodynamic interaction between alfuzosin and hydrochlorothiazide in the 8 patients in this study.

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 coadministration of alfuzosin and ketoconazole 400 mg. 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. Mean QT and QTc changes in msec (95% CI) from baseline at Tmax (relative to placebo) with different methodologies to correct for effect of heart rate. 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 Torsades de Pointes in the extensive post-marketing experience with alfuzosin.

- **Adverse Reactions**

The incidence of treatment-emergent adverse events has been ascertained from 3 placebo controlled clinical trials involving 1,608 men in which daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3 trials, 473 men received alfuzosin hydrochloride 10 mg extended release tablets. In these studies, 4% of patients taking alfuzosin hydrochloride extended release 10 mg tablets withdrew from the study due to adverse events, compared with 3% in the placebo group. Following treatment emergent adverse events were reported in 2% of patients receiving alfuzosin

Table. Treatment Emergent Adverse Events reported in 2% of Patients receiving Alfuzosin hydrochloride

Adverse Event	Placebo (n=678)	Alfuzosin (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 following adverse events, reported by between 1% and 2% of patients receiving alfuzosin 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, and nausea

Reproductive system: impotence

Respiratory system: bronchitis, sinusitis, and pharyngitis
The following adverse events have also been reported in post marketing experience: rash, tachycardia, chest pain, and priapism.

Signs and Symptoms of Orthostasis in Clinical Studies: The adverse events related to orthostasis that occurred in the double-blind phase 3 studies with alfuzosin 10 mg are given in table below. Approximately 20% to 30% of patients in these studies were taking antihypertensive medication.

Table. Number (%) of Patients with Symptoms Possibly Associated with Orthostasis in a 3-Month Placebo-Controlled Clinical Studies

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

Multiple testing for blood pressure changes or orthostatic hypotension was conducted in the three controlled studies at each scheduled clinic visit (Days 14, 28, 56, and 84). Patients with a decrease in systolic blood pressure of >20 mmHg after 2 minutes standing following being supine were excluded from the three trials. These tests were considered positive for blood pressure decrease if (1) supine systolic blood pressure was ≤90 mmHg, with a decrease ≥20mm Hg versus baseline, and/or (2) supine diastolic blood pressure was ≤50 mmHg, with a decrease ≥15 mmHg versus baseline. The tests were considered positive for orthostatic hypotension if there was a decrease in systolic blood pressure of ≥20 mmHg upon standing from the supine position during the orthostatic tests. According to these definitions, decreased systolic blood pressure was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 alfuzosin 10 mg patients. Decreased diastolic blood pressure was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the alfuzosin 10 mg patients. A positive orthostatic test was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the alfuzosin 10 mg patients.
No vital sign measurements were obtained following first dose administration in the phase 3 studies, except for a subset of patients in study 1 who had blood pressure measurements 12 to 16 hours after the first dose to assess the potential to produce orthostatic hypotension. None of these 35 alfuzosin 10 mg treated patients showed a positive test for systolic, diastolic or orthostatic blood pressure change.

OVERDOSAGE[1,2]

Should overdose of alfuzosin hydrochloride prolonged-release lead 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 is 82% to 90% protein-bound; therefore, dialysis may not be of benefit.

STORAGE : Store at controlled room temperature (15-25°C), protected from moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

SUPPLY : Blister of 10's.

REFERENCES

1. Product information of **UROXATRAL** Sanofi-Synthelabo June 2003.
2. APBI compendium of data sheets Summary of Product Characteristics for **XATRAL XL**. Sanofi-aventis. UK; April 2004.

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