UROXATRAL - alfuzosin hydrochloride tablet, extended release
Stat Rx USA

UROXATRAL (alfuzosin hydrochloride) tablet, extended release

1 INDICATIONS AND USAGE

UROXATRAL is indicated for the treatment of signs and symptoms of benign prostatic hyperplasia. UROXATRAL is not indicated for the treatment of hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one 10 mg UROXATRAL (alfuzosin HCl) extended-release tablet once daily. The extent of absorption of Uroxatral is 50% lower under fasting conditions. Therefore, Uroxatral should be taken immediately after the same meal each day. The tablets should not be chewed or crushed.

3 DOSAGE FORMS AND STRENGTHS

UROXATRAL (alfuzosin HCl) extended-release tablet 10 mg is available as a round, three-layer tablet: one white layer between two yellow layers, debossed with X10.

4 CONTRAINDICATIONS

UROXATRAL is contraindicated for use in patients with moderate or severe hepatic impairment (Childs-Pugh categories B and C), since alfuzosin blood levels are increased in these patients. *[see Clinical Pharmacology (12.3)]*.

UROXATRAL is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, and ritonavir, since alfuzosin blood levels are increased. *[see Clinical Pharmacology (12.3)]*.

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

5 WARNINGS AND PRECAUTIONS

5.1 Postural Hypotension

Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of UROXATRAL. 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 UROXATRAL concomitantly with anti-hypertensive medication and nitrates. Care should be taken when UROXATRAL is administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

5.2 Renal Impairment

Caution should be exercised when UROXATRAL is administered in patients with severe renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.3 Hepatic Impairment

UROXATRAL is contraindicated for use in patients with moderate or severe hepatic impairment *[see*

Use in Specific Populations (8.7) and Contraindications (4)]. The pharmacokinetics of UROXATRAL have not been studied in patients with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

5.4 Pharmacodynamic Drug-Drug Interactions

UROXATRAL is a selective alpha-blocker and should not be used in combination with other alpha-blockers *[see Drug Interactions (7.2)]*.

Because of the vasodilatory effects of alpha-blockers and inhibitors of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5-inhibitors), patients treated with alpha-blocker therapy should be hemodynamically stable before treatment with PDE5-inhibitors is initiated. *[see Drug Interactions (7.4)]*.

5.5 Pharmacokinetic Drug-Drug Interactions

UROXATRAL is contraindicated for use with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) since alfuzosin blood levels are increased *[see Contraindications (4), Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

5.6 Prostatic Carcinoma

Carcinoma of the prostate and benign prostatic hyperplasia (BPH) cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting treatment with UROXATRAL to rule out the presence of carcinoma of the prostate.

5.7 Intraoperative Floppy Iris Syndrome (IFIS)

IFIS has been observed during cataract surgery in some patients on or previously treated with alpha-1 blockers. 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-1 blocker therapy prior to cataract surgery.

5.8 Coronary Insufficiency

If symptoms of angina pectoris should appear or worsen, UROXATRAL should be discontinued.

5.9 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 *[see Clinical Pharmacology (12.2)]*.

5.10 Laboratory Test Interactions

No laboratory test interactions with UROXATRAL tablets are known.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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

The incidence of treatment-emergent adverse events has been ascertained from 3 placebo-controlled

clinical trials involving 1,608 men where daily doses of 10 and 15 mg alfuzosin were evaluated. In these 3 trials, 473 men received UROXATRAL (alfuzosin HCl) 10 mg extended-release tablets. In these studies, 4% of patients taking UROXATRAL (alfuzosin HCl) 10 mg extended-release tablets withdrew from the study due to adverse events, compared with 3% in the placebo group.

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

Table 1 — Treatment-Emergent Adverse Events Occurring in ≥2% of UROXATRAL-Treated Patients and More Frequently than with Placebo in 3-Month Placebo-Controlled Clinical Studies

Adverse Event	Placebo (n=678)	UROXATRAL (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 UROXATRAL 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 reactions related to orthostasis that occurred in the double-blind phase 3 studies with alfuzosin 10 mg are summarized in Table 2. Approximately 20% to 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 Studies

Symptoms	Placebo (n=678)	UROXATRAL (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 mm Hg, with a decrease ≥20 mm Hg from baseline) was observed in none of the 674 placebo patients and 1 (0.2%) of the 469 UROXATRAL patients. Decreased diastolic blood pressure (≤50 mm Hg, with a decrease ≥15 mm Hg from baseline) was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the UROXATRAL patients. A positive orthostatic test (decrease in systolic blood pressure of ≥20 mm Hg upon standing from the supine position) was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the UROXATRAL patients.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of UROXATRAL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

General disorders: edema

Cardiac disorders: tachycardia, chest pain, angina pectoris in patients with pre-existing coronary artery disease

Gastrointestinal disorders: diarrhea

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, pruritis, urticaria, angioedema

Vascular disorders: flushing

During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in some patients on or previously treated with alpha-1 blockers *[see Warnings and Precautions (5.7)]*.

7 DRUG INTERACTIONS

7.1 CYP3A4 Inhibitors

UROXATRAL is contraindicated for use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole, or ritonavir, since alfuzosin blood levels are increased. *[see Contraindications (4), Warnings and Precautions (5.5) and Clinical Pharmacology (12.3)]*.

7.2 Alpha-blockers

The pharmacokinetic and pharmacodynamic interactions between UROXATRAL and other alpha-blockers have not been determined. However, interactions may be expected, and UROXATRAL should NOT be used in combination with other alpha-blockers *[see Warnings and Precautions (5.4)]*.

7.3 Antihypertensive Medication and Nitrates

There may be an increased risk of hypotension/postural hypotension and syncope when taking UROXATRAL concomitantly with anti-hypertensive medication and nitrates *[see Warnings and Precautions (5.1)]*.

7.4 PDE5 Inhibitors

Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Patients treated with alpha-blockers should be hemodynamically stable before treatment with PDE5 inhibitors initiation *[see Warnings and Precautions (5.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. UROXATRAL 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.

8.4 Pediatric Use

UROXATRAL is not indicated for use in children.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of UROXATRAL, 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 *[see Clinical Pharmacology (12.3)]*

8.6 Renal Impairment

Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal impairment *[see Clinical Pharmacology (12.3)]*. 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 UROXATRAL is administered in patients with severe renal impairment *[see Warnings and Precautions (5.2)]*.

8.7 Hepatic Impairment

The pharmacokinetics of UROXATRAL have not been studied in patients with mild hepatic impairment. UROXATRAL is contraindicated for use in patients with moderate or severe hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

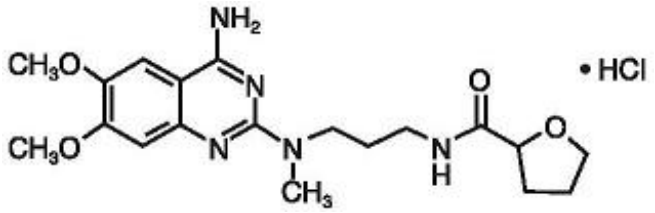
10 OVERDOSAGE

Should overdose of UROXATRAL 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.

11 DESCRIPTION

Each UROXATRAL extended-release tablet contains 10 mg alfuzosin hydrochloride as the active ingredient. Alfuzosin hydrochloride is a white to off-white crystalline powder that melts at approximately 240°C. It is freely soluble in water, sparingly soluble in alcohol, and practically insoluble in dichloromethane.

Alfuzosin hydrochloride is (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is $C_{19}H_{27}N_5O_4$•HCl. The molecular weight of alfuzosin hydrochloride is 425.9. Its structural formula is:



The tablet also contains the following inactive ingredients: colloidal silicon dioxide (NF), ethylcellulose (NF), hydrogenated castor oil (NF), hydroxypropyl methylcellulose (USP), magnesium stearate (NF), mannitol (USP), microcrystalline cellulose (NF), povidone (USP), and yellow ferric oxide (NF).

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

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 exhibits selectivity for alpha$_1$-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 UROXATRAL 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
Active control				
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)

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.

12.3 Pharmacokinetics

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

Effect of Food

As illustrated in Figure 1, the extent of absorption is 50% lower under fasting conditions. Therefore, UROXATRAL should be taken immediately following a meal *[see Dosage and Administration (2)]*.

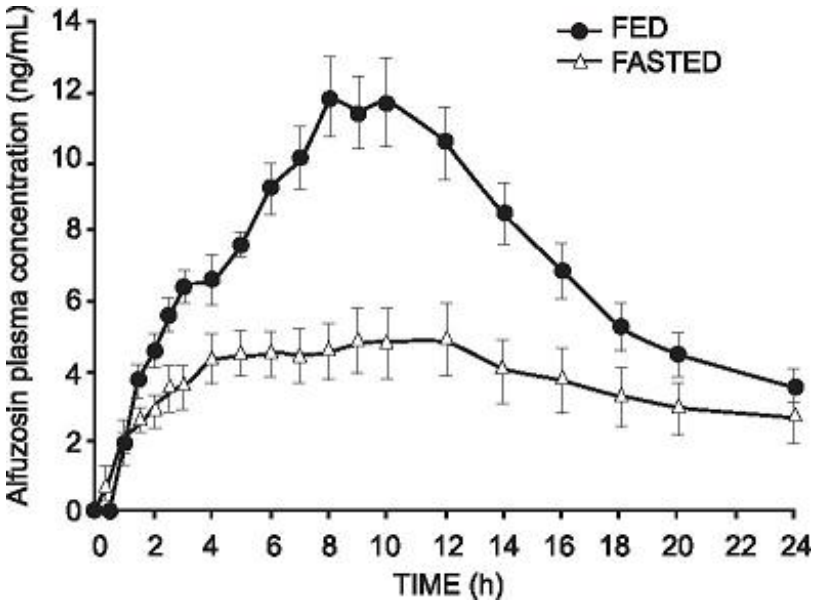


Figure 1 – Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles after a Single Administration of UROXATRAL 10 mg tablets to 8 Healthy Middle-Aged Male Volunteers in Fed and Fasted States

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

Metabolism

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 in its metabolism.

Excretion

Following oral administration of ^{14}C-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 UROXATRAL 10 mg tablets, the apparent elimination half-life is 10 hours.

Specific Populations

Elderly: 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.

Renal Impairment: The Pharmacokinetic profiles of UROXATRAL 10 mg tablets in subjects with normal renal function (CL_{CR}>80 mL/min), mild impairment (CL_{CR} 60 to 80 mL/min), moderate impairment (CL_{CR} 30 to 59 mL/min), and severe impairment (CL_{CR} less than 30 mL/min) were compared. These clearances were calculated by the Cockcroft-Gault formula. Relative to subjects with normal renal function, the mean C_{max} and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.

Hepatic Impairment: The pharmacokinetics of UROXATRAL 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, UROXATRAL is contraindicated in patients with moderate to severe hepatic impairment *[see Contraindications (4), Warnings and Precautions (5.3) and Use in Specific Populations (8.7)]*.

Drug-Drug Interactions

Metabolic Interactions

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

Potent CYP3A4 Inhibitors

Repeated oral administration of 400 mg/day of ketoconazole, a potent inhibitor of CYP3A4, increased alfuzosin C_{max} by 2.3-fold and AUC_{last} by 3.2-fold, following a single 10 mg dose of alfuzosin.

In another study, repeated oral administration of a lower (200 mg/day) dose of ketoconazole increased alfuzosin Cmax by 2.1-fold and AUC_{last} by 2.5-fold, following a single 10 mg dose of alfusion.

Therefore, UROXATRAL is contraindicated for co-administration with potent inhibitors of CYP3A4 because exposure is increased, (e.g., ketoconazole, itraconazole, or ritonavir) *[see Contraindications (4), Warnings and Precautions (5.5) and Drug Interactions (7.1)]*.

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 UROXATRAL) increased the C_{max} and $AUC_{0–24}$ of alfuzosin 1.5- and 1.3-fold, respectively. Alfuzosin 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 UROXATRAL and antihypertensive medications has the potential to cause hypotension in some patients *[see Warnings and Precautions (5.1)]*.

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 UROXATRAL 10 mg tablets 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 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 tablet in eight healthy young male volunteers increased alfuzosin C_{max} and AUC values by 28% and 21%, respectively. Alfuzosin increased atenolol C_{max} 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. *[see Warnings and Precautions (5.1)].*

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.

13 NONCLINICAL TOXICOLOGY13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of a drug-related increase in the incidence of tumors in mice following dietary administration of 100 mg/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 100 mg/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.

14 CLINICAL STUDIES

Three randomized placebo-controlled, double-blind, parallel-arm, 12-week studies were conducted with the 10 mg daily dose of alfuzosin. In these three studies, 1,608 patients [mean age 64.2 years, range 49–92 years; Caucasian (96.1%), Black (1.6%), Asian (1.1%), Other (1.2%)] were randomized and 473 patients received UROXATRAL 10 mg daily. Table 4 provides the results of the three studies that evaluated the 10 mg dose.

There were two primary efficacy variables in these three studies. The International Prostate Symptom Score (IPSS, or AUA Symptom Score) consists of seven questions that assess the severity of both irritative (frequency, urgency, nocturia) and obstructive (incomplete emptying, stopping and starting, weak stream, and pushing or straining) symptoms, with possible scores ranging from 0 to 35. The second efficacy variable was peak urinary flow rate. The peak flow rate was measured just prior to the

next dose in study 2 and on average at 16 hours post-dosing in studies 1 and 3.

There was a statistically significant reduction from baseline to last assessment (Week 12) in the IPSS versus placebo in all three studies, indicating a reduction in symptom severity (Table 5 and Figures 2, 3, and 4).

Table 4 — Mean Change (SD) from Baseline to week 12 in International Prostate Symptom Score in Three Randomized, Controlled, Double Blind Studies

	Study 1		Study 2		Study 3	
Symptom Score	**Placebo (n=167)**	**UROXATRAL 10 mg (n=170)**	**Placebo (n=152)**	**UROXATRAL 10 mg (n=137)**	**Placebo (n=150)**	**UROXATRAL 10 mg (n=151)**
Difference between baseline and week 12.						
Total symptom score						
Baseline	18.2 (6.4)	18.2 (6.3)	17.7 (4.1)	17.3 (3.5)	17.7 (5.0)	18.0 (5.4)
Change	-1.6 (5.8)	-3.6 (4.8)	-4.9 (5.9)	-6.9 (4.9)	-4.6 (5.8)	-6.5 (5.2)
p-value	0.001	0.002	0.007			

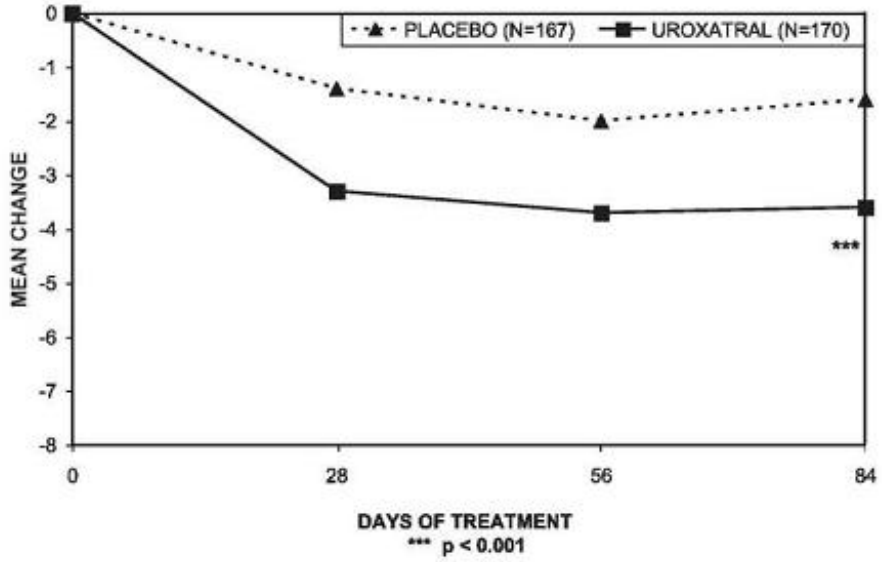


Figure 2 — Mean Change from Baseline in Total Symptom Score: Study 1

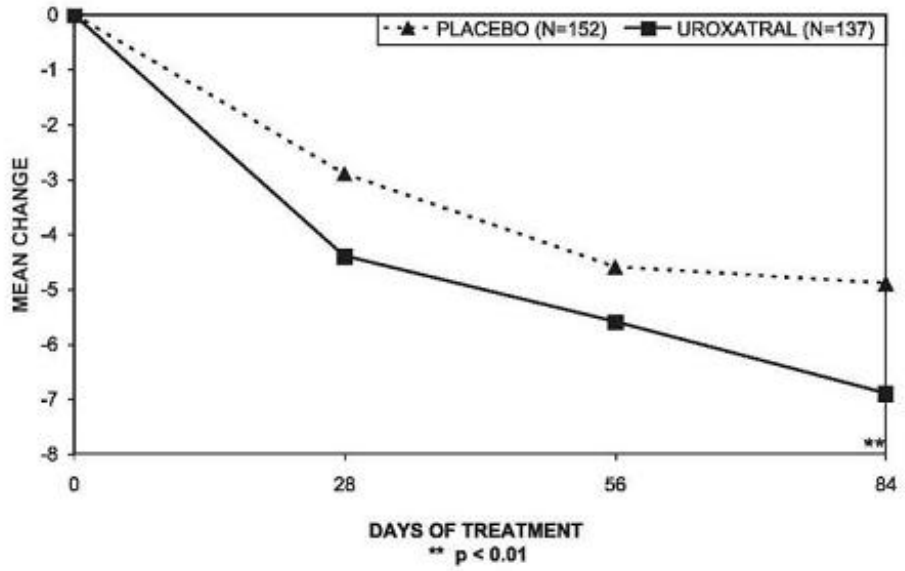


Figure 3 — Mean Change from Baseline in Total Symptom Score: Study 2

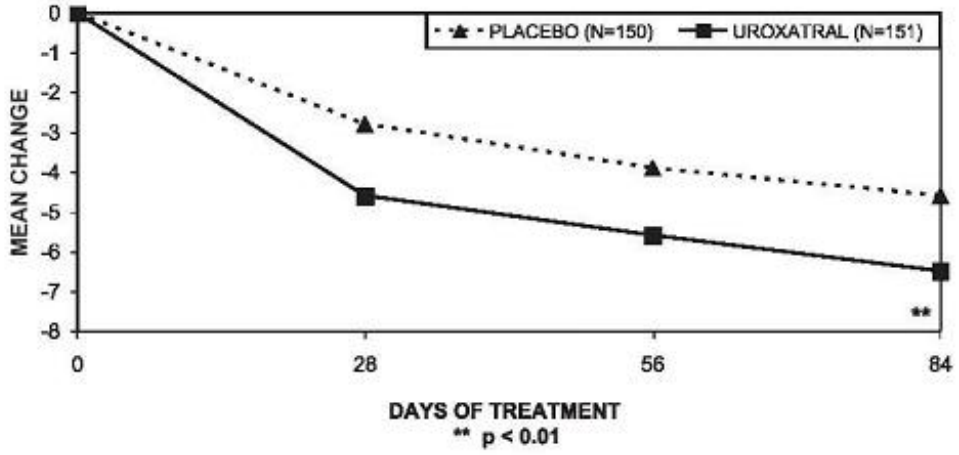


Figure 4 — Mean Change from Baseline in Total Symptom Score: Study 3

Peak urinary flow rate was increased statistically significantly from baseline to last assessment (Week 12) versus placebo in studies 1 and 2 (Table 5 and Figures 5, 6, and 7).

Table 5 — Mean (SD) Change from Baseline to Week 12 in Peak Urine Flow Rate (mL/sec) in Three Randomized, Controlled, Double-Blind Studies

	Study 1		Study 2		Study 3	
	Placebo	UROXATRAL 10 mg	Placebo	UROXATRAL 10 mg	Placebo	UROXATRAL 10 mg

	(n=167)	10 mg (n=170)	(n=147)	10 mg (n=136)	(n=150)	10 mg (n=151)
Difference between baseline and week 12.						
Mean Peak flow rate						
Baseline	10.2 (4.0)	9.9 (3.9)	9.2 (2.0)	9.4 (1.9)	9.3 (2.6)	9.5 (3.0)
Change	0.2 (3.5)	1.7 (4.2)	1.4 (3.2)	2.3 (3.6)	0.9 (3.0)	1.5 (3.3)
p-value	0.0004	0.03	0.22			

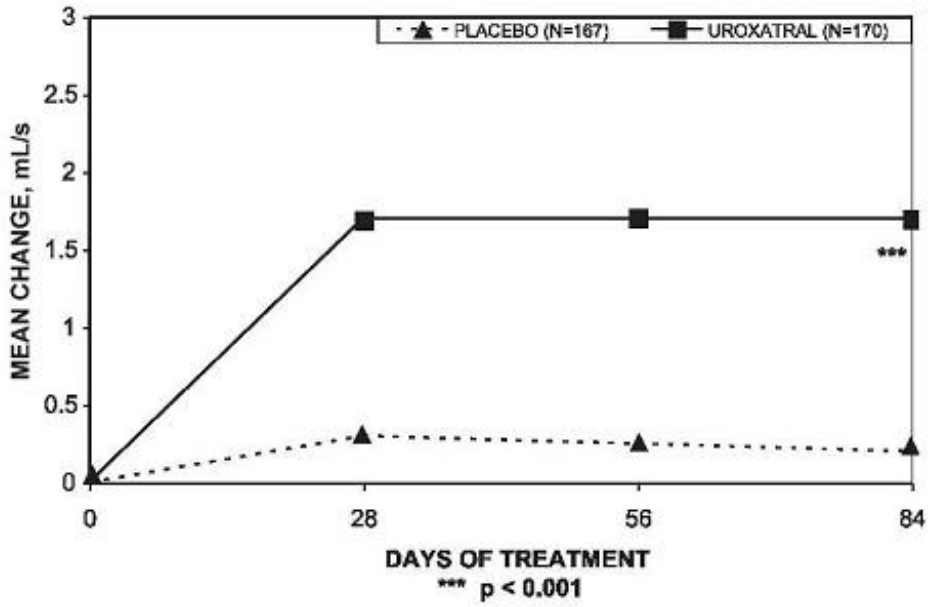


Figure 5 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s): Study 1

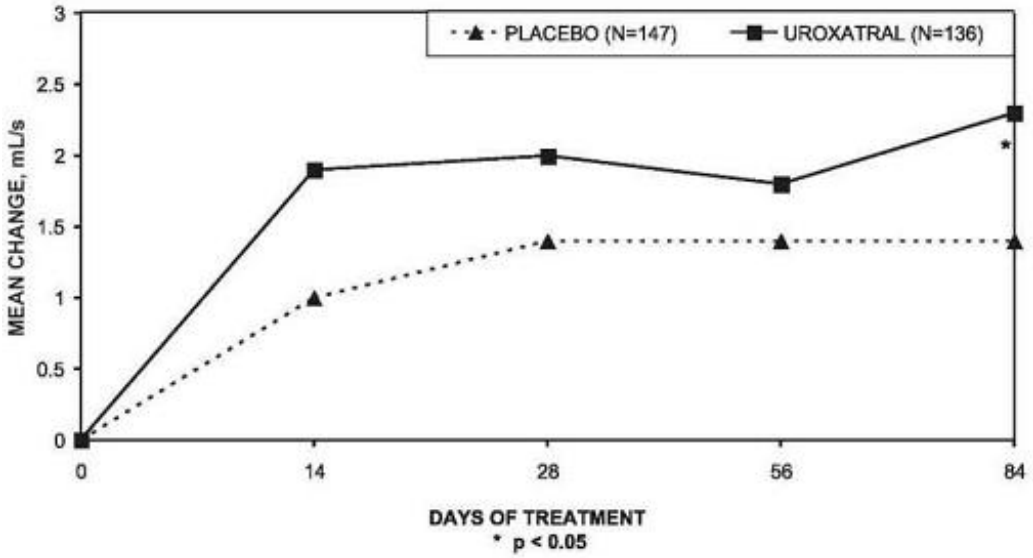


Figure 6 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s): Study 2

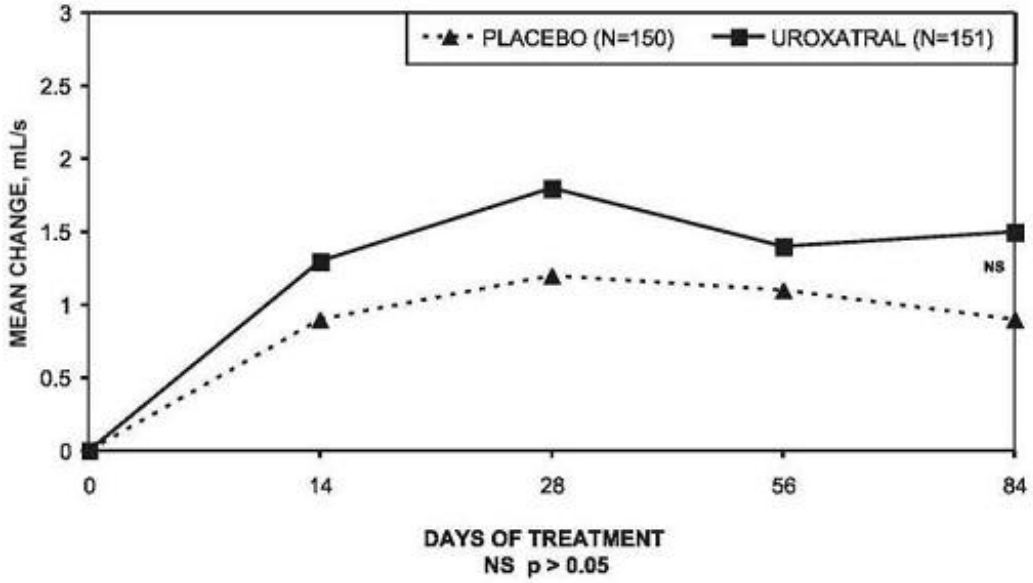


Figure 7 — Mean Change from Baseline in Peak Urine Flow Rate (mL/s): Study 3

Mean total IPSS decreased at the first scheduled observation at Day 28 and mean peak flow rate increased starting at the first scheduled observation at Day 14 in studies 2 and 3 and Day 28 in study 1.

16 HOW SUPPLIED/STORAGE AND HANDLING

UROXATRAL is supplied as follows:

Package	NDC Number
Bottles of 30	0024-4200-30
Bottles of 100	0024-4200-10
Hospital Unit Dose (blister packs containing 10 cards of 10 tablets each)	0024-4200-20

UROXATRAL (alfuzosin HCl) extended-release tablet 10 mg is available as a round, three-layer tablet: one white layer between two yellow layers, debossed with X10.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Protect from light and moisture.

Keep UROXATRAL out of reach of children.

17 PATIENT COUNSELING INFORMATION

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning UROXATRAL, 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 UROXATRAL before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking UROXATRAL.

UROXATRAL should be taken with food and with the same meal each day.

Patients should be advised not to crush or chew UROXATRAL tablets.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

FDA-Approved Patient Labeling

Patient Information
UROXATRAL®
(Alfuzosin hydrochloride
extended-release tablets)

Read the Patient Information that comes with UROXATRAL before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or your treatment. You and your doctor should talk about all your medicines, including UROXATRAL, now and at your regular checkups.

What is the most important information I should know about UROXATRAL?

UROXATRAL can cause:

- a sudden drop in blood pressure, especially when you start treatment. This may lead to fainting, dizziness, or lightheadedness. Do not drive, operate machinery, or do any dangerous activities until you know how UROXATRAL affects you. This is especially important if you already have a problem with low blood pressure or take medicines to treat high blood pressure. If you begin to feel dizzy or lightheaded, lie down with your legs and feet up, and if your symptoms do not improve call your doctor.

What is UROXATRAL?

UROXATRAL is a prescription medicine that is called an "alpha-blocker". UROXATRAL is used in

adult men to treat the symptoms of benign prostatic hyperplasia (BPH). UROXATRAL may help to relax the muscles in the prostate and the bladder which may lessen the symptoms of BPH and improve urine flow.

Before prescribing UROXATRAL, your doctor may examine your prostate gland and do a blood test called a prostate specific antigen (PSA) test to check for prostate cancer. Prostate cancer and BPH can cause the same symptoms. Prostate cancer needs a different treatment.

UROXATRAL is not for use in women or children.

Some medicines called "alpha-blockers" are used to treat high blood pressure. UROXATRAL has not been studied for the treatment of high blood pressure.

Who should not take UROXATRAL?

Do not take UROXATRAL if you:

- have liver problems
- are taking antifungal drugs like ketoconazole or HIV drugs called protease inhibitors
- are already taking an alpha-blocker for either high blood pressure or prostate problems
- are a woman
- are a child under the age of 18
- are allergic to UROXATRAL. The active ingredient is alfuzosin hydrochloride. See the end of this leaflet for a complete list of ingredients in UROXATRAL.

Before taking UROXATRAL, tell your doctor:

- if you have liver problems
- if you have kidney problems
- if you or any family members have a rare heart condition known as congenital prolongation of the QT interval.
- about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Some of your other medicines may affect the way you respond or react to UROXATRAL.
- if you have had low blood pressure, especially after taking another medicine. Signs of low blood pressure are fainting, dizziness, and lightheadedness.
- if you have a heart problem called angina (pain in your chest, jaw, or arm).

What you need to know while taking UROXATRAL (alfuzosin HCl) tablets

- If you have an eye surgery for cataract (clouding of the eye) planned, tell your ophthalmologist that you are using UROXATRAL or have previously been treated with an alpha-blocker.

How do I take UROXATRAL?

- Take UROXATRAL exactly as your doctor prescribes it.
- Take one UROXATRAL tablet after the same meal each day. UROXATRAL should be taken just after eating food. Do not take it on an empty stomach.
- Swallow the UROXATRAL tablet whole. Do not crush, split, or chew UROXATRAL tablets.
- If you take too much UROXATRAL call your local poison control center or emergency room right away.

What are the possible side effects of UROXATRAL?

The most common side effects with UROXATRAL are:

- dizziness
- headache
- tiredness

Call your doctor if you get any side effect that bothers you.

These are not all the side effects of UROXATRAL. For more information ask your doctor or pharmacist.

How do I store UROXATRAL?

Store UROXATRAL between 59°F and 86°F (15°C and 30°C).

Protect from light and moisture.

Keep UROXATRAL and all medicines out of the reach of children.

General information about UROXATRAL:

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use UROXATRAL for a condition for which it was not prescribed. Do not give UROXATRAL to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about UROXATRAL. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about UROXATRAL that is written for health professionals.

You may also visit our website at www.UROXATRAL.com or call 1-800-446-6267.

What are the ingredients of UROXATRAL?

Active Ingredient: alfuzosin hydrochloride

Inactive Ingredients: colloidal silicon dioxide (NF), ethylcellulose (NF), hydrogenated castor oil (NF), hydroxypropyl methylcellulose (USP), magnesium stearate (NF), mannitol (USP), microcrystalline cellulose (NF), povidone (USP), and yellow ferric oxide (NF).

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

NDC 0024-4200-10
X-010

Uroxatral®

alfuzosin HCl 10 mg
Extended-Release Tablets

1 Bottle
100 Tablets

Keep out of reach of children

Rx only

sanofi aventis

UROXATRAL LABEL IMAGE

UROXATRAL

alfuzosin hydrochloride tablet, extended release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:16590-279(NDC:0024-4200)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Alfuzosin Hydrochloride (UNII: 75046A1XTN) (Alfuzosin - UNII:90347YTW5F)	Alfuzosin Hydrochloride	10 mg

Product Characteristics			
Color	white	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	X10
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:16590-279-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021287	06/05/2009	

Labeler - Stat Rx USA (786036330)

Revised: 10/2009 Stat Rx USA