PRODUCT MONOGRAPH

PR APO-ALFUZOSIN

Alfuzosin Hydrochloride Prolonged-Release Tablets

10 mg

Pharmaceutical Standard: Professed

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

Adjunctive Therapy in Acute Urinary Retention (AUR)

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PR**APO-ALFUZOSIN**
Alfuzosin Hydrochloride Prolonged-Release Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Prolonged-Release Tablets 10 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

APO-ALFUZOSIN (alfuzosin hydrochloride) is indicated for:

- **Benign Prostatic Hyperplasia**

APO-ALFUZOSIN is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

- **Acute Urinary Retention**

APO-ALFUZOSIN is indicated as adjunctive therapy with urethral catheterization for Acute Urinary Retention related to BPH and management following catheter removal.

Geriatrics (>65 years of age):

Alfuzosin hydrochloride has been found to be safe and effective when administered at the therapeutic dose (10 mg once-daily) to patients over the age of 65 years.

Women:

APO-ALFUZOSIN is not indicated nor recommended for use in women.

Pediatrics (<18 years):

APO-ALFUZOSIN is not indicated for use in children.

CONTRAINDICATIONS

APO-ALFUZOSIN (alfuzosin hydrochloride) is contraindicated in:

- Patients with a known hypersensitivity to APO-ALFUZOSIN or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

- Patients with moderate to severe hepatic insufficiency, since alfuzosin blood levels are increased in these patients (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

- Combination with other alpha1-blockers.

- Combination with potent CYP3A4 inhibitors such as ketoconazole, ritonavir and itroconazole, because alfuzosin blood levels and exposure (AUC) are increased (See DRUG INTERACTIONS, Overview).

WARNINGS AND PRECAUTIONS

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 APO-ALFUZOSIN (alfuzosin hydrochloride) to rule out the presence of carcinoma of the prostate.

Patients with known hypersensitivity to alpha1-blockers should be closely monitored while on APO-ALFUZOSIN.

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

Patient should be warned that the tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions (see DOSAGE AND ADMINISTRATION, Administration).

Cardiovascular

APO-ALFUZOSIN is not indicated for the treatment of hypertension.

As with all alpha1-blockers in some patients, in particular, patients receiving antihypertensive medications, postural hypotension with or without dizziness or other symptoms may develop within a few hours following administration of APO-ALFUZOSIN. However, these effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. In such cases, the patients should lie down until the symptoms have completely disappeared. **As with other alpha1-blockers (alpha1-adrenergic blocking agents), there is a potential for syncope. Patients beginning treatment should be warned of the possible occurrence of such events.**

Care should be taken when APO-ALFUZOSIN is administered to patients with symptomatic orthostatic hypotension or patients who have had a pronounced hypotensive response to another alpha1-blocker.

As with all alpha1-blockers, alfuzosin has been observed to increase heart rate. Caution should be taken in patients with histories of tachyarrhythmia or with certain cardiovascular conditions, such as myocardial ischemia. The heart rate increasing effects of alfuzosin are additive to those of other heart rate increasing drugs (see DRUG INTERACTIONS).

Coronary insufficiency:

Specific treatment for coronary insufficiency should be continued; however, if angina pectoris reappears or becomes worse, APO-ALFUZOSIN should be discontinued.

Patients with congenital QTc prolongation, with a known history of acquired QTc prolongation or who are taking drugs known to increase the QTc interval should be evaluated before and during the administration of alfuzosin.

Co-administration of alfuzosin with a drug known to be a QTc prolonging drug should be evaluated by the physician based on individual patient's condition (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Electrocardiography).

Ophthalmologic

Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with some alpha-1-blockers.

Cases of IFIS have been observed with alfuzosin hydrochloride use. Ophthalmic surgeons should be informed in advance of cataract surgery of current or past use of alpha-1-blockers, as IFIS may lead to increased procedural complications. The ophthalmologists should be prepared for possible modifications to their surgical technique.**Special Populations**

Pregnant Women:

APO-ALFUZOSIN is not indicated nor recommended for use in women. No embryotoxic and/or teratogenic effects in the rat and rabbit were observed with alfuzosin hydrochloride. Parameters of male and female fertility, parturition, lactation and pup development were not modified by alfuzosin hydrochloride.

Nursing Women:

APO-ALFUZOSIN is not indicated nor recommended for use in women. It is unknown if the drug is excreted in human milk.

Pediatrics (<18 years):

APO-ALFUZOSIN is not indicated for use in children.

Geriatrics (>65 years of age):

The pharmacokinetics parameters (C_{max} and AUC) are not increased in elderly patients when compared to healthy male volunteers. Alfuzosin hydrochloride has been found to be a safe and effective alpha1-blockers when administered at the therapeutic dose (10 mg once-daily) to patients over the age of 65 years.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Dizziness and headache are the most frequent adverse drug reactions with alfuzosin hydrochloride.

Alfuzosin hydrochloride was associated with a low incidence of postural symptoms. As with all alpha1-blockers, there is also a potential for syncope.

Alfuzosin hydrochloride was not associated with deleterious effects on sexual function.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety information was derived from placebo-controlled clinical trials involving 1,608 men with BPH. The safety profile of alfuzosin hydrochloride in the ALFAUR study which included 363 patients with Acute Urinary Retention due to BPH was similar to the safety profile reported in previous BPH studies.

In the BPH studies, 4% of patients taking alfuzosin hydrochloride 10 mg prolonged release tablets withdrew from the study due to adverse events, compared with 3% in the placebo group. Dizziness and headache were the most frequent cause in each of the groups, although no single symptom was predominant. The withdrawal rate was similar in the alfuzosin hydrochloride group following long-term use in open-label extension studies for up to 1 year.

Table 1 summarizes the treatment-emergent adverse events that occurred in ≥2% of patients receiving alfuzosin hydrochloride prolonged-release tablets and placebo, in three 3-month trials. 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 Patients with BPH treated with Alfuzosin Hydrochloride and with Placebo in 3-Month Placebo-Controlled Clinical Studies

Adverse Event	Placebo (N=678)	Alfuzosin Hydrochloride (N=473)
General Disorders and Administration Site Conditions		
Fatigue[a]	12 (1.8%)	13 (2.7%)
Musculoskeletal and Connective Tissue Disorders		
Joint Disorders[b]	15 (2.2%)	10 (2.1%)
Infection and Infestations		
Upper respiratory tract infection[c]	23 (3.4%)	29 (6.1%)
Nervous System Disorders		
Dizziness[d]	19 (2.8%)	27 (5.7%)
Headache	12 (1.8%)	14 (3.0%)

[a]Includes: fatigue and asthenia
[b]Includes: arthritis, arthrosis, arthropathy, arthritis aggravated, arthralgia, and bursitis
[c]Includes: upper respiratory tract infection, rhinitis, sinusitis, laryngitis, pharyngitis
[d]Includes: dizziness and malaise

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The following adverse events, reported by between 1% and 2% of patients receiving alfuzosin hydrochloride prolonged-release tablets and placebo are listed and are as follows:

Table 2 – Treatment-Emergent Adverse Events Occurring Between 1% and 2% of Patients with BPH treated with Alfuzosin Hydrochloride Prolonged-release Tablets and Placebo in 3-Month Placebo-Controlled Clinical Studies

Adverse Event	Placebo (N=678)	Alfuzosin Hydrochloride (N=473)
Gastrointestinal Disorders		
Abdominal Pain	7 (1.0)	7 (1.5)
Dyspepsia	7 (1.0)	6 (1.3)
Constipation	3 (0.4)	5 (1.1)
Nausea	4 (0.6)	5 (1.1)
General Disorders and Administration Site Conditions		
Influenza-like symptoms	14 (2.1)	9 (1.9)
Pain	4 (0.6)	7 (1.5)
Infection and Infestations		
Bronchitis	5 (0.7)	7 (1.5)
Injury, Poisoning and Procedural Complications		
Inflicted injury[a]	3 (0.4)	6 (1.3)
Musculosqueletal and Connective Tissue Disorders		
Back pain[b]	11(1.6)	7 (1.5)
Reproductive System and Breast Disorders		
Impotence	4 (0.6)	7 (1.5)

[a]Includes: bite and inflicted injury
[b]Includes: ischial neuralgia, neuralgia, neuropathy, back pain, and lumbar disc lesion

Reproductive System and Breast Disorders

Impotence and other events related to sexual function are commonly associated with other alpha1-blockers, however, with alfuzosin hydrochloride, there were minimal effects regarding sexual function and ejaculatory disorders/abnormalities with no reports of priapism. Also, no patient discontinued treatment with alfuzosin hydrochloride due to ejaculation disorders. The reported incidence of ejaculation disorders was not associated with the study drug and is consistent with that reported in the untreated population.

Vascular Disorders

Signs and Symptoms of Orthostasis in Clinical Studies

The number of patients with symptoms of orthostasis are summarized in Table 3.

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

Symptoms	Placebo (N=678)	Alfuzosin Hydrochloride Prolonged-release tablets (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. These tests were considered positive for blood pressure decrease if (1) supine systolic blood pressure was ≤ 90 mmHg, with a decrease ≥ 20 mmHg 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. The percentage of patients with a positive test at any visit was 7.7% for placebo and 6.6% for alfuzosin hydrochloride prolonged-release tablets, as shown in Table 4.

Table 4 – Number (%) of Patients with BPH with Clinically Meaningful Decreases in Blood Pressure at Any Visit in 3-Month Placebo-Controlled Clinical Studies

Clinically Meaningful Change	Placebo (N=674)	Alfuzosin Hydrochloride Prolonged-Release Tablets (N=469)
Decreased systolic blood pressure	0	1 (0.2%)
Decreased diastolic blood pressure	3 (0.4%)	4 (0.9%)
Positive orthostatic test	52 (7.7%)	31[a] (6.6%)

[a] N = 471

A subset of patients from Study 1 had blood pressure measurements 12 to 16 hours after the first dose to assess the potential to produce orthostatic hypotension. None of the 35 alfuzosin hydrochloride prolonged release tablet-treated patients showed a positive test for systolic, diastolic, or orthostatic blood pressure change.

No age effect on the overall incidence of patients reporting adverse events was observed in the alfuzosin hydrochloride prolonged-release tablet group; elderly patients (≥ 65 years) did not experience more vasodilatory adverse events than the younger patients.

Post-Market Adverse Drug Reactions

The following adverse events have also been reported in postmarketing experience:

The following frequency rating is used; very common (≥ 10%), Common (≥ 1% and < 10%), Uncommon (≥ 0.1% and < 1%), Rare (≥ 0.01% and < 0.1%), Very rare (< 0.01%)

Cardiac Disorders:
Uncommon: tachycardia
Very Rare: angina pectoris in patients with pre-existing coronary artery disease (see also WARNINGS AND PRECAUTIONS, Cardiovascular). Isolated spontaneous cases of QT interval prolongation, ventricular arrhythmias, including Torsade de Pointes, ventricular tachycardia and fibrillation have been reported particularly in patients with preexisting cardiovascular diseases; however, a relationship between these adverse events and the alfuzosin hydrochloride treatment was not clearly established due to concomitant cardiac disorders, concomitant medications or absence of pre-treatment ECG measurement.

Vascular Disorders:
Uncommon: flushing

Gastrointestinal disorders:
Uncommon: diarrhea

General Disorders and Administration Site Conditions:
Uncommon: edema, chest pain

Ear and Labyrinth Disorders:
Uncommon: vertigo

Eye disorders:
Cases of intraoperative floppy iris syndrome have been reported (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Hepato-biliary disorders:
Cases of hepatocellular injury and cholestatic liver disease have been reported.

Respiratory, thoracic and mediastinal disorders:
Uncommon: Rhinitis.

Skin and Subcutaneous Tissue Disorders:
Uncommon: rash, pruritus
Very rare: urticaria, angioedema

DRUG INTERACTIONS

Overview

APO-ALFUZOSIN (alfuzosin hydrochloride) is not an inducer or an inhibitor of any of the principal hepatic enzymes involved in the metabolism of other drugs.

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of APO-ALFUZOSIN.

Potent CYP3A4 inhibitors, such as ketoconazole,
itraconazole and ritonavir, increased alfuzosin hydrochloride blood levels and exposure (AUC). Therefore, APO-ALFUZOSIN should not be co-administered with potent inhibitors of CYP3A4 (See CONTRAINDICATIONS). **See Drug-Drug Interactions for details of increased alfuzosin hydrochloride blood levels. As this is only a partial list, the physician is advised to consult current scientific literature regarding other CYP 3A4 competitive inhibitors prior to prescribing APO-ALFUZOSIN if other concomitant medications are used as high blood levels of APO-ALFUZOSIN can result.**

It is not known how combined exposure of any medications metabolized by the CYP3A4 hepatic enzyme isoform (such as modern alpha1-blockers), herbal remedies (particularly St. John's Wort, Milk thistle) and grapefruit juice may influence the overall efficacy and unwanted side effects of these medications, therefore, caution should be exercised.

APO-ALFUZOSIN should be prescribed carefully in combination with antihypertensive drugs (see WARNINGS AND PRECAUTIONS, Cardiovascular and Drug-Drug Interactions, Cardiovascular Drugs).

Drug-Drug Interactions

Anti-Infectious Drugs

Imidazole

Ketoconazole
CYP3A4 is the principal hepatic enzyme involved in the metabolism of APO-ALFUZOSIN. Ketoconazole is a strong-potency inhibitor of CYP3A4. Repeated 200 mg daily dosing of ketoconazole, for seven days **increased alfuzosin hydrochloride C_{max} 2.11-fold and AUC_{last} 2.46-fold following a single 10 mg dose of alfuzosin hydrochloride** under fed condition. Other parameters such as t_{max} and $t_{1/2}$ were not modified. The 8-day repeated administration of ketoconazole 400 mg daily **increased C_{max} of alfuzosin hydrochloride by 2.3-fold, AUC_{last} and AUC by 3.2 and 3.0 respectively**.

Cardiovascular Drugs

Alpha1-Blocker

APO-ALFUZOSIN should not be used in combination with other alpha1-blockers (see CONTRAINDICATIONS).

Anticoagulant

Warfarin
The potential drug interactions of alfuzosin hydrochloride with warfarin were studied in clinical trials. The results showed that alfuzosin hydrochloride can be prescribed without risk of interactions in combination with warfarin.

Beta-Blocker

Atenolol
The potential drug interactions of alfuzosin hydrochloride with atenolol were studied in clinical trials. The results showed that alfuzosin hydrochloride may be used with atenolol taking into account the hypotensive effects specific to drugs in this group.

Calcium Channel Blocker

Diltiazem
Repeated coadministration of 240 mg/day of diltiazem, a moderate-potency inhibitor of CYP3A4, with 7.5 mg/day alfuzosin (equivalent to the exposure with alfuzosin hydrochloride prolonged-release tablets) 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. No changes in blood pressure were observed.

Cardiotonic Glycoside

Digoxin
Repeated coadministration of alfuzosin hydrochloride and digoxin for 7 days did not influence the steady-state pharmacokinetics of either drug.

Diuretic

Hydrochlorothiazide
The potential drug interactions of alfuzosin hydrochloride with hydrochlorothiazide were studied in clinical trials. The results showed that alfuzosin hydrochloride can be prescribed without risk of interactions in combination with hydrochlorothiazide.

Nitrates

APO-ALFUZOSIN should be prescribed carefully in combination with nitrates.

Gastrointestinal Drugs

Histamine H_2 Receptor Antagonist

Cimetidine
The potential drug interactions of alfuzosin hydrochloride with cimetidine were studied in clinical trials. The results showed that alfuzosin hydrochloride can be prescribed without risk of interactions in combination with cimetidine.

Sexual Function Drugs

Inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5)

Tadalafil
The potential drug interaction of alfuzosin hydrochloride with tadalafil was studied in a clinical trial. The results showed that there is no clinically significant hemodynamic interaction between alfuzosin hydrochloride 10 mg once daily and tadalafil 20 mg. APO-ALFUZOSIN can be prescribed in combination with tadalafil.

Sildenafil
The effect on QT/QTc interval of the combination of alfuzosin 10 mg and sildenafil 100 mg has been studied in an electrophysiology trial (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics, Electrocardiography).

Drug-Food Interactions

APO-ALFUZOSIN should be taken after a meal.

It is not known how combined exposure of grapefruit juice may influence the overall efficacy and unwanted side effects of these types of medications, therefore, caution should be exercised.

Drug-Herb Interactions

Interactions with herbal products have not been established. It is not known how combined exposure of herbal remedies (particularly St. John's Wort, Milk thistle) may influence the overall efficacy and unwanted side effects of these medications, therefore, caution should be exercised when taking herbal remedies with these types of medications.

Drug-Laboratory Interactions

Treatment with alfuzosin hydrochloride for up to 12 months produced no clinically significant changes in urinalysis, the routine biochemical and hematologic tests as well as in prostate specific antigen (PSA).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Benign Prostatic Hyperplasia: The recommended dosage is one 10 mg APO-ALFUZOSIN (alfuzosin hydrochloride) tablet daily to be taken after the same meal each day.

Acute Urinary Retention: The recommended dosage is one 10 mg APO-ALFUZOSIN tablet daily after a meal to be taken from the first day of catheterization and continued beyond catheter removal unless there is a relapse of acute urinary retention or disease progression.

Administration

The tablet should be swallowed whole. Any other mode of administration, such as crunching, crushing, chewing, grinding or pounding to powder should be prohibited. These actions may lead to an inappropriate release and absorption of the drug and therefore possible early adverse reactions.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centres.

Should overdose of APO-ALFUZOSIN (alfuzosin hydrochloride) 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, vasopressor should then be used and the renal function should be monitored and supported as needed. Alfuzosin hydrochloride is 87% (82 - 90%) protein-bound, therefore, dialysis may not be of benefit.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

APO-ALFUZOSIN (alfuzosin hydrochloride), indicated for the treatment of benign prostatic hyperplasia (BPH) and as adjunctive therapy with urethral catheterization for acute urinary retention related to BPH and management following catheter removal, is an uroselective antagonist of post-synaptic α_1-adrenoceptors located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

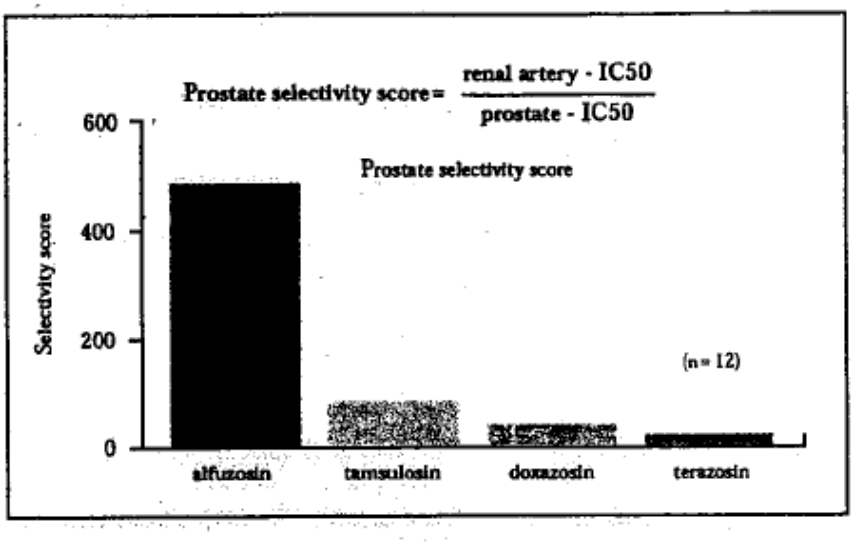
Pharmacodynamics

The clinical manifestations of benign prostatic hyperplasia are due to bladder outlet obstruction caused by anatomical (static) and functional (dynamic) factors. The static component is related to an increase in prostate size which may not cause symptoms. The dynamic component is related primarily to an increase in smooth muscle tone in the prostate, prostatic capsule, bladder base,

bladder neck, and prostatic urethra. This increased tone is mediated by the activation of α_1-adrenoceptors and leads to an increased resistance to urinary voiding and the symptoms of BPH such as a hesitant, interrupted, weak stream; urgency and leaking or dribbling; and/or more frequent urination, especially at night. Alfuzosin hydrochloride blocks α_1-adrenoceptors leading to a relaxation of the smooth muscle in the bladder neck and prostate.

In animal studies, alfuzosin was shown to be functionally uroselective by preferentially decreasing urethral blood pressure over arterial blood pressure. In human tissue, *in vitro*, alfuzosin has induced preferential α_1-adrenoceptor antagonist activity on prostatic cells relative to renal artery cells. This is illustrated in the figure below:

Figure 1: Prostatic Selectivity Score



In placebo-controlled clinical studies in patients with BPH, alfuzosin hydrochloride was shown to:

- significantly increase urine peak flow rate (Qmax) by 30% which is observed after the first dose
- significantly reduce detrusor pressure and increase bladder capacity
- significantly reduce residual urine volume

These favourable urodynamic effects lead to an improvement of lower tract irritative and obstructive symptoms without any deleterious effect on sexual function. The Quality of Life Index was also significantly improved by 33% in the alfuzosin hydrochloride prolonged-release tablet - treated patients.

In addition, the efficacy of alfuzosin 10 mg OD on peak flow rate and the limited effect on blood pressure have been demonstrated to be related to its pharmacokinetic profile. Moreover, the efficacy on peak flow rate is maintained up to 24 hours after intake.

A lower frequency of acute urinary retention was observed in the alfuzosin treated patient than in the untreated patient.

Electrocardiography 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 40 mg dose of alfuzosin was chosen because this dose achieves higher blood levels than those achieved with the co-administration of alfuzosin hydrochloride and ketoconazole 400 mg (CYP3A4 inhibitor). QT interval, obtained with 12-lead ECGs, was measured from 2h to 12h post treatment administration. Table 5 summarizes the mean effect and the maximum mean effect on heart rate (HR) and corrected QT interval (QTc) with different methods of correction [Bazett (QTcB), Fridericia (QTcF) and population-specific (QTcN) correction methods]. There is a trend to lower values for QTc interval changes from QTcB→ QTcF → QTcN, demonstrating the critical role of the correction formula used to minimize the biased overestimation linked to the heart rate increase. The maximum mean change of heart rate associated with a 10 mg dose of alfuzosin in this study was 3.69 beats/minute and 5.45 beats/minute with 40 mg alfuzosin. The change in heart rate with moxifloxacin was 2.85 beats/minute.

Table 5: 12-lead ECG – Mean change in HR and QTc data from T7 – T11h and maximum mean baseline- and placebo-adjusted HR and QTc interval changes over the observation period T2-T12h

		Mean difference		Largest time-matched analysis (bootstrap adjusted)	
Parameter	**Treatment**	**Mean change from baseline vs placebo**	**95% CI (upper bound)**	**Estimation of largest time-matched mean difference**	**95% CI (upper bound)**
HR (bpm)	Alfuzosin 10 mg	1.5	3.0	3.69	5.83
	Alfuzosin 40 mg	3.7	5.2	5.45	7.06
	Moxifloxacin*	1.5	3.0	2.85	4.26
QTcB (msec)	Alfuzosin 10 mg	3.3	6.9	6.08	9.59
	Alfuzosin 40 mg	10.8	14.4	13.27	16.71
	Moxifloxacin*	11.9	15.6	12.57	16.12
QTcF (msec)	Alfuzosin 10 mg	1.6	4.3	4.01	6.68
	Alfuzosin 40 mg	6.9	9.5	10.73	13.49
	Moxifloxacin*	10.3	13.0	11.17	14.06
QTcN (msec)	Alfuzosin 10 mg	0.5	3.0	2.74	5.27
	Alfuzosin 40 mg	4.6	7.0	9.30	12.14
	Moxifloxacin*	9.4	11.9	10.78	13.67

*****_Active control_

The maximum mean effect on QTcN 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.

A separate post-marketing study evaluated the effect of the co-administration of 10 mg alfuzosin and a drug with similar QT effect size. It was a double-blind, randomized, placebo and active-controlled (moxifloxacin 400 mg), 5-way crossover study conducted in 39 healthy white male subjects aged 19 to 46 years. QT interval, obtained with 12-lead ECGs, was measured from 4h to 12h post treatment administration. Maximum mean effect on HR and QT interval were extracted from a time-matched placebo adjusted analysis. In this study, the maximum mean placebo-substracted QTcN increase of alfuzosin 10 mg alone was 4.41 msec (upperbound 95% CI, 7.09 msec), shown in Table 6 below. The concomitant administration of the two drugs (alfuzosin and sildenafil) showed an increased QT effect when compared with either drug alone. This maximum mean QTcN increase [8.27 msec (UB 95% CI, 10.90 msec)] was not more than additive. Although this study was not designed to make direct statistical comparisons between drugs, the maximum mean QTcN increase with both drugs given together appeared to be lower than the maximum mean QTcN increase seen with the positive control moxifloxacin 400 mg [11.44 msec (UB 95% CI, 14.01 msec)]. The combination of alfuzosin + sildenafil produced a statistically significant increase in the mean heart rate [+ 4 bpm, $p<0.0001$].

Table 6: 12-lead ECG – Mean change in HR and QTc data from T7 – T10h and maximum mean baseline- and placebo-adjusted HR and QT interval changes over the observation period T4-T12h

		Mean difference		Largest time-matched analysis (bootstrap adjusted)	
Parameter	**Treatment**	**Mean change from baseline vs placebo**	**95% CI (upper bound)**	**Estimation of largest time-matched mean difference**	**95% CI (upper bound)**
HR (bpm)	Alfuzosin 10 mg	1.1	2.9	3.78	5.54
	Alfuzosin + Sildenafil	4.0	5.8	5.53	7.25
	Sildenafil 100 mg	1.4	3.2	2.13	3.82
	Moxifloxacin*	1.3	3.2	2.80	4.39
QTcB (msec)	Alfuzosin 10 mg	5.0	8.8	7.49	10.68
	Alfuzosin + Sildenafil	13.3	17.1	14.99	18.35
	Sildenafil 100 mg	6.3	10.1	7.85	11.30
	Moxifloxacin*	9.4	13.2	17.18	20.72
QTcF (msec)	Alfuzosin 10 mg	3.7	6.6	5.72	8.19
	Alfuzosin + Sildenafil	9.5	12.4	10.47	12.97
	Sildenafil 100 mg	4.8	7.7	6.40	8.97
	Moxifloxacin*	7.8	10.7	13.80	16.48
QTcN (msec)**	Alfuzosin 10 mg	2.2	5.1	4.41	7.09
	Alfuzosin + Sildenafil	7.0	10.0	8.27	10.90
	Sildenafil 100 mg	3.5	6.4	5.26	7.87
	Moxifloxacin*	6.5	9.4	11.44	14.01

******Active control*

***For the analysis of the mean difference, only QTcNi data are available (QT interval corrected by a subject specific formula)*

QT interval prolongation has not been studied in patients with BPH, therefore similar data is not available. This population may suffer from other conditions and have a higher risk to develop QT interval prolongation due to concomitant risk factors or pre-existing cardiovascular disorders. Based on individual patient's condition, monitoring for ECG abnormalities should be considered by the physician during treatment.

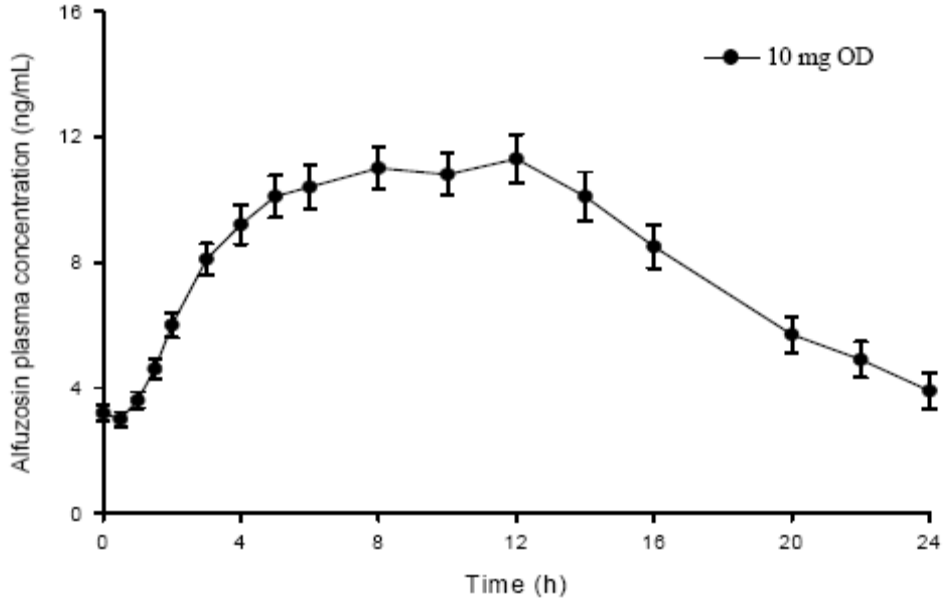
Pharmacokinetics

Absorption:

Bioavailability is reduced when alfuzosin hydrochloride is administered under fasting conditions. A consistent pharmacokinetic profile is obtained when alfuzosin hydrochloride is administered following a meal. A mean peak plasma concentration of 12.3 ± 6.6 ng/mL is reached in 6 to 14 hours after a single dose.

Under fed conditions and after repeated doses, mean C_{max} and $C_{through}$ values are 13.6 (SD = 5.6) and 3.1 (SD = 1.6) ng/mL respectively. Mean AUC0-24 is 194 (SD = 75) mg.h/mL. A plateau of concentration is observed from 3 to 14 hours with concentrations above 8.1 ng/mL (Cav) for 11 hours.

Figure 2: Mean (SEM) alfuzosin plasma concentration-time profiles after a repeated administration of alfuzosin 10 mg OD tablet in healthy middle-aged male volunteers (N=42)



Distribution:

The volume of distribution calculated following intravenous administration is 2.5 L/kg which indicates a distribution into extracellular fluids of the body. Alfuzosin hydrochloride is moderately bound to plasma proteins with the free fraction accounting for 13.3% in healthy volunteers. Fractions bound to serum albumin and α1-glycoproteins are 68.2 and 52.5%, respectively. Salicylic acid, hydrochlorothiazide, diltiazem, digoxin and indomethacin do not affect the binding of alfuzosin hydrochloride to human plasma proteins. Based on *in vivo* data, it is not likely that alfuzosin hydrochloride will affect the extent of binding of these drugs to human plasma proteins. There is an increase in free fraction in renal insufficiency patients (16.8%) and in patients with hepatic disease (20.8%).

Metabolism:

Alfuzosin hydrochloride undergoes metabolism by the liver, with only 11% of the parent compound being excreted as unchanged in the urine. The metabolites which are all inactive are eliminated in the urine (15-30%) and feces (75-91%). Alfuzosin hydrochloride is metabolized by three metabolic pathways (oxidation, O-demethylation, N–dealkylation) which are qualitatively identical to those observed in the animal (rat and dog).

CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion:

Following intravenous or oral administration, the elimination of alfuzosin hydrochloride is characterized, in healthy young subjects and in the target population, by a terminal half-life of about 4.8 hours and a total clearance of 0.3 L/h/kg.

The apparent half-life of alfuzosin hydrochloride is increased to 9.1 hours in healthy middle-aged volunteers and to 10.1 hours in elderly volunteers.

Special Populations and Conditions

Geriatrics:
Compared to healthy middle-aged volunteers, the pharmacokinetic parameters of alfuzosin hydrochloride (C_{max} and AUC) are not increased in elderly patients.

Renal Insufficiency:
Compared to subjects with normal renal function, the mean C_{max} and AUC values of alfuzosin hydrochloride are moderately increased (1.5 to 1.6 fold) in patients with various stages of renal impairment, with no change in the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant; and therefore, does not necessitate a dosing adjustment. Alfuzosin hydrochloride prolonged-release tablet has not been evaluated in patients with end-stage renal disease.

Hepatic Insufficiency:
After a single oral administration of alfuzosin hydrochloride in patients with severe hepatic insufficiency, the elimination half-life is prolonged. A two-fold increase in C_{max} values and a three-fold increase in the AUC is observed. Bioavailability is increased in comparison with that in healthy volunteers (See CONTRAINDICATIONS).

Chronic Cardiac Insufficiency:
The pharmacokinetic profile of alfuzosin hydrochloride administered intravenously is not affected by chronic cardiac insufficiency.

STORAGE AND STABILITY

Store at room temperature (15-30° C). Keep in a safe place out of the reach of children.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

APO-ALFUZOSIN (alfuzosin hydrochloride) 10 mg once-daily prolonged release tablet: Each yellow, round, flat-faced, beveled-edge tablet, engraved "APO" on one side and "ALF" over "10" on the other side, contains 10 mg alfuzosin hydrochloride. Available in bottles of 100 tablets.

In addition to the active ingredient, alfuzosin hydrochloride, each tablet also contains the non-medicinal ingredients: dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate phthalate, and yellow ferric oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

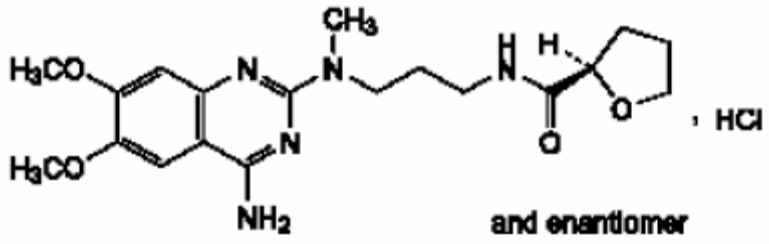
Drug Substance

Proper Name: Alfuzosin hydrochloride

Chemical Name: (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride

Molecular formula and molecular mass: $C_{19}H_{27}N_5O_4$•HCl; 425.92

Structural Formula:



Physicochemical properties:

White to off-white crystalline powder. Alfuzosin is readily soluble in water (> 10%). Its solubility at saturation over a range of pH values is given in the following table:

pH	Solubility (mg/mL)
1.5	338
4.6	171
5.5	337
6.8	332
7.4	253

The pH of a 2% solution is between 4.0 and 6.0. The pKa = 8.1 (by spectrophotometry).

Partition Coefficient (octanol/water at pH 7.4): The Partition Coefficient (D) between octanol and a pH 7.4 aqueous buffer was determined by an HPLC method and the result obtained, expressed as a logarithm, is Log $D_{7.4}$ = 1.51.

The two enantiomers (S and R) have the same pharmacological activity as the racemate.

CLINICAL TRIALS

Study Results

Benign Prostatic Hyperplasia (BPH):

Four placebo-controlled, double-blind, 12-week studies were conducted with alfuzosin hydrochloride (prolonged-release) tablets for BPH at doses ranging from 7.5 to 15 mg once-daily. These studies enrolled 1,949 patients with signs and symptoms of BPH. Based on the results of these studies, a dose of 10 mg was selected.

Below are the results of two studies that extensively evaluated alfuzosin hydrochloride prolonged-release tablets.

There were two primary efficacy variables in these studies: International Prostate Symptom Score (IPSS) and Peak Flow Rate (PFR). The International Prostate Symptom Score consists of questions that assess the severity of both irritative and obstructive symptoms, with possible scores ranging from 0 to 35. In addition, the Quality of Life Index was also measured, with possible scores ranging from 0 to 6. The second efficacy variable was peak flow rate.

As evident in Table 7 and Figures 2 and 3, there was a statistically significant reduction in the Symptom Score versus placebo in both studies, indicating a reduction in symptom severity. This was due to a statistically significant improvement in both the irritative and obstructive subscores. The Quality of Life Index was also significantly improved by 33% in the alfuzosin hydrochloride -treated patients.

Table 7 – Mean Change (±SD) from Baseline in Symptom Score in Patients with BPH

	Study 1*		**Study 2***	
Symptom Score	Placebo (N=167)	Alfuzosin Hydrochloride Prolonged-Release Tablets 10 mg (N=170)	Placebo (N=152)	Alfuzosin Hydrochloride Prolonged-Release Tablets 10 mg (N=137)
Total symptom score				
Baseline[a]	18.2 (±6.4)	18.2 (±6.3)	17.7 (±4.1)	17.3 (±3.5)
Change[b]	-1.6 (±5.8)	-3.6 (±4.8)	-4.9 (±5.9)	-6.9 (±4.9)
p-value	0.001		0.002	
Irritative subscore				
Baseline[a]	7.9 (±3.0)	8.1 (±3.0)	7.0 (±2.6)	6.8 (±2.5)
Change[b]	-0.4 (±2.5)	-1.4 (±2.5)	-1.6 (±2.6)	-2.3 (±2.3)
p-value	0.0006		0.02	
Obstructive subscore				
Baseline[a]	10.3 (±4.3)	10.1 (±4.4)	10.7 (±3.2)	10.4 (±3.2)
Change[b]	-1.1 (±3.8)	-2.2 (±3.4)	-3.3 (±4.0)	-4.6 (±3.5)
p-value	0.02		0.005	
Quality of Life Index				
Baseline[a]	3.7 (±1.1)	3.8 (±1.1)	3.3 (±1.0)	3.3 (±0.9)
Change[b]	-0.3 (±1.1)	-0.7 (±1.1)	-0.6 (±1.2)	-1.1 (±1.1)

p-value	0.002	0.0008

* Data analysis used for Study 1 was the Dunnett test and for Study 2, a One-way ANOVA was used.
[a] The pretreatment days on which the baseline values were obtained in both Study 1 and 2 were 28 days before randomization (D -28 to D0).
[b] Absolute difference between baseline value and last value

Figure 3 - Mean Change from Baseline to Total Symptom Score, by Visit: Study 1

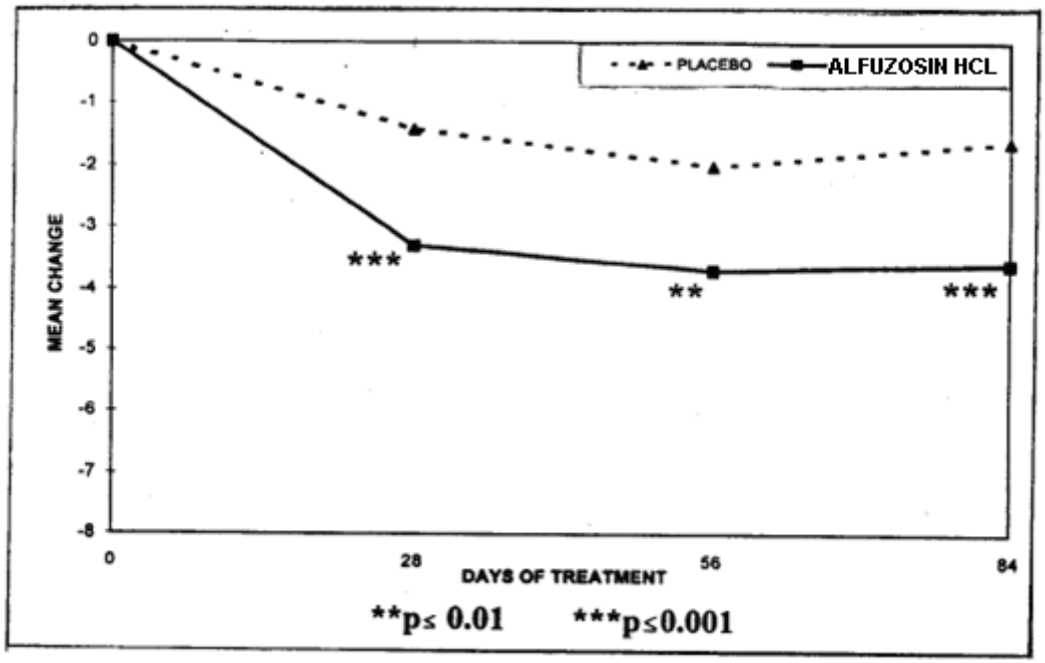
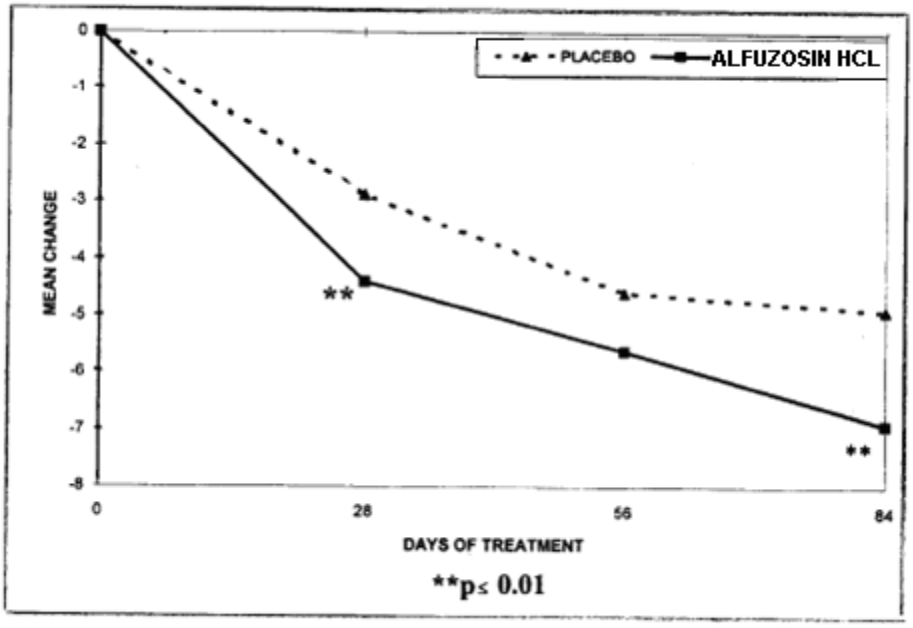


Figure 4 - Mean Change from Baseline in Total Symptom Score, by Visit: Study 2



Peak flow rate was also increased, indicating a lessening of obstruction to flow. As can be seen in Table 8 and Figures 5 and 6, the peak flow rate was increased significantly versus placebo in both studies. In Study 2, the assessment of peak flow rate was made at the end of the dosing interval (at approximately 20 hours after the initial dose when trough levels were expected), confirming the efficacy of the once-daily regimen.

Table 8 - Mean Change (±SD) from Baseline in Peak Flow Rate in Patients with BPH

	Study 1*		**Study 2***	
Peak Flow Rate	Placebo (N=167)	Alfuzosin Hydrochloride Prolonged-Release Tablets 10 mg (N=170)	Placebo (N=147)	Alfuzosin Hydrochloride Prolonged-Release Tablets 10 mg (N=136)
Baseline,[a] mL/sec	10.2 (±4.0)	9.9 (±3.9)	9.2 (±2.0)	9.4 (±1.9)
Change,[b] mL/sec	0.2 (±3.5)	1.7 (±4.2)	1.4 ±(3.2)	2.3 (±3.6)
p-value	0.0004		0.03	

* Data analysis used for Study 1 was the Dunnett test and for Study 2, a one-way ANOVA was used.
[a] The baseline was obtained on the day when uroflowmetry was performed before randomization (Day 0) for both Study 1 and 2.
[b] Absolute difference between baseline value and last value

Figure 5 - Mean Change from Baseline in Peak Flow Rate (mL/sec), by Visit: Study 1

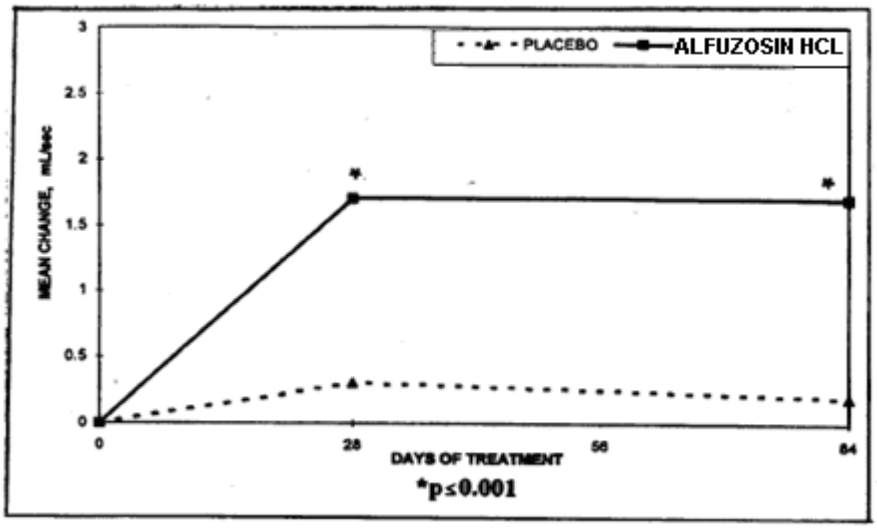
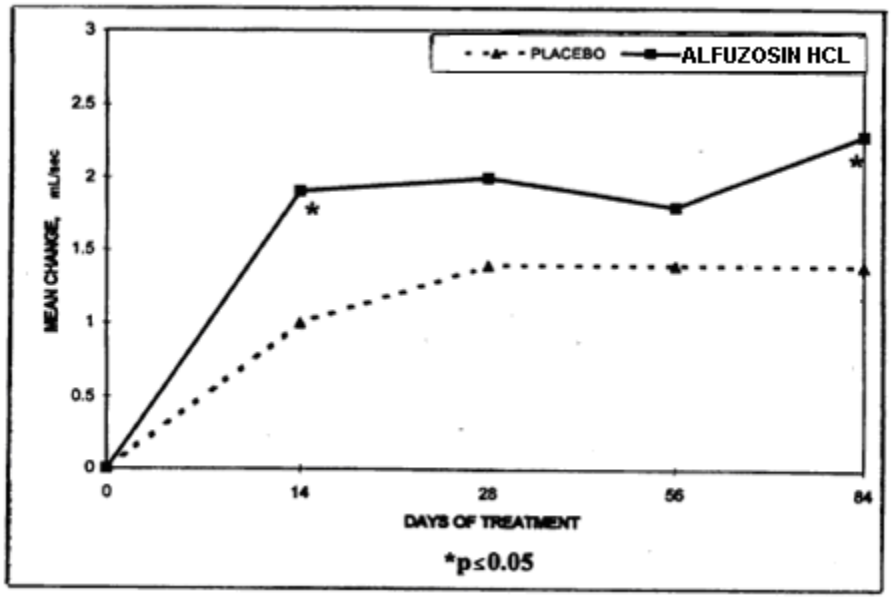


Figure 6 - Mean Change from Baseline in Peak Flow Rate (mL/sec), by Visit: Study 2



Efficacy was maintained in the open-label extension phases of these studies, for up to 1 year in duration.

Alfuzosin hydrochloride prolonged-release tablets were superior over placebo for both IPSS and PFR in both studies. Peak flow rate which was assessed at the end of the dosing interval, demonstrated the 24 hour coverage of this once-daily formulation.

In addition to the studies mentioned above, a 6-month, double blind, multicentre study to assess the comparative efficacy and safety of alfuzosin hydrochloride prolonged-release tablets, finasteride and the combination of both in 1,051 patients with signs and symptoms of BPH was performed. Symptomatic improvement was significantly higher with alfuzosin hydrochloride prolonged-release tablets from the first month of treatment, alone or in combination, compared with finasteride alone (alone: *P*= 0.01; combination: *P*= 0.03).

Acute Urinary Retention (AUR):

The ALFAUR study assessed the efficacy of alfuzosin hydrochloride prolonged-release tablets over placebo in patients with a first episode of AUR related to BPH (ALFAUR-1) as well as the need for surgery during the six months following initial AUR (ALFAUR-2). In the first phase of the double-blind, randomized, placebo-controlled, multicenter study, alfuzosin hydrochloride prolonged-release 10 mg (N= 241) or placebo (N=122) was administered once daily to patients for a duration of 3 to 4 days following urethral catheterization for AUR (starting during the first day of catheterization to one day after catheter removal). Patients were catheterized for a minimum period of 39 hours to a maximum of 70 hours. The primary endpoint was the number of patients with successful voiding after catheter removal. Successful voiding was defined as a return to spontaneous voiding, as determined by the patient's assessment, at 24 hours following catheter removal without re-catheterization. This endpoint is often used clinically to judge the necessity for urgent surgery.

In the alfuzosin hydrochloride prolonged-release tablet group, 62% of patients returned to successful voiding after catheter removal following a first episode of AUR compared with 48% of patients in the placebo group (p=0.012). In three countries that recruited more than 20 patients who received placebo during the period of catheterization following AUR, a placebo response rate of 20 to 79% was observed indicating a variability of this endpoint (patient self-assessment of voiding).

One hundred and sixty-five (165), out of 204 patients (alfuzosin hydrochloride prolonged-release tablets or placebo), who voided successfully during the first phase (ALFAUR-1), were re-randomized and entered the second phase (ALFAUR-2) of the study. The need for surgery during the 6 months following initial AUR episode was assessed. Alfuzosin hydrochloride reduced the risk of need for surgery (emergency surgery due to recurrence of urinary retention or non-emergency surgery) compared to placebo; risk reduction of 60% (p=0.04), 50% (p=0.04) and 30% (p=0.2) at months 1, 3 and 6, respectively, indicating a statistically significant difference with placebo up to 3 months.

Comparative Bioavailability Studies

A randomized, single-dose, blinded, 2-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on 51 healthy male volunteers. The rate and extent of absorption of alfuzosin was measured and compared following a single oral dose of APO-ALFUZOSIN Prolonged-Release Tablets (alfuzosin hydrochloride; Apotex Inc.) or XATRAL® Prolonged-Release Tablets (Sanofi-Aventis Canada Inc.). The results from measured data are summarized in the following table:

Table 9: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Alfuzosin Hydrochloride (A single 10 mg dose: 1 x 10 mg) From Measured Data/Fasting Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	**Apo-Alfuzosin**	**Xatral®†**	**Ratio of Geometric Means (%)##**	**90% Confidence Interval (%)##**
AUCt (ng•h/mL)	153.532 172.190 (46)	147.644 166.725 (51)	104.0	95.6 – 113.1
AUCinf (ng•h/mL)	163.987 185.554 (48)	155.883 177.243 (52)	105.2	96.6 – 114.6
Cmax (ng/mL)	9.778 10.556 (40)	8.399 9.192 (49)	116.4	107.6 – 126.0
Tmax# (h)	5.13 (36)	7.03 (82)		
Thalf# (h)	9.52 (42)	9.49 (44)		

Arithmetic means (CV%) only.
Based on the least squares estimate.
† Xatral® is manufactured by Sanofi-Aventis and was purchased in Canada.

A randomized, single-dose, blinded, 2-way crossover comparative bioavailability study, conducted under fed conditions, was performed on 29 healthy male volunteers. The rate and extent of absorption of alfuzosin was measured and compared following a single oral dose of APO-ALFUZOSIN Prolonged-Release Tablets (alfuzosin hydrochloride; Apotex Inc.) or XATRAL® Prolonged-Release Tablets (Sanofi-Aventis Canada Inc.). The results from measured data are summarized in the following table:

Table 10: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Alfuzosin Hydrochloride (A single 10 mg dose: 1 x 10 mg) From Measured Data/Fed Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	**Apo-Alfuzosin**	**Xatral®†**	**Ratio of Geometric Means (%)##**	**90% Confidence Interval (%)##**
AUCt (ng•h/mL)	234.520 253.273 (38)	226.020 244.723 (39)	103.8	95.3 – 112.9
AUCinf (ng•h/mL)	240.842 260.186 (38)	231.246 250.554 (39)	104.1	95.8 – 113.2
Cmax (ng/mL)	15.200 16.139 (32)	15.602 17.110 (41)	97.4	84.9 – 111.8
Tmax[#] (h)	7.28 (38)	7.83 (39)		
Thalf[#] (h)	10.52 (36)	9.77 (31)		
# Arithmetic means (CV%) only. ## Based on the least squares estimate. † Xatral® is manufactured by Sanofi-Aventis and was purchased in Canada.				

A double-blinded, multi-dose, randomized, 2-way crossover comparative bioavailability study, conducted under steady-state conditions, was performed on 30 healthy male volunteers. The rate and extent of absorption of alfuzosin was measured and compared following multiple doses of APO-ALFUZOSIN Prolonged-Release Tablets (alfuzosin hydrochloride; Apotex Inc.) or XATRAL® Prolonged-Release Tablets (Sanofi-Aventis Canada Inc.). The results from measured data are summarized in the following table:

Table 11: Summary Table of the Comparative Bioavailability Data

Summary Table of the Comparative Bioavailability Data Alfuzosin Hydrochloride (A multi 10 mg dose: 5 x 10 mg) From Measured Data/Steady State Conditions Geometric Least Square Mean Arithmetic Mean (CV%)				
Parameter	**Apo-Alfuzosin**	**Xatral®†**	**Ratio of Geometric Means (%)##**	**90% Confidence Interval (%)##**
AUCtau (ng•h/mL)	252.116 265.251 (33)	246.203 262.928 (34)	102.4	96.2 – 109.0
Cmax (ng/mL)	16.849 17.758 (35)	15.860 16.705 (31)	106.2	98.0 – 115.2
Cmin (ng/mL)	5.676 6.330 (43)	5.213 6.346 (53)	108.9	93.4 – 126.9
Tmax[#] (h)	5.167 (67)	5.400 (61)		
Fluc[#] (%)	106.380 (43)	102.398 (41)		
# Arithmetic means (CV%) only. ## Based on the least squares estimate. † Xatral® is manufactured by Sanofi-Aventis and was purchased in Canada.				

DETAILED PHARMACOLOGY

General animal pharmacological profile

Alfuzosin is a selective blocker of α_1-adrenoceptors which potently inhibits [^{3}H]-prazosin binding to the α_1-adrenoceptors in the cerebral cortex of male rats. Conversely alfuzosin inhibits binding of [^{3}H]-idazoxan or [^{3}H]-clonidine to α_2-adrenoceptors at concentrations 33 to 50 fold greater to those needed to inhibit [3H] prazosin binding.

In human prostatic adenomyofibroma tissue alfuzosin inhibits [^{3}H]-prazosin binding to α_1-adrenoceptors with a potency similar to that exerted to inhibit [^{3}H]-prazosin binding to the α_1-adrenoceptors in the cerebral cortex.

Alfuzosin has a balanced binding affinity for the three α1-adrenoceptor subtypes either in animal tissues (native: α_{1A}, α_{1B}) or cloned from human tissues and expressed in isolated cells (α_{1a}, α_{1b}, α_{1d}).

Alfuzosin has a selective binding profile in favor of α_1-adrenoceptors with little or no affinity for D_2-dopaminergic, $5HT_1$-and $5HT_2$-serotoninergic, H_1-histaminergic, ß-adrenergic or muscarinic cholinergic receptors.

Effects on lower urinary tract

Alfuzosin is a potent competitive antagonist of contractions induced by α_1-adrenoceptor stimulation by phenylephrine in trigone and urethra from male rabbits.

Noradrenaline- or electrically-induced contractions of isolated trigone were also potently inhibited by alfuzosin and only slightly reduced by the α_2-adrenoceptor antagonist idazoxan.

In the anaesthetized cat, by the intravenous (i.v.) route of administration, alfuzosin potently inhibited urethral hypertonia induced by electrical stimulation of the hypogastric nerve.

Accordingly, in anaesthetized dogs, alfuzosin potently inhibited urethral hypertonia induced by electrical stimulation of the hypogastric nerve. These results show that alfuzosin is a competitive antagonist of α_1-adrenoceptors in the lower urinary tract and may thereby, reduce the urethral pressure component related to sympathetic tone.

Uroselectivity

Since decrease in urethral pressure with minimal side-effects is the targeted end point of clinical use of α_1-adrenoceptor antagonists, the assessment of functional uroselectivity (preferential effect on urethral pressure without significant effects either on the cardiovascular or central nervous systems) in animal models is an essential pathway in the prediction of clinical uroselectivty.

The first models allowed to measure the effects of drugs on urethral pressure (UP) in anaesthetized cats and the effects on blood pressure (BP) in spontaneously hypertensive rats. The ratio of doses needed to reduce UP by 50% in cats over the dose needed to reduce BP by 20% in SHR therefore provided a first uroselectivity index. Under these conditions, the ratio calculated for alfuzosin was equal to 11, i.e. the dose needed to reduce BP was 11 fold higher than the dose required to reduce UP. This ratio was equal to 1 for prazosin i.e. both pressures were decreased at the same dose whereas for terazosin a ratio of 3.5 was achieved.

In another model allowing simultaneous measurement of urethal and arterial blood pressure in the same conscious animal, alfuzosin was administered by the i.v. route dose-dependently and selectively decreased urethral pressure. Arterial pressure was only slightly decreased at the highest dose for less than 15 min. No significant effects on heart rate were observed throughout the study. Within the dose-range tested and under normal sympathetic tone, alfuzosin exhibits functional uroselectivity in contrast with other α_1-adrenoceptor antagonists like prazosin, terazosin or tamsulosin.

Tissue distribution

One hour following oral administration of alfuzosin to rats, a prostate/plasma concentration ratio of 4.6 was reached. At 6 hours, prostatic tissue concentration was still about 9 times higher than plasma concentration.

In the same study, an index of the antagonistic activity of alfuzosin against phenylephrine-induced urethral contractions was directly correlated with prostatic tissue concentrations. This

study, demonstrating that alfuzosin concentrates in the prostate at levels 4 - 9 fold above the plasma levels, may thus provide an explanation for its preferential activity in the lower urinary tract compared to vascular effects.

In rat hippocampus, serotonin release is modulated by α_1-adrenoceptor activation and the local measurement of serotonin concentration may provide an index of central activity of adrenoceptor antagonists which penetrate the brain. Alfuzosin, at doses 10 to 40 times higher than those effective on urethral pressure, does not modify hippocampal serotonin release. Thus, in the rat, alfuzosin shows functional uroselectivity by decreasing urethral pressure at doses which do not modify blood pressure or penetrate the brain.

Cardiovascular profile

In anaesthetized cats, electrical stimulation of the sympathetic nerves induced a sustained increase in heart rate which was in a dose-dependent manner inhibited by the α_2-adrenoceptor agonist UK-14,304. Alfuzosin at 1mg/kg i.v. did not reverse this antagonism, indicating its absence of interaction with cardiac α_2-adrenoceptors.

Alfuzosin reduced the aortic blood pressure of normotensive dogs anaesthetized with sodium pentobarbital in a dose-dependent manner, without significantly modifying the heart rate. The reduction in the aortic pressure was due to a lowering of the total peripheral vascular resistance with redistribution of the cardiac output (which is only transiently increased), and the preferential dilatation of the femoral vascular bed. No change in cardiac contractility in dogs with intact cardiac innervation has been shown following alfuzosin treatment.

Alfuzosin was not cardiotoxic in conscious normotensive dogs with or without an experimental myocardial infarction induced 5 to 8 days before treatment. Hence, the compound slightly reduced the systolic aortic pressure of dogs with a healthy or infarcted heart, without notably modifying the heart rate. Alfuzosin caused no ECG abnormality either in healthy dogs or in animals.

Alfuzosin decreased but did not reverse, the rise in blood pressure seen when conscious normotensive dogs stood up on their hind legs, an experimental model allowing an evaluation of the action of various drugs on the orthostatic reflex. It was also shown that alfuzosin in this model, unlike prazosin at equiactive doses, did not lead to orthostatic hypotension and has a much less effect on the orthostatic reflex than prazosin.

Specific non-clinical safety pharmacology studies have been performed both *in vitro* and *in vivo* to examine effects on ventricular polarization. The most relevant *in vitro* study uses the hERG channel potassium current for assessment of the potential to prolong the QT/QTc interval. In this study at concentrations of up to 1000µM, the IC_{50} was calculated to be 83.5µM (35500ng/mL), indicating an extremely weak inhibition of the potassium channel. The positive control cisapride, well known for prolonging QT/QTc interval shows an IC_{50} of 0.0065 µM. At the dose of 83.5µM of alfuzosin, the concentration in the experimental system is over 3000-fold that seen in plasma (C_{max} of 11.2 ng/mL) at the therapeutic dose of 10mg/day. In the other *in vitro* studies performed using the guinea pig papillary muscle preparation and the piglet Purkinje fibre assay, very slight effects (increases of 4 to 6%) were seen on the *in vitro* action potential at doses of around 10µM (4000 ng/mL), equivalent to around 350-fold the human exposure at the

therapeutic dose. In the *in vivo* haemodynamic study in anaesthetized dogs, at the dose of 10mg/kg i.v., an increase in the QTc interval of 13% was seen associated with a weakly depressed atrioventricular conduction. At this dose, the estimated exposure (AUC) in the animals was around 12000 ng/mL.h, equivalent to 50-fold the human exposure at the therapeutic dose.

The package of safety pharmacology studies show that there is a very weak signal in the nonclinical studies, but that the effects occur at exposures which vary between 50 to 3000-fold that seen at therapeutic doses in man.

TOXICOLOGY

Acute toxicity

The results of single dose toxicity studies in mice and rats after oral and intraperitoneal administration are summarized in the table 12 below.

Table 12 - Single dose toxicity studies in mice and rats after oral and intraperitoneal administration

Species	Route	Sex	LD_{50}-values (mg/kg)
mouse	oral	M & F (10, 20, 40, 60 mice/sex)	2300 + 94 in males 1950 ± 79 in females
rat		M & F (10, 20 rats/sex)	≥ 4000 in males 3000 in females
mouse	intraperitoneal	M & F (20 mice/sex)	600 ± 25 in males 650 ± 20 in females
rat		M & F (10, 20 rats/sex)	480 in males and females

Clinical symptoms included palpebral ptosis, motor disturbances, sedation, prostration, cyanosis and clonic convulsions. Symptoms disappeared within 4 to 5 days after administration.

After intravenous administration in mice and rats, no deaths were observed as the maximum deliverable dose under experimental conditions was 40 mg/kg for both mice and rats.

Chronic toxicity

The chronic toxicity of orally administered alfuzosin was studied in rats and dogs in 1 month and 3 month toxicity studies. In addition, chronic oral toxicity was evaluated in rats up to 6 months. The dosages administered in these studies are given in the following table.

Table 13 - Chronic 1-month and 3-month toxicity studies in rats and dogs.

Study	Alfuzosin doses in mg/kg/day (Oral administration)
1 week intravenous study in rats (5M, 5F/dose group)	30, 60 and 100
1 week intravenous study in dogs (1M, 1F/dose group)	10, 15 and 30 mg/kg bid
1 month intravenous study in rats (3M, 3F/dose group)	2, 10 and 50
1 month oral study in rats (12M, 12F/dose group)	30, 100 and 400 in males 100, 200 and 400 in females
1 month intravenous study in dogs (3M, 3F/dose group)	2, 5 and 20 mg/kg bid
1 month oral study in dogs (1M, 1F/dose group)	5, 100 and 200 as gelatin capsules 60 for 1 week then 100 for 3 weeks
1 month study in dogs (2M, 2F/dose group)	50, 100 and 200 as gelatin capsules
1 month study in dogs (3M, 3F/dose group)	20 mg/animal of 5 mg SR tablets
3 month toxicity in rats (20M, 20F/dose group)	5, 30 and 200
3 month study in dogs (3M, 3F/dose group)	5, 20 and 80
6 month toxicity in rats (25M, 25F/dose group)	10, 50 and 250
1 year study in rats (20M, 20F/dose group)	1, 5 and 25
1 year study in dogs (7M, 7F/dose group)	5, 20 and 80

In the 1 week intravenous studies in rats, 3 animals died on days 1, 3 and 5 as a result of severe cardiac depression. Survivors exhibited prostration, dyspnea, sialorrhea, peripheral vasodilation and palpebral ptosis. No lesions were observed at injection sites. When dogs were administered alfuzosin intravenously for one week, no deaths occurred and clinical symptoms consisted of peripheral vasodilation, nasal dryness, diarrhea, hypotonia, tremor, protrusion of the nictitating membrane and hyperdacryorrhea. Palpebral ptosis was observed at 15 and 30 mg/kg bid with vomiting and salivation occurring at 30 mg/kg bid. In a one month intravenous study in dogs, no deaths occurred and no lesions were evident at injection sites. However clinical symptoms such as peripheral vasodilation, palpebral ptosis, nasal dryness, tachypnea, tachycardia and some hypotonia, vomiting, and ptyalism were recorded.

In one month oral studies in rats, clinical signs began to appear at 100 mg/kg/day for males and 200 mg/kg/day for females and consisted mainly of sedation, hypersalivation, slight changes in haematology as well as increased triglycerides. When rats where treated by i.v. route with 2, 10 or 50 mg/kg/day alfuzosin three deaths occurred in the first week. Clinical symptoms included palpebral ptosis, hypotonia, ocular secretions, peripheral vasodilation, respiratory difficulties and vaginal dilation.

Beagle dogs treated with 200 mg/kg/day for 4 weeks demonstrated motor incoordination and loss of appetite accompanied by a reduction in water intake. A dose of 200 mg/kg/day also produced an increase in SGPT, proteinuria, haematuria and renal lesions. When dogs were treated with 60 mg/kg/day for one week followed by 100 mg/kg/day for 3 weeks, clinical symptoms were mild and consisted of vomiting and diarrhea, tremor, sedation, vasodilation, palpebral ptosis and abnormal gait. Similar symptoms were observed in dogs treated for 3 months with 80 mg/kg/day. When dogs were treated with the 5 mg SR formulation for one month (20 mg/animal/day) no clinical signs and no deaths were observed. Body weight and food consumption were normal. In addition, dogs treated with 2, 5 or 20 mg/kg bid by IV route demonstrated typical clinical symptoms but no deaths were observed.

In 3 month toxicity studies in rats, 200 mg/kg /day caused transient hypersalivation, mild anaemia, increased urine output and weight changes of adrenal glands and spleen in males. When dogs were treated with alfuzosin 5, 20 or 80 mg/kg/day for 3 months, no deaths occurred and clinical symptoms included soft feces, vomiting, tremor, peripheral vasodilation and hyper salivation at 20 and 80 mg/kg/day. In addition, abnormal quietness was observed at all doses.

Rats treated with alfuzosin for 6 months demonstrated marked accumulation of the compound in blood and histopathological changes in adrenal tissue at 50 mg/kg/day in males and 250 mg/kg/day in females as well as liver cell changes such as necrosis of cells around acinus and cytoplasmic eosinophilia. In a this 6 month toxicity study, rats of both sexes were divided into four groups and administered 10, 50 or 250 mg/kg/day alfuzosin or control. Twenty-two animals died out of which 4 cases were considered not related to treatment. The deaths were dose-related (2 males at 50 mg/kg/day, 7 males and 9 females at 250 mg/kg/day). Rats administered 250 mg/kg/day and 2 males at 50 mg/kg/day died within 30 minutes after oral gavage and exhibited respiratory difficulties, hypersalivation and peripheral vasodilation prior to death. The other animals died between 2 and 22 hours following administration of alfuzosin. Alfuzosin also caused ptosis and peripheral vasodilation from Week 1 and peripheral redness of the eyes and vaginal dilation from Week 2. Rats receiving 50 and 250 mg/kg/day showed a dose-related frequency of salivation (from Week 2) and urogenital wetness (from Week 7). Food consumption slightly increased in all animals with the exception of males receiving 250 mg/kg/day who lost all appetite from Week 9.

When rats were treated with alfuzosin 1, 5 or 20 mg/kg/day for one year clinical symptoms were ptosis at 5 and 25 mg/kg/day and scrotal reddening and vaginal dilation in all treatment groups. Increased weight gain was observed in females at 25 mg/kg/day after Month 1. Food consumption was increased in males at the two higher doses and females at 25 mg/kg/day. Water consumption was normal. Twelve animals died or were sacrificed, however 8 cases were not treatment related. Organ weight examination revealed increases in the pituitary gland in females, the kidney and thyroid in males and the liver and spleen in both sexes.

Oral administration of alfuzosin to dogs for 53 weeks is characterized by a fairly wide range of clinical symptoms such as photophobia, tremor, palbebral ptosis, nasal dryness and soft feces. However laboratory and physiological tests did not show any treatment related effects. Macroscopic and microscopic examinations revealed impairment of the female reproductive cycle.

Carcinogenicity Studies

Carcinogenicity studies were carried out in the mouse and rat. Alfuzosin was shown to have no carcinogenic effect. In a 98-week oral carcinogenicity study in mice, alfuzosin was administered at doses with vehicle control to groups of 51 males and 51 females in 2 sub-groups. Mortality was increased in males at 100 mg/kg/day (53% in controls, 78% in the 100 mg/kg/day group). There were very slight increases in the relative weight of the liver in a few males who received 100 mg/kg/day of alfuzosin. No tumoral or other types of lesions were observed. At doses up to 100 mg/kg/day, alfuzosin had no carcinogenic potential in mice.

In a 104-weeks oral carcinogenicity study in rats, alfuzosin was administered at doses of 10, 30 and 100 mg/kg/day, with vehicle control, to groups of 50 males and 50 females in 2 sub-groups. Mortality was comparable in all doses. No oncogenic effect was noted.

Mutagenicity Studies

Alfuzosin did not show any mutagenic potential in the AMES test, mouse lymphoma test, chromosomal aberrations test in Chinese hamster ovary cells, unscheduled DNA repair test and mouse micronucleus test.

Reproduction and Teratogenicity Studies

Studies were carried out in the Sprague Dawley rat and the New Zealand rabbit. Alfuzosin was not embryotoxic, produced no teratogenic effects and did not affect fertility, parturition or lactation at dose levels many-fold greater than therapeutic levels in man.

A preliminary fertility study in Sprague Dawley rats established that the maximum dose to be used in the principal fertility study should be < 200 mg/kg/day. The principal study utilized groups of 26 male and female animals who received alfuzosin by gavage at doses of 5, 25 and 125 mg/kg/day, with vehicle control. Males were treated from Day 71 prior to mating to the end of gestation of the female. Females were treated from Day 15 prior to mating to Day 21 post-coitum and half of the females to Day 25 post-partum. The vaginal cytological cycle was altered at doses of 25 and 125 mg/kg/day of alfuzosin, but alfuzosin had not effect on mating, ovulation or pre- and post-natal development. The “No Adverse Effect Level” for the F0 generation was 5 mg/kg/day. The viability of the offspring was reduced at a dose of 125 mg/kg/day but the reproductive behaviour of the F1 generation was not changed following treatment of the parents. Consequently, the “No Adverse Effect Level” for the F1 and F2 generations was considered to be 25 mg/kg/day.

In a peri- and post-natal study in the rat, alfuzosin was administered from Day 15 post-coitum to Day 21 post-partum at doses of 5, 25 and 125 mg/kg/day, with vehicle control, to groups of 20 females. Alfuzosin at these doses caused no abnormalities in parents or pups. The “No Adverse Effect Level” for the F0 generation was 5 mg/kg/day and for the F1 generation was 125 mg/kg/day.

Teratogenicity studies were carried out in the rat and rabbit. Alfuzosin produced no teratogenic effects.

Alfuzosin was administered by gavage to three groups of females rats at various dose levels, with vehicle control, from Day 6 to Day 15 of gestation. In a preliminary study, 15 animals received 100 or 200 mg/kg/day. In the main study, 20 animals received 10, 50 or 250 mg/kg/day. These studies showed no effect of alfuzosin on organogenesis up to a dose of 250 mg/kg/day. The "No Adverse Effect Level" for the F0 and F1 generations was 250 mg/kg/day.

Alfuzosin was administered by gavage to two groups of females rabbits at various dose levels, with vehicle control from Day 6 to Day 18 of gestation. In a preliminary study, 4 animals received 50, 100 or 250 mg/kg/day. In the main study, 14 animals received 10, 30 or 100 mg/kg/day. These studies showed no effect of alfuzosin on organogenesis up to a dose of 100 mg/kg/day. The "No Adverse Effect Level" for the F0 generation was 10 mg/kg/day and for the F1 generation was 30 mg/kg/day.

Cytotoxicity Studies

Alfuzosin was administered in vitro to cultures of hepatocytes from males Sprague Dawley rats and male Beagle dogs at concentration from 1.25 to 100 μM. Findings were similar in both species: Alfuzosin induced gradual membrane and metabolic damage. However the IC_{50} was >100 μM. Alfuzosin was otherwise well tolerated by hepatocytes at these concentrations.

Immunotoxicity Studies

Sensitization studies carried out in male and female Dunkin Hartley albino guinea pigs showed that alfuzosin had a mild sensitizing capacity at oral doses of 6-10 mg/kg.