CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Medical Review(s)

NDA 21,287 Amendment 36
Alfuzosin 10mg extended-release tablets, Tradename Uroxatral™
Sponsor: Sanofi-Synthelabo, Inc.
Primary goal date: June 12, 2003
Prepared for 45-day filing meeting on January 31, 2003

Medical Officer NDA Filing Review

I. Summary

Alfuzosin is a selective alpha$_1$-adrenergic receptor blocker to be used for "the treatment of signs and symptoms of benign prostatic hyperplasia." The immediate-release formulation (2.5mg TID) has been marketed in foreign markets since 1987. The sustained-release formulation (5mg BID) and extended-release formulations (10mg QD) have been approved in foreign markets since 1993 and 1999, respectively.

The original NDA submission of December 8, 2000 contained the following deficiencies which were outlined in the "approvable" letter dated October 5, 2001.

- **The "application lacks adequate information, including clinical pharmacology data, to determine whether the product is safe for use because alfuzosin may increase QTc interval. QTc must be measured using an FDA agreed upon validated method."**
- **"Additional pharmacokinetic and pharmacodynamic studies are necessary to determine the effect of maximum doses of inhibitor of CYP450 3A4 isoenzyme (e.g. ketoconazole) on QTc interval."**

In addition, the agency requested updated draft labeling to reflect the new data collected. All safety information was also requested.

Amendment #36 was submitted by the sponsor December 12, 2002 to address these deficiencies. The amendment contains data from two Phase I studies that include a ketoconazole study and QT study. The ketoconazole protocol was previously submitted and was found to be adequate. The QT protocol was also previously submitted, reviewed by the CardioRenal Division and was found to be acceptable. These actions were conveyed via regulatory letters on May 1, 2002 and September 16, 2002, respectively. An updated safety report and revised labeling were also submitted within the amendment.

Conclusion: After preliminary review of Amendment #36 to NDA submission #21,287, this reviewer has not identified any deficiencies that would constitute the basis for a Refuse-to-File action. This reviewer concluded that the requested information has been submitted and is sufficiently complete to permit a substantive clinical review. However, clarification will be requested from the sponsor regarding why the number of patients fluctuated in data interpretation.

II. NDA Filing Review

1) QT issue

i. Original NDA submission 21,287

The sponsor had previously submitted data in protocol PKD4532 using 10mg, 20mg and 40mg of alfuzosin and protocol PCALF96US1 using a dose range of 7.5mg to 30mg." As stated in the NDA review dated September 14, 2001, "The primary conclusion of the review of the clinical studies was that 'the drug appears to be increasing the corrected QT by perhaps 10msec.'" And, "heart rate, QTcB, and QTcF are significantly increased from baseline for the 20 and 40mg doses compared to placebo." In essence, there remained insufficient clinical pharmacologic evidence whether alfuzosin has an effect on the QT interval.

Both Holter monitoring and 12-lead ECG methods were included in the measurement of the QT interval. The sponsor believes "Holter monitoring provides a sensitive and robust method for detection of QT interval changes in the presence of HR increases, thereby avoiding the bias of QT correction formulae. The CardioRenal consultant did not agree that the analysis of the Holter monitor data was superior to the QTcB or QTcF.

ii. **Amendment**

The QT issue was addressed by the sponsor in protocol PDY 5105 submitted with the amendment entitled **"Effect of supra-therapeutic doses of alfuzosin ER on QT interval, using a rate-independent method, compared to placebo and to moxifloxacin in healthy volunteers"**. It was a Phase I, single center, 4 way-crossover, randomized, double-blind placebo-controlled study. Each period consisted of a 2-day run-in placebo period, followed by a single-dose day, with a washout of 5 to 9 days between successive periods. Therapeutic (10mg) and supratherapeutic (40mg) doses of alfuzosin were used and measured with both 12-lead EKGs and Holters. Moxifloxacin was used as a "positive control". 48 healthy Caucasian male patients between 18 and 50 years of age with BMI between 18-30kg/m^2 were randomized.

The objectives were as follows: 1) To assess the mean change from baseline of QT interval after alfuzosin 10mg, 40mg, placebo, and moxifloxacin 400mg using Holter-monitoring with endpoints of 1000msec RR bin, largest-sample size RR bin, and average of all RR bins; 2) To evaluate change from baseline of QTc, corrected by QTcB, QTcF, QTcN (population-specific), QtcNi (subject-specific) with alfuzosin 10mg, 40mg, and moxifloxacin 400mg at Cmax using the 12-lead ECG; 3) To document systemic exposure after alfuzosin 10mg, 40mg, and moxifloxacin 400mg; and 4) To assess safety

Study Results: Holter

Table 1. Placebo-subtracted changes in QT by Holter at Cmax (taken from CardioRenal consult)

	Moxifloxacin N=37-43	Alfuzosin	
		10mg N=36-42	40mg N=35-45
1000 ms RR bin	7.0 (4.4, 9.6)	0.1 (-2.5, 2.6)	2.9 (0.3, 5.5)
Largest RR bin	6.9 (4.8, 9.1)	0.4 (-1.8, 2.6)	2.5 (0.4, 4.7)
Mean all RR bins	6.6 (4.6, 8.6)	0.1 (-1.9, 2.0)	2.0 (0.0, 3.9)

- Moxifloxacin at therapeutic dose (400mg) increased QT interval by 6.6 – 7.0 msec at all endpoints ($p < 0.00001$).
- Alfuzosin 10mg produced no significant change in QT interval. (0.1-0.4msec)
- Alfuzosin 40mg produced a QT change of no more than 2.9msec (range 2.0-2.9msec) which was statistically significant. ($p=0.0278$)
- Conclusion: Sponsor believes that these results confirm that alfuzosin does not cause meaningful increase to QT interval. The sponsor cites that in the almost 14 years of post-marketing experience providing over ~ billion therapy-days of exposure there have been no reports of Torsades de Pointe and no signal of ventricular arrhythmia risk.

Reviewer's Comments: 1) The results of the QT study were sent to CardioRenal Division for consultation. 2) The clinical significance of the statistical significant QT change with alfuzosin 40mg is unknown.

Study Results: EKG

At C_{max}: Comparison of moxifloxacin vs placebo

- Moxifloxacin produced statistically significant QT interval length increase at Cmax in comparison with placebo with conventional formulae (Bazzett 15.7msec and Fridericia 12.7msec).
- Similar but smaller results were found using QTcN and $QTcN_i$ (11.0 and 11.1 msec, respectively).

At C_{max}: Comparison of alfuzosin 10mg and 40mg vs placebo

- Sponsor believes that QTcB and QTcF calculations are inappropriate due to the increase in HR observed with alfuzosin (mean of 5 to 6 bpm).
  - For alfuzosin 10mg, QTcN and QtcNi values, changed less than 2msec (*but these values were not statistically significant).*
  - For alfuzosin 40mg, QTcN and QtcNi values, changed approximately 4msec *(again not statistically significant).*
  - The sponsor believes that the HR drove the QTcB and QTcF changes.

Table 2. Placebo-subtracted changes in QT by 12-lead EKG at Cmax (taken from CardioRenal consult)

	Moxifloxacin N=44	Alfuzosin	
		10mg N=44	40mg N=44
HR	2.8 (1.3,4.2)	5.2 (2.2, 8.3)	5.8 (3.2, 8.4)
QTcB	15.7 (10.8, 20.6)	10.2 (3.9, 16.6)	13.9 (5.0, 22.0)
QTcF	12.7 (8.6, 16.8)	4.9 (0.9, 8.8)	7.7 (1.9, 13.5)
QTcNi	11.1 (7.2,15.0)	1.8 (-1.3, 5.0)	4.3 (-0.5, 9.2)

Similar calculations were done to illustrate the change from baseline from T7 through T11 hours. Results showed similar trends as above Cmax data.

CardioRenal Comments: "The sponsors should be asked to clarify why all subjects' data did not contribute to these analyses, but the answers are not likely to change the overall interpretation. A carefully designed and well-executed study is capable of demonstrating an effect of alfuzosin on cardiac repolarization, but the effect is small. **At 40mg, the effect is less than half as large as that produced with the 400mg dose of moxifloxacin. Ten milligrams is probably also on the dose-response curve, but it would take a substantially larger study to resolve its effect. Although the 40mg dose does not cause concern in this regard, it is reassuring that symptoms will probably prevent many patients from using doses much above 10mg."**

2) **Ketoconazole interaction**

The agency had requested additional pharmacokinetic and pharmacodynamic studies to determine the effect of maximum doses of inhibitor of the CYP P450 3A4 isoenzyme (ketoconazole 400mg) on QTc interval in combination with alfuzosin treatment. The original NDA submission only contained data using 200mg of ketoconazole. The sponsor felt that there would only be a 30% increase in alfuzosin exposure by using 400mg ketoconazole.

The ketoconazole issue is addressed by the sponsor in protocol INT5056 entitiled, "**Assessment of pharmacokinetic drug interaction between alfuzosin 10mg QD formulation and ketoconazole 400mg per day in healthy male subjects.**" It is a Phase I, single-center, open-labeled, non-randomized, two-period study performed in 12 healthy male subjects between 18 and 40 years of age

and BMI of 18-25 kg/m^2. Period 1: Day 1, single dose of 10mg alfuzosin ER. Period 2: Days 1-8, single dose of ketoconazole 400mg. Day 7, single dose of 10mg alfuzosin co-administered with ketoconazole.

The objectives were as follows: 1) To assess the effect of repeated oral doses of 400mg ketoconazole on the PK profile of a single oral dose of 10mg alfuzosin extended –release formulation; 2) To assess the clinical and biological safety and tolerability of 10mg alfuzosin given alone and co-administered with 400mg ketoconazole after repeated daily doses of ketoconazole.

Study Results:

After 8 days of repeated administration of ketoconazole 400mg:

- Cmax of alfuzosin increased by 2.3-fold.
- AUC_{last} and AUC increased by 3.2 and 3.0, respectively.
- $t_{1/2}$ was statistically different with a slight mean increase of 1.16-fold.
- There was no statistical significant difference in T_{max}.

Sponsor Conclusion: Exposure (AUC) is increased by a factor of only 3 in the presence of maximum dose of ketoconazole (400mg).

III. Safety update

Sponsor believes that there is no evidence that the safety profile of alfuzosin has changed. There has been substantial use in Europe without evidence of cardiac repolarization problems.

AE during studies submitted

- Headache was observed most frequently and occurred after co-administration of ketoconazole and alfuzosin (6 cases).
- Other reported adverse events were nausea, vomiting, hot flushes, vagal malaise, thrombocytopenia (90,000/mm^3 - the pre-study level was 119,000 /mm^3).
- There was creatine kinase elevation (1 case) 5 days after coadministration of ketoconazole and alfuzosin and returned to normal after study.
- No subjects experienced orthostatic or relative hypotension.
- No QTc>450 or change from baseline QTc >60msec were observed.

IV. Labeling

A revised label has been submitted.

V. Financial disclosure

No financial disclosure was submitted.

Marcea Whitaker
Medical Officer
DRUDP

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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NDA 21287

Date submitted: December 8, 2000
Date received: December 8, 2000
Draft review completed: August 29, 2001
Review completed: September 14, 2001

Medical Officer Review

Sponsor:	Sanofi-Synthelabo Research 9 Great Valley Parkway Malvern, PA 19355
Drug:	Trade: **Uroxatral** Generic: **alfuzosin hydrochloride**
Route:	Oral
Dosage form:	Tablet
Strength:	10 mg
Proposed indication:	Treatment of the signs and symptoms of benign prostatic hyperplasia
Related IND's:	[redacted]

George S. Benson, MD
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Executive Summary:

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, alfuzosin hydrochloride 10 mg extended release (ER) tablets taken once/day should receive an "approvable" action for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia." The drug could be approved following resolution of issues concerning the presence and/or significance of QT prolongation. The risks associated with the use of this drug are otherwise acceptable and can be managed adequately with labeling.

II. Summary of Clinical Findings

A. Brief overview of clinical program

Alfuzosin is a selective alpha$_1$ adrenergic receptor blocking agent. This class of drugs has been used for the treatment of benign prostatic hyperplasia for more than 10 years and 3 selective alpha$_1$ adrenergic blocking agents have been previously approved by the FDA (terazosin, doxazosin, and tamsulosin). The drug product is alfuzosin hydrochloride extended release (ER) 10 mg tablets; the dose is 1 tablet/day.

Alfuzosin first received approval for foreign marketing for the immediate release (IR) (2.5 mg TID dose) in November, 1987, and is now registered in 87 countries for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia." The sustained release (SR) (5 mg BID dose) formulation was first approved for foreign marketing in September, 1993, and the extended release (ER) (10 mg daily dose) formulation, the subject of this NDA, was first approved for foreign marketing in September, 1999. As of May, 2000, the 10 mg ER tablet was approved in 11 European countries. Alfuzosin has never been withdrawn from the market in any country.

In support of NDA 21287, the sponsor submitted 4 Phase 3 trials of the ER formulation. Three of the trials (ALFUS, ALFOTAM, and ALFORTI) studied the 10 mg ER formulation and 1 (ALFOD) studied a 7.5 mg ER formulation. ALFUS was conducted in the United States and the other 3 studies were conducted in Europe. All 4 studies were 12 week, double-blind, multicenter, randomized, parallel-group trials and all had open label extensions ranging from 6 to 21 months. In all 12 week double-blind studies combined, 474 patients comprised the intent-to-treat population for the alfuzosin 10 mg ER formulation. In addition, 340 patients received 15 mg ER OD during 12 week double-blind studies. In the extension safety studies, 282 patients completed 9 additional months of therapy with the alfuzosin 10 mg ER OD dose and 363 patients completed 9 additional months with the alfuzosin 15 mg ER OD dose.

B. Efficacy

The primary efficacy endpoints in the trials were change from baseline in the International Prostate Symptom Score (IPSS) and the peak urinary flow rate (Q_{max}). The

IPSS is identical to the American Urologic Association Symptom Index (AUASI). These two endpoints are currently recommended for all drug studies dealing with the symptoms of BPH. (In ALFORTI, improvement in Q_{max} was a secondary endpoint.) In ALFOD, the 7.5 mg ER dose was not significantly superior to placebo. Because the dose of alfuzosin (ER) was only 7.5 mg in trial ALFOD, this trial was not included in the efficacy analysis (Table 1).

Table 1. Drug Doses (Alfuzosin ER) in Pivotal Studies

Study	N (completed)	Dose (Double blind phase)	Dose (Open label phase)
ALFOD	188 drug 182 placebo	7.5 mg/day placebo	7.5 mg/day
ALFORTI	136 drug **127 Uroxatral** 144 placebo	2.5 mg tid **10 mg/day** placebo	**10 mg/day**
ALFUS	**157 Uroxatral** 149 drug (15 mg) 158 placebo	**10 mg/day** 15 mg/day placebo	15 mg/day
ALFOTAM	**145 Uroxatral** 142 drug (15 mg) 142 placebo 149 tamsulosin	**10 mg/day** 15 mg/day placebo 0.4 mg/day	15 mg/day

With respect to the IPSS, the mean decreases in total score ranged from –3.6 to –6.9, with a net improvement of approximately 2 points relative to placebo that was consistent across the 3 studies (Table 2).

Table 2. Changes in IPSS scores in the 3 pivotal trials.

	ALFUS		ALFORTI		ALFOTAM	
	Placebo N=167	Alfuzosin 10 mg N=170	Placebo N=152	Alfuzosin 10 mg N=137	Placebo N=150	Alfuzosin 10 mg N=151
D_0 (mean)	18.2	18.2	17.7	17.3	17.7	18.0
D_{end}-D_0 (mean)	-1.6	-3.6	-4.9	-6.9	-4.6	-6.5
P-value	0.001		0.002		0.007	

(D_0 is baseline; D_{end} is end of 12 week treatment phase)

The changes in peak flow rate (Q_{max}) (cc/sec) are shown in Table 3.

Table 3. Changes in Q_{max} (cc/sec) in the 3 pivotal studies

	ALFUS		ALFORTI		ALFOTAM	
	Placebo N=167	Alfuzosin 10 mg N=170	Placebo N=147	Alfuzosin 10 mg N=136	Placebo N=150	Alfuzosin 10 mg N=151
D_0 (mean)	10.2	9.9	9.2	9.4	9.3	9.5
D_{end}-D_0 (mean)	0.2	1.7	1.4	2.3	0.9	1.5
P-value	0.0004		0.03		0.22	

(D_0 is baseline; D_{end} is end of 12 week treatment phase)

Improvement in both IPSS and Q_{max} were achieved by the first post-baseline visit (4 weeks) and the effect was maintained throughout the remainder of the 12 week double-blind treatment phase. The improvement in IPSS is clinically and statistically meaningful. The change is Qmax is modest but statistically significant in ALFUS and ALFORTI and trends toward effectiveness in ALFOTAM. There is minimal data directly comparing alfuzosin to other alpha$_1$ adrenergic receptor blocking agents. The improvements in IPSS and Q_{max}, however, appear similar to those reported for the other alpha$_1$-adrenergic blocking agents approved for the treatment of symptoms of benign prostatic hyperplasia.

C. Safety

Between 1988 and May, 2000, a total of [redacted] alfuzosin 2.5 mg IR tablets, [redacted] mg SR tablets, and [redacted] 10 mg ER tablets have been sold. In the 3 randomized, 12 week, placebo-controlled pivotal studies, 474 patients were randomized to the alfuzosin 10 mg ER and 340 patients to the alfuzosin 15 mg ER doses. As of the October 31, 1999, cutoff, 282 patients had completed 9 months of the 10 mg ER extension trials and 363 patients had completed 9 months of the 15 mg ER extension trials.

The primary safety concern with alpha$_1$-adrenergic blocking agents is hypotension and related symptoms (dizziness and syncope). "Vasodilatory" adverse events associated with the 7.5 mg, 10 mg, and 15 mg doses of alfuzosin ER tablets are shown in Table 4.

Table 4. Number (%) of patients reporting "vasodilatory" adverse events in double-blind phase of 4 pivotal trials - placebo and alfuzosin ER treatment groups

	Placebo N=678	Alfuzosin 7.5 mg N=(204)	**Alfuzosin 10 mg (N=473)**	Alfuzosin 15 mg (N=335)
Patients with at least 1 event	19 (2.8%)	5 (2.5%)	**29 (6.1%)**	33 (9.9%)
Dizziness	19 (2.8%)	3 (1.5%)	**25 (5.3%)**	27 (8.1%)
Hypotension	0	0	**2 (0.4%)**	2 (0.6)
Malaise	0	1 (0.5%)	**2 (0.4%)**	3 (0.9%)
Syncope	0	1 (0.5%)	**1 (0.2%)**	2 (0.6%)
Postural hypotension	0	0	**0**	0

Alpha$_1$ blocking agents may have a "first dose vasodilatory" effect and 2 currently approved drugs (terazosin and doxazosin) in this class require upward dose titration. The number (%) of patients with "vasodilatory" adverse events reported on Day 1 in the double-blind phase of the 4 pivotal trials is shown in Table 5.

Table 5. Number (%) of patients reporting "vasodilatory" adverse events reported on Day 1 in double-blind phase of 4 pivotal trials – placebo and alfuzosin ER groups

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	**Alfuzosin 10 mg (N=473)**	Alfuzosin 15 mg (N=335)
Patients with at least 1 event	0	3 (1.5%)	**4 (0.8%)**	4 (1.2%)
Dizziness	0	1 (0.5%)	**3 (0.6%)**	3 (0.9%)
Syncope	0	1 (0.5%)	**1 (0.2%)**	0
Hypotension	0	0	**0**	2 (0.6%)
Malaise	0	1 (0.5%)	**0**	0
Postural hypotension	0	0	**0**	0

In the open-label extension phases, when placebo patients began alfuzosin treatment, 3 additional cases of syncope occurred on the first day of dosing with 15 mg alfuzosin ER. The possibility of dizziness, hypotension, and syncope are adequately addressed in the "Warnings" section of the label. A "first-dose" effect does occur with alfuzosin 10 mg ER, but the incidence of adverse events (primarily hypotension and syncope) is low and dose titration does not appear to be warranted. Although data concerning direct comparisons with other alpha$_1$ blockers is limited, "vasodilatory" adverse effects seen with alfuzosin appear to be similar to other agents in this drug class.

EKG effects:

The results of 2 pre-clinical and 2 clinical studies dealing with the effect of alfuzosin on the QT interval were submitted with the 120 Day Safety Update. In Trial PKD4532, placebo and doses of alfuzosin of 10, 20, and 40 mg were studied. The mean changes in heart rate, QT, QTcB, and QTcF for study PKD4532 are shown in Table 6.

Table 6. Statistical Analysis of Changes in ECG Parameters from Baseline: Mean (One-sided 95% CI, Upper Bound) Average Difference from Placebo over 0.5 to 24 Hours: Study PKD4532.

Parameter	Overall Treatment Effect	Alfuzosin 10 mg versus placebo	Alfuzosin 20 mg versus placebo	Alfuzosin 40 mg versus placebo
Heart rate	P=0.0001	0.6 (1.3)	4.6 (5.4)***	5.8 (6.5) ***
QT (ms)	P=0.0001	-1.1 (0.3)	-6.3 (-4.9)	-4.7 (-3.3)
QTcB (ms)	P=0.0001	1.2 (3)	8.5 (10.3) ***	13.2 (15.0) ***
QTcF (ms)	P=0.0001	0.5 (1.8)	3.4 (4.7) ***	7.1 (8.4) ***

*** = p-value vs. placebo = 0.001

The sponsor believes that the QTcB is "biased toward reporting normal QT as abnormally long when corrected." The sponsor also believes that Holter monitor recording and analysis of QT/RR pairs is more accurate and this analysis showed no clinically significant difference between alfuzosin and placebo.

The sponsor's conclusions are as follows:

"Alfuzosin belongs to the alpha$_1$-blockers drug class, which is widely known to produce an increase in heart rate but which is not associated with ventricular arrhythmias. The information presented in this document, derived from pre-clinical and clinical development and a large post-marketing experience, indicates a lack of arrhythmogenic potential, as supported by the following conclusions:

1) Alfuzosin has only a slight in vitro electrophysiologic effect, and only at concentrations several hundred times the expected therapeutic levels. Alfuzosin is a very weak I_{kr} channel blocker, based on inhibition of HERG potassium current. In this model, alfuzosin is 4 to 30 times weaker than the alpha$_1$-blockers doxasozin, terazosin, and prazosin.
2) Using the best available technique for evaluating change in repolarization independent of heart rate, alfuzosin at doses up to 40 mg appears to prolong the QT interval by only about 2 ms. This effect is not dose-related and is not clinically relevant.
3) Review of the large safety experience from a substantial clinical database and extensive post-marketing information provides no evidence for arrhythmia-induced risk."

Because of the discrepancies in the QTc results depending upon which correction method was used, a consultation was requested from the Division of CardioRenal Drug Products (see consult from Division of CardioRenal Drug Products). The consultant concluded that

"the drug appears to be increasing corrected QT by perhaps 10 msec." The consultant does not agree with the sponsor's argument that Holter monitor assessment is the best available technique for evaluating change in repolarization independent of heart rate. In addition, the risk of dangerous adverse events secondary to this degree of QT prolongation can not be estimated with certainty. In the opinion of this reviewer, alfuzosin 10 mg ER should not be approved until issues concerning the presence and/or risk of QT prolongation associated with this drug are resolved.

Alfuzosin is not an inducer or inhibitor of any of the primary hepatic enzymes involved in the metabolism of other drugs. Administration of alfuzosin does not effect the pharmacological response to warfarin and does not influence the steady state pharmacokinetics of digoxin. CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin. Repeated administration of ketoconazole increases alfuzosin C_{max} 2-fold following a single 10 mg dose of alfuzosin.

No other significant safety concerns were identified in the controlled trials and their extension phases or in the large post-marketing experience with the IR, SR, and ER formulations.

D. Dosing:

During clinical development, results from the Phase 3 ALFOD study showed that the 7.5 mg ER dose was not significantly more effective than placebo. Ten and 15 mg ER doses were subsequently evaluated. The 10 mg ER dose was shown to be effective in Phase 3 studies ALFOTAM, ALFUS, and ALFORTI. No additional benefit was demonstrated with the 15 mg dose. The 10 mg dose was the lowest effective dose and demonstrated a better safety profile than the 15 mg dose.

E. Special populations:

Gender differences: Alfuzosin is not indicated for use in women.

Ethnic/racial differences: The number of non-Caucasians in the clinical trials was too small to make meaningful decisions concerning racial differences.

Geriatric issues: In the clinical trials, 48% of patients were 65 years of age or over and 11% were 75 years of age or over. No overall differences in safety or effectiveness were observed between these and younger patients. In a pharmacokinetic assessment during Phase 3 clinical studies in BPH patients, no clinically relevant differences were detected in peak plasma levels of alfuzosin on the basis of age.

Renal impairment: In comparison to patients with normal renal function, patients with various degrees of renal impairment (mild, moderate, severe) had mean C_{max} and AUC values that were increased up to 1.5-fold at the 10 mg dose. These values are similar to those observed with alfuzosin 15 mg in patients with normal renal function. The sponsor believes that the alfuzosin 15 mg ER dose has an acceptable safety profile based on the

results of Phase 3 studies ALFUS and ALFOTAM and their extensions, even though there was a dose-related increase in adverse event rates and blood pressure changes with the 15 mg dose as compared to the 10 mg dose. The section on "Patients with Renal Impairment" in the label should be revised to reflect this increase in adverse events rate.

- Hepatic impairment: Patients with moderate to severe hepatic insufficiency have increased blood levels of alfuzosin. Alfuzosin is contraindicated in these patients and this is stated in the label. The pharmacokinetics of alfuzosin 10 mg ER have not been evaluated in patients with mild hepatic insufficiency. The label states that "the physician should consider the risks and benefits of administering Uroxatral in this population."

Pediatric: Alfuzosin is not indicated for use in children. A pediatric waiver has been requested and granted (August 20, 2000).

Pregnancy: Alfuzosin is not indicated for use in women.

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Clinical Review

I. Introduction and Background

A. Proposed Drug and State of Armamentarium for Drug Therapy of the Symptoms of Benign Prostatic Hyperplasia

Alfuzosin hydrochloride (trade name Uroxatral) is an alpha$_1$ adrenergic receptor antagonist. The proposed indication is 'treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland." The recommended dose is 10 mg alfuzosin ER formulation once daily.

Benign prostatic hyperplasia (BPH) is a common condition in aging men. Historically, symptomatic BPH has been treated primarily by surgery consisting either of transurethral or open surgical prostatectomy. Several "minimally invasive" techniques including microwave therapy and laser vaporization have been introduced. The frequency of surgery for BPH has markedly decreased in recent years primarily because of the development of effective pharmacologic therapy.

Two major approaches to drug development have led to the approval of 2 major classes of drugs for treating the symptoms of BPH. The first drugs to be approved for this indication were the alpha$_1$-adrenergic receptor blocking agents. These drugs are thought to improve symptoms of BPH by blocking alpha$_1$-adrenergic receptor mediated smooth muscle contraction in the prostatic stroma (and probably bladder neck) and thereby decreasing the magnitude of bladder outlet obstruction. The second major approach to drug therapy of BPH consists of 5 alpha-reductase inhibition. Dihydrotestosterone (DHT) is thought to be the primary androgen responsible for facilitating hyperplastic growth of the prostate. DHT is produced from testosterone by the action of the enzyme 5 alpha-reductase. Treatment with a 5 alpha-reductase inhibitor is thought to decrease the size of the prostate (acting primarily on prostatic epithelium) and thereby decrease the degree of prostatic obstruction. Finasteride (Proscar) is the only currently approved 5 alpha-reductase for use in treating the symptoms of BPH.

Currently approved alpha$_1$ adrenergic receptor blocking agents for the treatment of symptoms of BPH are terazosin (Hytrin), doxazosin (Cardura), and tamsulosin (Flomax). Alfuzosin (under the trade name Xatral) was initially approved for foreign marketing as an immediate release (IR) for the treatment of BPH in 1988.

B. Milestones in Product Development

An End-of-Phase 2 meeting was held with the sponsor in August, 1997. The results of ALFORTI were discussed and the sponsor accepted the Division's recommendation to conduct 2 additional studies. At the pre-NDA meeting held on May 24, 2000, the sponsor submitted the results of 4 trials (ALFORTI, ALFUS, ALFOTAM, and ALFOD).

C. Foreign Approval

The sponsor has developed and marketed in foreign countries three alfuzosin-containing oral tablet dosing regimens for the treatment of benign prostatic hyperplasia. The immediate release (IR) tablet is a 2.5 mg tablet for tid dosing. The IR formulation was approved for use abroad in 1987. The sustained release (SR) tablet is a 5.0 mg tablet for bid dosing. The SR formulation was approved for use abroad in 1993. The IR and SR formulations of alfuzosin have been approved for marketing in 87 countries. The third regimen (the subject of this NDA) is the extended release (ER) formulation. The sponsor is proposing to market only the 10 mg strength in the United States. The sponsor has manufactured investigational ER tablets in 7.5 mg, 10 mg, and 15 mg strengths. As of May 31, 2000, the 10 mg ER formulation has been approved in 11 countries (Denmark, Finland, France, Ireland, Italy, Latvia, Netherlands, Portugal, Sweden, Switzerland, and the United Kingdom). From October, 1988, to May, 2000, a total of — 2.5 mg IR tablets, — 5 mg SR tablets, and — 10 mg ER tablets have been sold. The number of therapy days has been estimated at about — million (

). Alfuzosin has not been withdrawn from the market in any country.

D. Issues with Pharmacologically Related Agents

The primary concern of therapy of symptoms of BPH with alpha adrenergic blocking agents is the occurrence of "vasodilatory" side effects including dizziness, hypotension, and syncope. These side effects also occur with alfuzosin. A comparison of alfuzosin to other drugs of this class is difficult because of the lack of direct comparison data. This issue is adequately addressed in the label.

II. Clinically relevant findings from chemistry, toxicology, and statistics

There are no significant unresolved chemistry issues.

No significant problems were identified from a toxicology standpoint. No unexpected or unusual toxicity was demonstrated. The Pharmacology/Toxicology reviewer believes that from a pharmacology/toxicology standpoint that the drug is approvable with a minor labeling change.

No significant problems were identified in the statistical review.

III. Human pharmacokinetics and pharmacodynamics

Cmax and AUC values were 2.5 times and 2.1 times higher, respectively, in the fed condition than in the fasted condition. In the clinical trials, patients were instructed to take the medication with meals. This is consistent with the proposed label.

A plateau of plasma concentration was observed between 3 and 16 hours after dosing. Steady-state plasma concentration was reached after two, once-daily administrations. Dose proportionality was demonstrated at single and repeated doses (from 7.5 mg up to

30 mg). Alfuzosin is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2.

Specific concerns identified during the review were:

1) Ketoconazole increases the alfuzosin C_{max} 2-fold and the AUC 2.5-fold. This reviewer agrees with the clinical pharmacology recommendation that ketoconazole and other potent CYP3A4 inhibitors should be "contraindicated."
2) The C_{max} of alfuzosin is increased 1.5-fold in patients with mild, moderate, and severe renal insufficiency. This reviewer agrees with the clinical pharmacology recommendation that this information should be included in the "Precautions" section of the label and that "caution should be exercised when UROXATRAL is administered in this population.".

IV. Description of clinical data and sources

The following materials were reviewed: 1) Overview section, integrated summary of safety, and integrated summary of efficacy from the NDA 2) 4 pivotal studies (ALFOD, ALFUS, ALFORTI, and ALFOTAM) and the open-label extension studies for 3 of the 4 pivotal trials (ALFUSEXT, ALFORTIEXT, and ALFOTAMEXT) 3) 120 Day Safety Update of the Integrated Summary of Safety and the NDA Final Safety Update 4) Post-Marketing Safety Synthesis for the IR, SR, and ER formulations 5) Study reports dealing with the effect of alfuzosin on the QT interval (#00-00312-EN-00 "Effects on the action potential of piglet Purkinje fibers" ; #00-00329-EN-00 "Effects on the herg channel stably expressed in mammalian cell line. Comparison with tamsulosin, doxazosin, prazosin, and terazosin" ; #INT4285 "Effect of ketoconazole on alfuzosin blood levels" ; #PKD4532 "Effect of supratherapeutic doses of alfuzosin on the ECG" ; #PCALF96US01 "Manual reading of QT intervals of ECG from PCALF96US01"). Two cases reports of adverse events reported in the literature were also submitted by the sponsor and reviewed.

V. Clinical review methods

Three of the four pivotal studies and their extension phases (ALFUS and ALFUSEXT, ALFORTI and ALFORTIEXT, and ALFOTAM and ALFOTAMEXT) were reviewed in detail and these reviews are attached as appendices A, B, C, D, E, and F. A summary of the 120 Day Safety Update and the NDA Final Safety Update is attached as Appendix G. DSI audits of 3 sites were reviewed and no significant problems were identified. Adequate documentation was submitted to comply with financial disclosure. The disclosure of financial interests from three investigators is unlikely to bias the outcome of the studies because none of these investigators enrolled a significant number of patients.

VI. Review of efficacy

A. Efficacy Conclusions

The results of the 3 Phase 3 Trials in which the 10 mg alfuzosin ER dose was studied showed statistically significant improvement in both primary endpoints (IPSS and Q_{max}). The magnitude of improvement was similar to that seen in currently approved alpha$_1$-adrenergic blocking agents approved for the treatment of the symptoms of BPH.

B. Approach to Review of Efficacy

The sponsor submitted 4 Phase 3 studies in support of the NDA (ALFOD, ALFUS, ALFORTI, and ALFOTAM. ALFOD studied only the 7.5 mg dose versus placebo. The other 3 Phase 3 studies evaluated the 10 mg alfuzosin ER dose and 2 of the 3 also evaluated the 15 mg alfuzosin ER dose. Each of the 4 Phase 3 trials consisted of a 12-week double-blind phase and a 9-month extension phase. Trials ALFUS, ALFORTI, and ALFOTAM and their extension phases ALFUSEXT, ALFORTIEXT, and ALFOTAMEXT were reviewed in detail (see Appendices A, B, C, D, E, and F). ALFOD, ALFODEXT, and the Integrated Summary of Efficacy were also reviewed.

C. Review of Trials

The four Phase 3 alfuzosin ER formulation trials all had a double-blind, multicenter, randomized, parallel-group design. Three of the studies were done in Europe (ALFOD, ALFORTI, and ALFOTAM) and one in the United States (ALFUS). The doses of alfuzosin ER studies were 7.5, 10, and 15 mg. The doses of alfuzosin used in the 12-week double-blind phase and the 9 month extension phase for each trial are shown in Table 1.

Table 1. Drug Doses (Alfuzosin ER) in Pivotal Studies

Study	N (completed)	Dose (Double blind phase)	Dose (Open label phase)
ALFOD	188 drug 182 placebo	7.5 mg/day placebo	7.5 mg/day
ALFORTI	136 drug **127 Uroxatral** 144 placebo	2.5 mg tid **10 mg/day** placebo	**10 mg/day**
ALFUS	**157 Uroxatral** 149 drug (15 mg) 158 placebo	**10 mg/day** 15 mg/day placebo	15 mg/day
ALFOTAM	**145 Uroxatral** 142 drug (15 mg) 142 placebo 149 tamsulosin	**10 mg/day** 15 mg/day placebo 0.4 mg/day	15 mg/day

Each study had a 4-week, single-blind placebo run-in period after which patients were randomized to a 12-week double-blind treatment period. This was followed by an optional open-label extension with an additional treatment period of 6 to 21 months.

In all 3 phase 3 studies utilizing the 10 mg alfuzosin ER dose, the study population consisted of men >50 years of age who had experienced lower urinary tract symptoms for

at least 6 months. Inclusion criteria included:) IPSS of greater than or equal to 13 2) Qmax greater than or equal to 5 and less than or equal to 12 cc/sec with a voided volume >150 cc and 3) residual urine <350cc. Exclusion criteria included patients with diseases known to affect lower urinary tract function and the use of alpha-adrenergic blocking agents, androgens, antiandrogens, 5 apha-reductase inhibitors and other drugs known to affect lower urinary tract symptoms.

The primary efficacy endpoints in the trials were change from baseline in the International Prostate Symptom Score (IPSS) and the peak urinary flow rate (Q_{max}) (In ALFORTI Q_{max} was a secondary endpoint.) The IPSS is a validated symptom scoring instrument and is identical to the American Urologic Association Symptom Index (AUASI). Because the dose of alfuzosin (ER) was only 7.5 mg in trial ALFOD, this trial was not included in the efficacy analysis (Table 1). In ALFOD, the change from baseline in IPSS was 1.0 greater than placebo (p-value = 0.07) and the change from baseline in Qmax (0.4 cc/sec greater than placebo) was not statistically significant (p-value = 0.85).

With respect to the IPSS, the mean decreases in total score ranged from –3.6 to –6.9, with a net improvement of approximately 2 points relative to placebo that was consistent across the 3 studies utilizing the alfuzosin 10 mg ER dose. (Table 2).

Table 2. Changes in IPSS scores in the 3 pivotal trials.

	ALFUS		ALFORTI		ALFOTAM	
	Placebo N=167	Alfuzosin 10 mg N=170	Placebo N=152	Alfuzosin 10 mg N=137	Placebo N=150	Alfuzosin 10 mg N=151
D_0 (mean)	18.2	18.2	17.7	17.3	17.7	18.0
D_{end}-D_0 (mean)	-1.6	-3.6	-4.9	-6.9	-4.6	-6.5
P-value	0.001		0.002		0.007	

(D_0 is baseline; D_{end} is end of 12 week treatment phase)

Improvement in IPSS was achieved by the first post-baseline visit (4 weeks) and the effect was maintained throughout the remainder of the 12 week double-blind treatment phase. The improvement in IPSS is clinically and statistically meaningful. Although the extension of ALFORTI (which utilized the 10 mg alfuzosin ER dose in the open-label extension trial) was not controlled, the results suggest that the beneficial effects on IPSS are maintained through 12 months.

The changes in peak flow rate (Q_{max}) (cc/sec) are shown in Table 3.

Table 3. Changes in Q_{max} (cc/sec) in the 3 pivotal studies

	ALFUS		ALFORTI		ALFOTAM	
	Placebo N=167	Alfuzosin 10 mg N=170	Placebo N=147	Alfuzosin 10 mg N=136	Placebo N=150	Alfuzosin 10 mg N=151
D_0 (mean)	10.2	9.9	9.2	9.4	9.3	9.5
D_{end}-D_0 (mean)	0.2	1.7	1.4	2.3	0.9	1.5
P-value	0.0004		0.03		0.22	

(D_0 is baseline; D_{end} is end of 12 week treatment phase)

The change is Qmax is modest but statistically significant for the 10 mg alfuzosin dose in ALFUS and ALFORTI and trends toward effectiveness in ALFOTAM. Although the changes for the alfuzosin 15 mg ER group in ALFUS and for both the 10 mg and 15 mg alfuzosin groups in ALFOTAM were higher than those seen with placebo, the differences were not statistically significant when compared to placebo. On average, patients who had received the 10 mg alfuzosin dose had an increase in Qmax ranging from 1.5 to 2.3 cc/sec (0.6 to 1.5 cc/sec higher than placebo) and patients who received the 15 mg alfuzosin dose had an improvement ranging from 0.9 cc/sec to 1.6 cc/sec. In ALFUS and ALFOTAM, the Qmax inclusion criteria of less than or equal to 12cc/sec was based only on the screening value at Day –28 while in ALFORTI this inclusion criteria had to be satisfied at 2 visits, Day –28 and Day 0.

D. Efficacy conclusions:

The improvement in IPSS is clinically and statistically significant across all three pivotal trials using the 10 mg alfuzosin ER formulation. Q_{max}, a more variable endpoint, achieved statistical significance in 2 of the 3 trials and tended toward significance in the third. Improvement in IPSS and Qmax seen with alfuzosin 10 mg ER appear comparable to those reported for the other alpha$_1$-adrenergic blocking agents currently approved for the treatment of symptoms of benign prostatic hyperplasia.

VII. Integrated review of safety

A. Introduction and Patient Exposure

The sponsor has developed and marketed three alfuzosin-containing oral tablet dosing regimens for the treatment of benign prostatic hyperplasia. The immediate release (IR) tablet is a 2.5 mg tablet for tid dosing. The IR formulation was approved for use abroad in 1987. The sustained release (SR) tablet is a 5.0 mg tablet for bid dosing. The SR formulation was approved for use abroad in 1993. The IR and SR formulations of alfuzosin have been approved for marketing in 87 countries. The third regimen (the subject of this NDA) is the extended release formulation. The sponsor is proposing to market only a 10 mg strength in the United States. The sponsor has manufactured investigational ER tablets in 7.5 mg, 10 mg, and 15 mg strengths. As of May 31, 2000, the 10 mg ER formulation has been approved in 11 countries (Denmark, Finland, France,

Ireland, Italy, Latvia, Netherlands, Portugal, Sweden, Switzerland, and the United Kingdom).

From October, 1988, to May, 2000, a total of —— 2.5 mg IR tablets, 5 mg SR tablets, and —— 10 mg ER tablets have been sold. The number of therapy days has been estimated at about —— million for the 2.5 mg formulation, —— for the 5.0 mg formulation, and —— for the 10 mg formulation).

Although the integrated summary of safety includes 22,912 patients in 194 trials, the majority of this patient data is taken from uncontrolled post-marketing surveys and observational studies. The primary safety data for the alfuzosin 10 mg ER formulation is derived from the 4 pivotal 12-week double-blind trials (including ALFOD which used a maximum dose of alfuzosin ER of 7.5 mg) and their open-label extension phases.

The number of patients (by treatment group) in the double-blind phase of the 4 pivotal trials are shown in Table 4.

Table 4. Number of Patients in Twelve-Week Double-Blind Portion in 4 Pivotal Studies Combined

	Placebo	Alfuzosin 2.5 mg tid	Alfuzosin 7.5 mg	Alfuzosin 10 mg	Alfuzosin 15 mg
Randomized	682	150	204	474	340
Exposed to drug	678	149	204	473	335
Completed	626	136	188	429	291
Discontinued	56 (8.2%)	14 (9.3%)	16 (7.8%)	45 (9.5%)	49 (14.4%)
Discontinued because of adverse event	22 (3.2%)	6 (4.0%)	10 (4.9%)	20 (4.2%)	22 (6.5%)

A total of 1150 patients were exposed to alfuzosin ER in the open label extension of ALFOD, ALFORTI, ALFOTAM, and ALFUS. As of the October 31, 2000 cut-off, 298 patients had completed the 6 month 7.5 mg extension (ALFODEXT), 282 patients had completed 9 months of the 10 mg extension, and 363 patients had completed 9 months of the 15 mg ER extension treatment. Thus, as of October 31, 2000, 645 patients had taken a dose of 10 mg alfuzosin ER or higher dose for one year.

B. Methods of Safety Review

The following material was reviewed for safety 1) The 4 pivotal trials (ALFUS, ALFORTI, ALFOTAM, and ALFOD and their 4 extensions (ALFUSEXT, ALFORTIEXT, ALFOTAMEXT, and ALFODEXT) – see Appendices A, B, C, D, E, and F 2) the Integrated Summary of Safety 3) the 120 Day Safety Update and the Final Safety Update – see Appendix G 4) the Post-Marketing Safety Summary 5) selected

literature reports of adverse events provided by the sponsor and 6) five studies dealing with the effect of alfuzosin on the QT interval (see section below on "EKG effects")

C. Review of Safety Data

- **Cardiovascular (vasodilatory) adverse events:**

The primary safety concern of alpha$_1$-adrenergic blocking agents is hypotension and the related cardiovascular symptoms of dizziness and syncope.

The number (%) of patients experiencing **vasodilatory adverse events** in patients in the double-blind phases of the pivotal studies is shown in Table 5.

Table 5. Vasodilatory Adverse Events in Double-Blind Phase of Pivotal Studies

	Placebo N=678	Alfuzosin 7.5 mg N=(204)	**Alfuzosin 10 mg (N=473)**	Alfuzosin 15 mg (N=335)
Patients with at least 1 event	19 (2.8%)	5 (2.5%)	**29 (6.1%)**	33 (9.9%)
Dizziness	19 (2.8%)	3 (1.5%)	**25 (5.3%)**	27 (8.1%)
Hypotension	0	0	**2 (0.4%)**	2 (0.6)
Malaise	0	1 (0.5%)	**2 (0.4%)**	3 (0.9%)
Syncope	0	1 (0.5%)	**1 (0.2%)**	2 (0.6%)
Postural hypotension	0	0	**0**	0

Alpha$_1$ blocking agents may have a "first dose vasodilatory" effect and 2 currently approved drugs (terazosin and doxazosin) in this class require upward dose titration. The number (%) of patients with "vasodilatory" adverse events" reported on Day 1 in the double-blind phase of the 4 pivotal trials is shown in Table 6.

Table 6. Number (%) of patients reporting "vasodilatory" adverse events reported on Day 1 in double-blind phase of 4 pivotal trials – placebo and alfuzosin ER groups

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	**Alfuzosin 10 mg (N=473)**	Alfuzosin 15 mg (N=335)
Patients with at least 1 event	0	3 (1.5%)	**4 (0.8%)**	4 (1.2%)
Dizziness	0	1 (0.5%)	**3 (0.6%)**	3 (0.9%)
Syncope	0	1 (0.5%)	**1 (0.2%)**	0
Hypotension	0	0	**0**	2 (0.6%)
Malaise	0	1 (0.5%)	**0**	0
Postural hypotension	0	0	**0**	0

The relatively low incidence of dizziness and syncope may be related to the fact that patients with orthostatic hypotension (a fall in systolic BP >20 mmHg after 2 minutes in a standing position at Day –28 or Day 0) were excluded from the trials.

In the open-label extension phases, when placebo patients began alfuzosin treatment, 3 additional cases of syncope occurred on the first day of dosing with 15 mg alfuzosin ER.

The majority of vasodilatory events were rated as "mild" or "moderate." Dizziness was reported as severe with placebo, and alfuzosin 10 mg ER and 15 mg ER in one patient each. One report of hypotension was rated "severe."

EKG assessment:

QT evaluation:
The 120 Day Update of Integrated Summary of Safety (received on April 6, 2001) contained 5 study reports involving studies to determine the effect of alfuzosin on the QT interval as well as the sponsor's "Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization" (Addendum 16.1).

The following QT study reports and information were included in the 120 day safety-update:

1) Study report for 00-00312-EN-00 ("Effects on the action potential of piglet Purkinje fibers")
2) Study report for 00-00329-EN-00 ("Effects on the herg channel stably expressed in mammalian cell line. Comparison with tamsulosin, doxazosin, prazosin, and terazosin")
3) Study report for INT4285 ("Effect of ketoconazole on alfuzosin blood levels")
4) Study report for PKD4532 ("Effect of supratherapeutic doses of alfuzosin on the ECG")
5) Study report for PCALF96US01 ("Manual reading of QT intervals of ECG from PCALF96US01")

These 5 studies were reviewed as well as the "Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization" included in Addendum 16.1. In PKD4532 (which studied placebo and 10, 20, and 40 mg of alfuzosin), the QTcB was prolonged greater than 60 msec in 2 of 24 placebo patients, in 3 of 24 10 mg alfuzosin patients, in 4 of 24 20 mg alfuzosin patients, and in 4 of 24 40 mg alfuzosin patients. None of the patients had QTcF prolongation of > 60 msec. The mean changes in heart rate, QT, QTcB, and QTcF for study 4532 are shown in Table 7.

Table 7. Statistical Analysis of Changes in ECG Parameters from Baseline: Mean (One-sided 95% CI, Upper Bound) Average Difference from Placebo over 0.5 to 24 Hours: Study PKD4532.

Parameter	Overall Treatment Effect	Alfuzosin 10 mg versus placebo	Alfuzosin 20 mg versus placebo	Alfuzosin 40 mg versus placebo
Heart rate	P=0.0001	0.6 (1.3)	4.6 (5.4)***	5.8 (6.5) ***
QT (ms)	P=0.0001	-1.1 (0.3)	-6.3 (-4.9)	-4.7 (-3.3)
QTcB (ms)	P=0.0001	1.2 (3)	8.5 (10.3) ***	13.2 (15.0) ***
QTcF (ms)	P=0.0001	0.5 (1.8)	3.4 (4.7) ***	7.1 (8.4) ***

*** = p-value vs. placebo = 0.001

The sponsor believes that the QTcB in the setting of an increased heart rate is "biased toward reporting normal QT as abnormally long when corrected." The sponsor also believes that Holter monitor recording and analysis of QT/RR pairs is more accurate and this analysis showed no clinically significant difference between alfuzosin and placebo.

The sponsor's conclusions are as follows:
"Alfuzosin belongs to the alpha$_1$-blockers drug class, which is widely known to produce an increase in heart rate but which is not associated with ventricular arrhythmias. The information presented in this document, derived from pre-clinical and clinical development and a large post-marketing experience, indicates a lack of arrhythmogenic potential, as supported by the following conclusions:

1) Alfuzosin has only a slight in vitro electrophysiologic effect, and only at concentrations several hundred times the expected therapeutic levels. Alfuzosin is a very weak I_{kr} channel blocker, based on inhibition of HERG potassium current. In this model, alfuzosin is 4 to 30 times weaker than the alpha$_1$-blockers doxasozin, terazosin, and prazosin.
2) Using the best available technique for evaluating change in repolarization independent of heart rate, alfuzosin at doses up to 40 mg appears to prolong the QT interval by only about 2 ms. This effect is not dose-related and is not clinically relevant.
3) Review of the large safety experience from a substantial clinical database and extensive post-marketing information provides no evidence for arrhythmia-induced risk."

Because of the discrepancies in the QTc results depending upon which correction method was used, a consultation was requested from the Division of CardioRenal Drug Products (see consult from Division of CardioRenal Drug Products).

The CardioRenal Division reviewed 2 preclinical (HERG channel study and the pig Purkinje fiber study) and 2 clinical QT studies (PKD4532 and PCALF96US1).

The review of the pre-clinical studies concluded: "Alfuzosin's in vitro elecrophysiologic effects suggest a low risk for repolarization abnormalities. However, while effects on

HERG current suggest a low risk, alfuzosin's potency was likely underestimated, and some drugs, e.g. sotalol, and quinolone and macrolide antibiotics weakly inhibit HERG yet prolong QT interval and induce torsade in humans. Additionally, human metabolites were not evaluated."

- The primary conclusion of the review of the clinical studies was that "the drug appears to be increasing the corrected QT by perhaps 10 msec."

Study PKD4532 was a single-center, double blind, placebo-controlled, single-dose, randomized, crossover study of three dose levels of alfuzosin (10, 20, and 40 mg) and placebo. Alfuzosin increased heart rate in a dose-dependent manner in comparison to placebo (+0.6, +4.6, and +5.8 bpm at the 10, 20, and 40 mg doses respectively). The 24-hour mean QTcB showed that the effect of the 40 mg dose was clearly different (and the lower doses less so) from the effect of placebo. The same findings, although to a lesser degree, were seen with QTcF (Table 1). The consultant concluded: "Heart rate, QTcB, and QTcF are significantly increased from baseline for the 20 and 40 mg doses compared to placebo."

Study PCALF96US1 was a single-center, double-blind, placebo controlled, parallel sequentially dosed trial. Study drug doses were 7.5 mg to 30 mg. Active drug showed a greater change from baseline in the corrected QT intervals compared to placebo; the only significant differences between drug and placebo were seen on Day 1. The mean changes from baseline with the Bazett's and Fridericias's corrections were always higher on drug but not necessarily in a dose related manner.

In summary, the CardioRenal Division believes that alfuzosin increases the corrected QT interval by "perhaps 10 msec." They do not agree with the sponsor's argument that the analysis of the Holter monitor data is superior to the QTcB or QTcF. Finally, although the reported arrythmia events in Europe since 1987 is small, the consultant believes that "it is hard to know how reassuring this lack of event reporting is."

The incidence of heart rate and rhythm disorders is shown in Table 8.

Table 8. Number of Patients with Heart Rate and Rhythm Disorders in Double-Blind Phase of Pivotal Trials

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	Alfuzosin 10 mg (N=473)	Alfuzosin 15 mg (N=335)
Patients with at least 1 rhythm disorder	4 (0.6%)	1 (0.5%)	2 (0.4%)	4 (1.2%)
Palpitation	2 (0.3%)	1 (0.5%)	1 (0.2%)	1 (0.3%)
Supraventricular tachycardia	0	0	1 (0.2%)	0
Atrial fibrillation	0	0	0	2 (0.6%)
Tachycardia	0	0	0	1 (0.3%)
Extrasystoles	2 (0.3%)	0	0	0

Adverse events related to coronary artery disease are shown in Table 9.

Table 9. Number of Patients with Coronary Artery Disease Related Adverse Events

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	Alfuzosin 10 mg (N=473)	Alfuzosin 15 mg (N=335)
Patients with at least 1 adverse event	4 (0.6%)	1 (0.5%)	2 (0.4%)	3 (0.9%)
Angina pectoris	1 (0.1%)	0	0	0
Angina pectoris aggravated	0	0	1 (0.2%)	1 (0.3%)
Myocardial infarction	1 (0.1%)	1 (0.5%)	0	1 (0.3%)
Chest pain	2 (0.3%)	0	1 (0.2%)	2 (0.6%)

Deaths: There were 4 deaths in the 4 pivotal studies and their extension phases. One patient in ALFORTI died of an infection following head trauma. Two patients in ALFOD died of cancer (one colon and one stomach). One patient in ALFODEXT died of pneumonia.

Serious adverse events: The number of SAE's (including deaths) from the Phase 3 double-blind studies and their extensions is shown in Table 10.

Table 10. Serious Adverse Events From Phase 3 Double-Blind Trials and Their Extension Phases

	Placebo	Alfuzosin ER 7.5 mg	Alfuzosin ER 10 mg	Alfuzosin ER 15 mg
Phase 3 double-blind	18/678 (2.7 %)	13/204 (6.4%)	15/473 (3.2 %)	13/335 (3.9%)
Phase 3 extension	NA	12/328 (3.7%)	18/311 (5.8%)	59/511 (11.5%)

In the double-blind portion of the Phase 3 studies, the SAE's in the 10 mg dose group consisted of one case each of arthrosis, diverticulitis, cholecystitis, angina pectoris aggrevated, coronary artery disorder, COPD, pulmonary granuloma, upper respiratory infection, renal stone, basal cell carcinoma, lung cancer, syncope, substernal chest pain, peripheral edema, and post-operative pain. In the 15 mg dose group, SAE's consisted of one case each of pneumonia, pulmonary embolism, infection, arthralgia, peritonitis, diabetes mellitus reactivated, myocardial infarction, atrial fibrillation, cerebrovascular disorder, varicose vein, and 3 cases of syncope.

In the double-blind and extension phases of the Phase 3 trials combined, there were 130 serious adverse events in 1608 patients. In the opinion of this reviewer, the majority of these serious adverse events were not related to study medication. There were 10 reports of angina pectoris (0.6%), 3 (0.2%) cerebrovascular disorder, 1 (0.1%) substernal chest pain, 3 (0.2%) coronary artery disorder, 2 (0.1%) fall, 1 (0.1%) hepatocellular damage, 4 (0.2%) myocardial infarction, and 13 (0.8%) syncope. Of these 13 cases of syncope, 1 (0.3%) occurred at the 7.5 mg dose (n=366), 3 (0.4%) at the 10 mg dose (n=690), and 9 (1.3%) at the 15 mg dose (n=707).

Overall frequency of adverse events:

The overall frequency of adverse events occurring in >1% of patients in the double-blind portion of the 4 pivotal studies is shown in Table 11.

Table 11. Frequency of Adverse Events Reported by >1% of Patients in Double-Blind Portion of Pivotal Trials.

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	Alfuzosin 10 mg (N=473)	Alfuzosin 15 mg (N=335)
Dizziness	19 (2.8%)	3 (1.5%)	25 (5.3%)	27 (8.1%)
Upper resp. infection	4 (0.6%)	1 (0.5%)	14 (3.0%)	9 (2.7%)
Headache	12 (1.8%)	5 (2.5%)	14 (3.0%)	8 (2.4%)
Flu-like Symptoms	14 (2.1%)	1 (0.5%)	9 (1.9%)	6 (1.8%)
Fatigue	7 (1.0%)	6 (2.9%)	8 (1.7%)	10 (3.0%)
Rhinitis	12 (1.8%)	2 (1.0%)	7 (1.5%)	6 (1.8%)
Impotence	4 (0.6%)	0	7 (1.5%)	4 (1.2%)

Bronchitis	5 (0.7%)	5 (2.5%)	7 (1.5%)	2 (0.6%)
Sinusitis	8 (1.2%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Pain	4 (0.6%)	0	7 (1.5%)	0
Abdominal pain	7 (1.0%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Dyspepsia	7 (1.0%)	3 (1.5%)	6 (1.3%)	1 (0.3%)
Back pain	8 (1.2%)	3 (1.5%)	6 (1.3%)	9 (2.7%)
Inflicted injury	2 (0.3%)	0	6 (1.3%)	3 (0.9%)
Asthenia	5 (0.7%)	0	5 (1.1%)	4 (1.2%)
Constipation	3 (0.4%)	3 (1.5%)	5 (1.1%)	3 (0.9%)
Pharyngitis	2 (0.3%)	2 (1.0%)	5 (1.1%)	3 (0.9%)
Nausea	4 (0.6%)	2 (1.0%)	5 (1.1%)	2 (0.6%)
Somnolence	5 (0.7%)	0	4 (0.8%)	4 (1.2%)
Arthralgia	6 (0.9%)	4 (2.0%)	4 (0.8%)	4 (1.2%)
Diarrhea	10 (1.5%)	2 (1.0%)	3 (0.6%)	3 (0.9%)
Perpheral edema	4 (0.6%)	1 (0.5%)	2 (0.4%)	4 (1.2%)
Hypertension	9 (1.3%)	2 (1.0%)	2 (0.4%)	3 (0.9%)
Urinary tract infection	9 (1.3%)	2 (1.0%)	2 (0.4%)	1 (0.3%)
Arthrosis	2 (0.3%)	3 (1.5%)	2 (0.4%)	0

Hepatic disorders:

In one patient in ALFORTIEXT hepatocellular liver damage was reported on Day 342 of the study and relationship to alfuzosin was not excluded by the investigator. This patient had experienced 3 or 4 similar episodes attributed to cholelithiasis prior to entering the study. In the large post-marketing experience, abnormal hepatic function was the most common hepatic serious adverse event and was reported in 4 spontaneous reports. In most of the 5 spontaneous reports of hepatitis (2 hepatitis and 3 hepatitis cholestatic) the role of alfuzosin was doubtful since an alternative etiology was present.

Hematological disorders:

Three cases of pancytopenia were reported in the Postmarketing Safety Synthesis (all formulations). In each case, alfuzosin was considered an unlikely cause of the event. One case each of granulocytopenia, agranulocytosis, and hemolytic anemia were reported in the Postmarketing Safety Synthesis. Alfuzosin was not thought to be a likely contributor to these events.

Other events:

Allergic reactions: In the phase 3 ER studies, one case of anaphylactic shock was reported. This patient was known to be allergic to penicillin and was re-exposed to penicillin.

Two spontaneous reports have appeared in the published literature. One case of dermatomyositis was reported in a 75-year-old man who had taken alfuzosin for 1 year prior to the diagnosis. Quinazoline derivatives (prazosin is an example) have been associated with an increased rate of anti-nuclear antibodies. This patient was subsequently found to have lung cancer and the dermatomyositis was ascribed to lung cancer and not to alfuzosin. Hypothermia was reported in a paraplegic patient who was taking bethanechol and alfuzosin. On re-challenge with bethanechol he again developed hypothermia, thereby excluding alfuzosin as the causative agent.

Clinical laboratory test results:

The incidence of Potentially Clinically Significant Abnormalities (PCSA) (pre-defined upper and lower limits) at any time during the double-blind phase of the pooled pivotal studies is shown in Table 12.

Table 12. Number of Patients with a Potentially Clinically Significant Abnormality (PCSA) for at Least One Laboratory Parameter During Double Blind Phase of 4 Pivotal Studies (all alfuzosin ER doses polled).

	Placebo (N=678)	Alfuzosin ER (N=1012)
Hematology	29/622 (4.66%)	39/904 (4.31%)
Liver function	4/635 (0.63%)	11/919 (1.20%)
Renal function	7/634 (1.10%)	15/912 (1.64%)

The most frequently reported abnormality (PCSA) in patients with a normal baseline value receiving alfuzosin was an increase in creatinine (>30%) in 2.3% of patients.

Small mean decreases in platelet and neutrophil counts were associated with alfuzosin treatment compared with placebo, but values remained in the normal range. Similar findings have been reported with other alpha$_1$-adrenergic blockers and have been ascribed to hemodilution. These changes, however, were not accompanied by a decrease in mean hematocrit.

Vital signs:

Mean changes from baseline in supine heart rate, standing heart rate, and heart rate change from the supine to the standing position in any alfuzosin group or placebo group in the double-blind phase of the pivotal studies were small and generally < 1 beat per minute.

Mean changes from baseline in systolic and diastolic blood pressure (both supine and standing) in each alfuzosin ER treatment group were comparable to those in the placebo group in the double-blind phase of the pivotal studies. Mean changes ranged from –2.0 to –4.0 mmHg in each parameter for the alfuzosin ER treatment groups and –1.1 to –2.3 mmHg for placebo.

Drug-disease interaction by baseline hypertensive status:

The incidence of vasodilatory events was higher among hypertensive patients compared to normotensive patients in the 10 alfuzosin ER group (8.3% versus 5.3%) primarily due to an increased incidence of dizziness. These same results were not observed at the 15 mg dose.

Long term safety:

In the pooled data from the Phase 3 alfuzosin ER open label extension studies (ALFODEXT, ALFORTIEXT, ALFOTAMEXT, and ALFUSEXT) no previously unidentified adverse events were seen. The incidence of vasodilatory adverse events in the 15 mg group increased in the double-blind plus extension phase compared to the double-blind phase (12.0% versus 9.9%). The incidence in patients treated with the 10 mg dose was essentially the same in the double-blind plus extension phases compared to the double-blind phase (5.8% versus 6.1%). (Table 13) As in the double-blind phase, dizziness was the most frequent vasodilatory adverse event.

Table 13. Patients with at Least One Vasodilatory Adverse Event in the Double-Blind and Double-Blind Plus Extension Phases

	Alfuzosin 7.5 mg	Alfuzosin 10 mg	Alfuzosin 15 mg
Double-blind	5 (2.5%)	29 (6.1%)	33 (9.9%)
Double-blind plus extension	6 (1.6%)	40 (5.8%)	85 (12.0%)

The incidence of Potentially Clinically Significant Abnormalities in laboratory data in the double-blind plus extension phases was similar to those in the double-blind period alone. In the extension, the most common abnormalities were decrease in eosinophils, increase in creatinine, and decrease in hematocrit. The mean changes in these values were not clinically significant.

No clinically meaningful mean changes in heart rate or blood pressure were observed in the extension studies. (Mean heart rate changes were < 1 beat per minute and blood pressure changes <5 mmHg.)

Summary of Safety Findings:

The primary safety concern with alpha$_1$-adrenergic blocking agents is hypotension and related symptoms (dizziness and syncope). These symptoms do occur with alfuzosin 10 mg ER, but the incidence is acceptable. Although data concerning direct comparisons with other alpha$_1$ blockers is limited, the incidence of "vasodilatory" adverse events seen with alfuzosin appear to be similar to other agents in this drug class. The possibility of dizziness, hypotension, and syncope are adequately addressed in the "Warnings" section of the label. A "first-dose" effect does occur with alfuzosin 10 mg ER, but the incidence of adverse events (primarily hypotension and syncope) is low and dose titration does not appear to be warranted.

According to the sponsor's analysis of the Holter monitor derived QT data, "alfuzosin at doses up to 40 mg appears to prolong the QT interval by only about 2 msec. This effect is not dose-related and is not clinically relevant." Consultation from the Cardiorenal Division concluded that there was a dose-related increase in corrected QT by "perhaps 10 msec."

VIII. Dosing and administration issues

Results from the Phase 3 study ALFOD showed that the 7.5 mg ER dose minimally improved IPSS and was not statistically superior to placebo with regard to Qmax. Subsequently, the 10 mg ER dose was shown to be effective in Phase 3 studies ALFOTAM and ALFUS. No additional efficacy was seen in the 15 mg compared with the 10 mg dose. In addition, the 10 mg dose had a better safety profile than the 15 mg dose. The 10 mg dose appears to be the dose with the most favorable risk/benefit profile.

IX. Use in special populations

A. Gender effects: Alfuzosin is not indicated for use in women.

B. Race effects: Greater than 95% of patients in the double-blind studies were Caucasian and no meaningful conclusions regarding the effect of race can be reached.

C. Age effects: In the double-blind studies, the overall incidence of vasodilatory events (contributed primarily by dizziness) was higher in elderly patients who received alfuzosin ER 15 mg (6.7% <65 years; 13.5% >65 years). In the other treatment groups (including the 10 mg alsuzosin ER dose), age had no effect. There were no age-related trends in other adverse events.

D. Pediatric plan: Alfuzosin is not indicated for use in children. A pediatric waiver was requested and granted.

E. Renal impairment: In comparison to patients with normal renal function, patients with various degrees of renal impairment (mild, moderate, severe) had mean C_{max} and AUC values that were increased up to 1.5-fold at the alfuzosin 10 mg dose. These values are similar to those observed with alfuzosin 15 mg in patients with normal renal function. The sponsor believes that the alfuzosin 15 mg ER dose has an acceptable safety profile based on the results of Phase 3 studies ALFUS and ALFOTAM and their extensions, even though there was a dose-related increase in adverse event rates and blood pressure changes with the 15 mg dose as compared to the 10 mg dose. The section on "Patients with Renal Impairment" in the label should be revised to reflect this increase in adverse events rate.

F. Hepatic compromised patients: Since alfuzosin blood levels are increased in patients with moderate to severe hepatic insufficiency, alfuzosin should not be used in these patients and the label includes these patients in the "Contraindications" section. The pharmacokinetics of alfuzosin have not been evaluated in patients with mild hepatic

insufficiency and the statement that "the physician should consider the risks and benefits of administering Uroxatral in this population" is also included in the label.

G. Pregnancy: Alfuzosin is not indicated for use in women.

X. Conclusions and recommendations

In the opinion of this reviewer, from a clinical perspective, alfuzosin hydrochloride 10 mg extended release (ER) tablets taken once/day should receive an "approvable" action for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia." The drug could be approved following resolution of the presence and/or significance of the QT prolongation. The risks associated with the use of this drug are otherwise acceptable and can be managed adequately with labeling.

In addition to future decisions regarding the QT issue, several labeling changes are recommended:

1) Information concerning 2 of the 3 pivotal trials are included in the proposed label. For balance, the results of the third trial (which did not show statistically significant improvement in Q_{max}) should be included. In addition, results of some secondary endpoints should be deleted.
2) Information concerning the possibility of increased incidence of adverse events in patients with renal impairment should be added to the "Precautions" section of the label.
3) Since ketoconazole increases the alfuzosin C_{max} 2-fold and the AUC 2.5-fold, this drug should be contraindicated. Information concerning moderate CYP3A4 inhibitors should be added to the "Precautions" section of the label.

XI. Appendices

Appendix A: Clinical Trial ALFUS – 2560 : "Efficacy and Safety of Alfuzosin Once-Daily Tablets at Two Dosage Levels (10 mg and 15 mg) Versus Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia: A Placebo-Controlled, Double-Blind Study, Conducted in Three Parallel Groups for 3 Months Followed by Two (A Nine Month and a 12 Month) Open-Label Extensions of Alfuzosin OD 15 mg"

Appendix B: Clinical Trial ALFORTI-2789: "Efficacy and Safety of Alfuzosin Geomatrix 10 mg OD versus Alfuzosin 2.5 mg tid and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo-Controlled , Double-Blind Study, Conducted in 3 Parallel Groups for 3 Months."

Appendix C: Clinical Trial ALFOTAM – 2440: "Efficacy and Safety of Two Dosage Levels of Alfuzosin Geomatix (10 mg OD and 15 mg OD) Versus Tamsulosin (0.4 mg OD) and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo Controlled, Double-Blind Study, Conducted in 4 Parallel Groups for Three Months

Followed by an Optional 9-Month Open-Label Extension with Alfuzosin Geomatrix 15 mg OD"

Appendix D: Clinical Trial ALFUSEXT (interim report of 9 month extension phase of ALFUS) ("Efficacy and safety of alfuzosin once-daily tablets at 2 dosage levels (10 mg and 15 mg) versus placebo in patients with symptomatic benign prostatic hyperplasia: A placebo-controlled double-blind study, conducted in 3 parallel groups for three months followed by two (a nine month and a twelve month) open label extensions of alfuzosin OD (15 mg).")

Appendix E: Clinical Trial ALFOTAMEXT (interim report of the 9 month extension phase of ALFOTAM) ("Efficacy and safety of two dosage levels of alfuzosin Geomatrix (10 mg OD and 15 mg OD) versus tamsulosin (0.4 mg) and placebo in patients with symptomatic benign prostatic hyperplasia: Nine-month open-label extension with alfuzosin Geomatrix 15 mg")

Appendix F: Clinical Trial ALFORTIEXT ("Efficacy and Safety of Alfuzosin Geomatrix 10 mg OD Versus Alfuzosin 2.5 mg TID and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo-Controlled, Double-Blind Study, Conducted in 3 Parallel Groups for Three Months, Followed by an Optional 9-Month Open Label Extension with Alfuzosin Geomatrix 10 mg OD")

Appendix G: 120 Day Update of Integrated Summary of Safety (received by the Division on April 6, 2001) and **NDA Final Safety Update** (received by the Division on July 11, 2001)

Appendix A:

Clinical Trial ALFUS – 2560 : "Efficacy and Safety of Alfuzosin Once-Daily Tablets at Two Dosage Levels (10 mg and 15 mg) Versus Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia: A Placebo-Controlled, Double-Blind Study, Conducted in Three Parallel Groups for 3 Months Followed by Two (A Nine Month and a 12 Month) Open-Label Extensions of Alfuzosin OD 15 mg" (Study began January 16, 1998, and ended August 5, 1999.)

A.1 Objectives: The primary objective of the trial was to assess, compared with placebo, the efficacy and safety of two dosage levels (10 and 15 mg) of a once-daily formulation of alfuzosin hydrochloride) administered over 3 months to patients with symptomatic BPH. The secondary objective of the trial was to assess, during a 9-month extension phase and a subsequent 12-month extension phase (provided for in amendment 2), the maintenance of efficacy and the long-term safety of treatment with alfuzosin 15 mg tablets.

A.2 Design and Conduct Summary: This protocol was a multicenter (30 United States and 2 Canadian sites), randomized, placebo-controlled, double-blind Phase 3 trial with 3 parallel groups (alfuzosin ER 10 mg, alfuzosin ER 15 mg, and placebo) consisting of a 4 week single-blind placebo run-in period (Phase A) followed by a 12 week double-blind treatment period (Phase B). The trial was originally designed to include a placebo run-in phase (Phase A), followed by a double-blind active treatment versus placebo phase (Phase B) and a 9 month open-label extension phase (Phase C). In amendment 2 to the protocol, this plan was expanded to include an additional 12 month open-label extension phase (Phase D). When the results of Phases A and B were analyzed, the sponsor believed that the data obtained were sufficient to proceed with FDA filing. Only the results of the double-blind phase are discussed in this review.

Six visits were scheduled during Phases A and B: a screening visit (D-28), a baseline visit on Day 0 (D0), three intermediate visits on Day 14, Day 28 (M1), and Day 56 (M2), and an endpoint visit at the end of the randomized phase on Day 84 (M3). On an optional basis, patients returned 12-16 hours after the first dose at visit D0 for one supine/standing blood pressure and heart rate measurement. Patients were randomized to treatment groups on D0. At screening (D-28) patients underwent a physical examination and laboratory tests including a urinalysis and PSA. In addition, IPSS, QOL index, Brief Sexual Function Inventory, 9-item Urolife scale, voiding flow rate, and residual urine were performed. On Day 0, IPSS, QOL index, Brief Sexual Function Inventory, 9-item Urolife scale, voiding flow rate, residual urine, TRUS, vital signs, and alfuzosin assay were performed. On Day 14, patients underwent determination of vital signs. On Day 28, IPSS, QOL index, voiding flow rate, residual urine, vital signs, and alfuzosin assay were repeated. On Day 56, IPSS, QOL index, vital signs, and alfuzosin assay were performed. On Day 84, laboratory tests (including PSA), urinalysis, physical examination, IPSS, QOL index, Brief Sexual Function Inventory, 9-item Urolife, Global Subjective Assessment Score, voiding flow rate, residual urine, TRUS, vital signs, and alfuzosin assay were repeated.

A.3 Study Population: The study population consisted of men aged greater than 50 years with at least a 6 month history of voiding symptoms. Baseline characteristics of the study population are shown in Table A.1.

Table A.1. Baseline characteristics of study population.

	Placebo (N=175)	Alfuzosin 10 mg (N=176)	Alfuzosin 15 mg (N=177)
Age (mean)	62.7	64.3	63.9
Age (range)	49-85	50-92	50-81
Age > 65 years (N)	66	78	83
Race (N) (%)			
Caucasian	158 (90)	160 (91)	160 (90)
Black	8 (5)	9 (5)	5 (3)
Asian	3 (2)	2 (1)	5 (3)
Other	6 (3)	5 (3)	7 (4)
IPSS (mean)	21.5	21.2	21.7
Qmax (cc/sec)	8.4	8.7	8.9

A.4 Inclusion/exclusion criteria: Inclusion criteria included 1) men > age 50 years 2) symptomatic BPH, diagnosed clinically by digital rectal examination 3) suffering for at least 6 months from micturition disturbances which include daytime frequency, nocturia, urgency, difficulty initiating micturition, impaired quality of the urinary stream, feeling of incomplete voiding, and interruption of the urinary stream 4) IPSS of greater than or equal to 13 at D -28 5) Q_{max} between 5 and 12 cc/sec with a voided volume of at least 150 cc at Day -28 6) Residual urine < 350 cc on D -28 7) score of 3, 4, 5, or 6 on the QOL index question "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" with scores of 0 to 6, a score of 0 being the response "delighted."

Exclusion criteria included: 1) neurogenic bladder dysfunction 2) bladder neck contracture 3) urethral stricture 4) acute or chronic prostatitis 5) active urinary tract infection 6) prostate cancer 7) carcinoma of the prostate suspected on DRE or TRUS or a serum PSA of > 10 ng/ml (patients with a PSA of between 4.0 and 10.0 must have prostate cancer ruled out to the satisfaction of the investigator) 8) bladder stones 9) hematuria of unknown etiology 10) previous prostate surgery or other invasive treatment for BPH 11) prior radiation to the pelvis 12) indwelling catheter 13) previously not improved by alpha-blocker therapy 14) Parkinson's disease or multiple sclerosis 15) poorly controlled insulin-dependent diabetes 16) stroke or myocardial infarction within 5 months prior to D -28 17) unstable angina or severe congestive heart failure 18) active liver disease (AST > 2x ULN, ALT > 2x ULN, alkaline phosphatase > 1x ULN, total bilirubin > 2x ULN), renal insufficiency (creatinine > 1.7mg/dl) or abnormal hemoglobin, white blood cell count, or platelet count 19) history of postural hypotension or patients who have a fall in systolic blood pressure of > 20 mmHg after 2 minutes in a standing position at the D -28 or D0 visit 20) alpha-blocker therapy within 1 month of Day -28 21) androgens, anti-androgens, 5-alpha reductase inhibitors, or LHRH analogues

within 3 months preceding D -28 22) tricyclic antidepressants, anticholinergics, sympathomimetics, antihistamines, or plant extracts within 1 month prior to D0 and 23) patients expected to take Viagra during the course of the study.

Reviewer's comment: Patients were excluded if they had postural hypotension (defined as a fall in systolic blood pressure of > 20 mmHg after 2 minutes in a standing position at the D -28 or D0 visit)

A.5 Primary and secondary endpoints:

The 2 primary efficacy endpoints were:

1) mean change from baseline to endpoint for IPSS
2) mean change from baseline to endpoint for Q_{max}

Secondary efficacy analyses included: change from baseline of > 3 points on IPSS, % of patients with change from baseline in IPSS of >50%, % of patients with change from baseline in Q_{max} of > 2 cc/sec, % of patients with change from baseline in Q_{max} of > 30%, change from baseline in residual urine, change in the QOL index, change in the Urolife total score, and change in the Global Subjective Assessment score.

A.6 Withdrawals, compliance, and protocol violations: Among the total of 536 patients randomized in this study, 178 received placebo, 177 received alfuzosin 10 mg, and 181 received alfuzosin 15 mg. Seventy-two patients were discontinued from the study after randomization, including 20 patients in the placebo group, 20 in the alfuzosin 10 mg group, and 32 in the alfuzosin 15 mg group. The most common reason for early withdrawal was an adverse event. Twice as many patients withdrew from each alfuzosin treatment arm than withdrew from placebo because of an adverse event. Patient # 38300874 was randomized to the placebo arm but withdrew shortly after randomization because of hematuria. The reasons for study withdrawal are shown in Table A.2.

Table A.2. Reasons for premature withdrawal

	Placebo	Alfuzosin 10mg	Alfuzosin 15mg	Total
Randomized	178	177	181	536
Completed	158	157	149	464
Total Number Discontinuing	20	20	32	72
Lost to follow-up	2	3	4	9
Lack of Efficacy	2	0	2	4
Adverse event	4	8	8	20
Uncooperative	6	2	8	16
Others	6	7	10	23

Of the 16 patients on alfuzosin who withdrew from the study, 8 were in the 10 mg group and 8 were in the 15 mg group. In the 10 mg group, the reasons for withdrawal were syncope (1) (0.6%), hypotension (1) (0.6%), dizziness (2) (1.1%), headache 1 (0.6%), vertigo (1) (0.6%), and constipation (1), nausea (1), pulmonary granuloma (1), and abnormal vision (1). In the 15 mg group, the reasons for withdrawal were hypotension (1) (0.6%). myocardial infarction (1) (0.6%), dizziness (3) (1.7%), headache (1) (0.6%), paralysis (1) (0.6%), and prostatic disorder (1).

Major protocol deviations at inclusion: Eight patients had major deviations from inclusion criteria concerning BPH severity and were excluded from the analysis of the per-protocol population.

Major protocol deviations during the study: One hundred and seventy-nine major protocol deviations were identified in 87 randomized patients. The most common protocol deviations were related to missing efficacy assessments (IPSS or uroflowmetry), less than 80% compliance with study drug, and a treatment hiatus of >5 days.

A.7 Efficacy analysis:

The primary population for the efficacy analyses was the ITT population. A total of 536 patients were randomized, of whom 528 were exposed to study drug or placebo. Five hundred two patients had the minimum efficacy assessments to meet the definition of the ITT population and 458 patients met the completers population definition. These data are summarized in Table A.3.

Table A.3. Study populations

	Placebo	**Alfuzosin 10mg**	Alfuzosin 15mg	Total
Randomized	178	**177**	181	536
Exposed	175	**176**	177	528
ITT	167	**170**	165	502
Per protocol	165	**161**	156	482
Completers	160	**153**	145	458

The results of the analysis of one of the primary efficacy variables, change from baseline in the mean IPSS, are shown in Table A.4.

Table A.4. IPSS total score at endpoint – ITT population

IPSS total score (mean)	Placebo	**Alfuzosin 10mg**	Alfuzosin 15mg
Day 0	18.2	**18.2**	17.7
Day end	16.6	**14.6**	14.3
Day end- Day 0	-1.6	**-3.6 ***	-3.4 **

* adjusted p = 0.001 compared with placebo

** adjusted p = 0.004 compared with placebo

The difference in improvement in the IPSS in the alfuzosin groups versus placebo was achieved by the first post-baseline visit at 4 weeks and was maintained throughout the study.

The results of the analysis of the other primary efficacy variable, change from baseline in the mean Q_{max}, are shown in Table A.5.

Table A.5. Mean change in Q_{max} from baseline to endpoint for the ITT population.

	Placebo	**Alfuzosin 10 mg**	Alfuzosin 15 mg
Day 0	10.2	**9.9**	10.0
Day end	10.3	**11.6**	11.0
Day end – Day 0	0.2	**1.7** *	0.9 **

* adjusted p= 0.0004 compared with placebo
** adjusted p= 0.12 compared with placebo

Reviewer's comment: Alfuzosin 10 mg, but not 15 mg, achieved statistical significance over placebo with regard to Q_{max}.

Secondary endpoints of most clinical relevance:

1) The percentage of patients showing an improvement in IPSS of 3 points or greater is shown in Table A.6.

Table A.6. Percentage of patients with a greater than 3 point improvement in IPSS score.

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg
N	167	170	165
% with > 3 point improvement	38.9%	55.9%	52.1%
P value vs. placebo		0.002	0.02

2) The percentage of patients with at least a 2 cc/sec improvement in Q_{max} is shown in Table A.7.

Table A.7. Percentage of patients with a greater than 2 cc/sec improvement in Q_{max}.

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg
% with > 2cc/sec improvement	25.7%	40.0%	40.6%
P value vs. placebo		0.005	0.004

3) The Quality of Life Index analysis in the ITT population improved in the alfuzosin treatment groups compared with placebo (p=0.002). The Global Subjective Assessment in symptoms improved in both the 10 mg (p=0.003) and 15 mg (p<0.0001) groups compared with placebo. No statistically significant change in prostate volume or transition zone size was demonstrated in either of the alfuzosin groups compared with placebo.

A.8 Safety analysis:

A.8.1 Extent of exposure: The mean duration of exposure is shown in Table A.8.

Table A.8. Duration (mean days) of drug exposure

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg
Number of patients	175	176	177
Mean duration of exposure (days)	81	81	78

A.8.2 Serious adverse events:

Deaths: No deaths occurred in the study population during the course of the study.

A total of 5 serious adverse events occurred during the placebo run-in period. Nineteen SAE's occurred during the double-blind treatment phase (5 on placebo, 8 on alfuzosin 10 mg and 6 on alfuzosin 15 mg).

The SAE's in the placebo group consisted of cholelithiasis, retinal hemorrhage, cerebrovascular accident, non-Hodgkin's lymphoma, and angina.

Of the 8 SAE's which occurred in the alfuzosin 10 mg group, 6 (COPD, lung cancer, coronary artery disease preceding receiving drug, dehydration, basal cell carcinoma, and pulmonary granuloma) were judged not related to study drug. Patient #33140474 had a syncopal event 150 minutes after the first dose of study drug and patient #32970253 had worsening angina. Narratives for these 2 patients are included in the section on cardiovascular events.

Of the 6 SAE's which occurred in the alfuzosin 15 mg group, 3 (toe infection, pneumonia, and diabetes mellitus) were judged not related to study drug. Patient #38310584 suffered a cerebrovascular accident, #33080174 experienced atrial fibrillation, and #33040229 had crescendo angina and a myocardial infarction 21 hours after the first drug dose. Narratives for these 3 patients are included in the section on cardiovascular events.

A.8.3 Premature discontinuation due to adverse event:

The number of withdrawals due to an adverse event was 3/175 (1.7%) in the placebo group, 8/176 (4.5%) in the alfuzosin 10 mg group, and 8/177 (4.5%) in the alfuzosin 15 mg group.

Of the 8 patients who discontinued due to an AE in the alfuzosin 10 mg group, the sponsor believes that 4 could be classified as "vasodilatory disorders" (1 syncope, 1 hypotension, and 2 dizziness). In addition, 1 patient had a recurrent headache after dosing and patient #33140474 withdrew following a syncopal event.

Of the 8 patients who discontinued due to an AE in the alfuzosin 15 mg group, the sponsor believes that 4 could be classified as "vasodilatory disorders"(1 hypotension and 3 dizziness.) In addition, 1 experienced a severe headache and patient #33040229 withdrew following a myocardial infarction.

A.8.4 Overall adverse events:

Adverse events reported by more than 1% of patients are shown in Table A.9.

Table A.9. Adverse events occurring in more than 1% of patients

Adverse event	Placebo (N=175)	Alfuzosin 10 mg (N=176)	Alfuzosin 15 mg (N=177)
Dizziness	5 (2.9%)	13 (7.4%)	16 (9.0%)
Headache	4 (2.3%)	9 (5.1%)	4 (2.3%)
Upper resp. inf.	4 (2.3%)	6 (3.4%)	5 (2.8%)
Back pain	4 (2.3%)	2 (1.1%)	6 (3.4%)
Rhinitis	4 (2.3%)	3 (1.7%)	4 (2.3%)
Fatigue	4 (2.3%)	4 (2.3%)	3 (1.7%)
Impotence	2 (1.1%)	5 (2.8%)	2 (1.1%)
Somnolence	0	4 (2.3%)	3 (1.7%)
Sinusitis	4 (2.3%)	5 (2.8%)	1 (0.6%)
Constipation	1 (0.6%)	4 (2.3%)	2 (1.1%)
Nausea	1 (0.6%)	4 (2.3%)	1 (0.6%)
Libido decreased	1 (0.6%)	2 (1.1%)	2 (1.1%)
Abdominal pain	4 (2.3%)	2 (1.1%)	2 (1.1%)
Hypertension	3 (1.7%)	1 (0.6%)	2 (1.1%)
Arthralgia	4 (2.3%)	2 (1.1%)	1 (0.6%)
Edema	2 (1.1%)	0	3 (1.7%)
Vision abnormal	1 (0.6%)	1 (0.6%)	2 (1.1%)
Hepatic enzymes increased	2 (1.1%)	2 (1.1%)	1 (0.6%)
Malaise	0	0	2 (1.1%)
Muscle weakness	0	2 (1.1%)	0
Confusion	0	2 (1.1%)	0
Flushing	2 (1.1%)	0	0

Reviewer's comment: A comparison of the rates of "dizziness" with other alpha adrenergic blocking agents is difficult. Information concerning direct comparisons is scant. Overall, the incidence of "dizziness" with alfuzosin appears to be similar to other alpha adrenergic blocking agents.

A.8.5 Laboratory abnormalities:

The number of patients with significant laboratory abnormalities is shown in Table A.10.

Table A.10. Number of patients with significant laboratory abnormalities

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg
Total bilirubin (>2 ULN)	0/166	0/162	0/156
AST (>2 ULN)	1/166	0/162	1/156
ALT (>2 ULN)	0/166	1/162	0/156
Creatinine (increase >30%)	6/166	4/163	4/157
White blood cells (< 3000/ml)	2/161	1/158	0/155
Neutophils (<1500/ml)	1/161	2/158	2/155
Hemoglobin (decrease > 2 g/dl)	4/161	4/158	1/155
Platelets (<100,000/ml	0/161	1/155	0/154

A.8.6 Special safety issues – vasodilatory events

"Vasodilatory" adverse events are shown in Table A.11.

Table A.11. "Vasodilatory" adverse events

	Placebo N=175	Alfuzosin 10 mg N=176	Alfuzosin 15 mg N=177
Dizziness	5 (2.9%)	13 (7.4%)	16 (9.0%)
Hypotension	0	1 (0.6%)	1 (0.6%)
Syncope	0	1 (0.6%)	0

"Vasodilatory" adverse events by age are shown in Table A.12.

Table A.12. "Vasodilatory" adverse events by age.

	Placebo		Alfuzosin 10 mg		Alfuzosin 15 mg	
	<65 yrs	>65 yrs	<65 yrs	>65 yrs	<65 yrs	>65 yrs
Dizziness	2 (2%)	3 (5%)	7 (7%)	6 (8%)	3 (3%)	13 (16%)
Hypotension	0	0	0	1 (1%)	0	1 (1%)
Syncope	0	0	1 (1%)	0	0	0

Dizziness: The frequency of dizziness suggested a dose-dependency. Dizziness led to study withdrawal in 2 (1.1%) patients in the 10 mg group and 3 (1.7%) patients in the 15 mg alfuzosin group.

Syncope: Syncope occurred in 1 patient in the 10 mg group.

Patient #33140474 (59-year-old) experienced syncope 150 minutes after the first dose of study drug (alfuzosin 10 mg). While urinating, he fainted, fell, and suffered a traumatic bursitis of the left shoulder. No BP values were available. He was hypertensive and was taking allopurinol, fosinopril, and atorvastatin.

Hypotension: One episode of hypotension occurred in each of the 10 mg and 15 mg alfuzosin groups.

Patient #33170125 (74-year-old) experienced hypotension on Day 2 of the study approximately 12 hours after taking 10 mg of alfuzosin. The hypotension persisted for 10 days and was associated with nausea and abnormal vision. His sitting BP was 100/60 and standing BP was 104/70. His screening and baseline BP's were 124/76 and 150/92, respectively. His medications included atenolol. He had a history of angina pectoris and coronary artery bypass surgery. Because of this event, he withdrew from the study.

Patient #33090847 (74-year-old) experienced hypotension associated with dizziness, disorientation, and headache approximately 9 hours after taking the first dose of study drug (alfuzosin 15 mg). His BP 15 hours after the first dose was 100/64 supine and 94/60 standing. Baseline values were 120/96 supine and 110/70 standing. He had no significant past medical history and was taking no other medications. He recovered without sequelae and withdrew from the study.

Other cardiac events:

One patient in the 10 mg group and 1 patient in the 15 mg group experienced aggravated angina pectoris. Patient #32980214 (72 year old) experienced increasing angina on Day 21 approximately 14 hours after his last dose of study drug (alfuzosin 10 mg). He was admitted to the hospital and had a coronary artery stent placed. He recovered without sequelae. Patient #33010798 experienced mild exacerbation of angina on Day 2 of treatment with 15 mg alfuzosin.

One patient in the 15 mg alfuzosin group experienced a myocardial infarction on Day 2 approximately 21 hours after his first dose of study drug. He was treated with coronary artery stent placement and withdrew from the study.

Other adverse events:

One patient experienced "delayed ejaculation."

A.9 Reviewer's assessment of efficacy and safety: The reviewer believes that the efficacy and safety data from the ALFUS trial supports the approval of alfuzosin ER 10 mg for the treatment of the signs and symptoms of benign prostatic hyperplasia.

Appendix B:

Clinical Trial ALFORTI-2789: "Efficacy and Safety of Alfuzosin Geomatrix 10 mg OD versus Alfuzosin 2.5 mg tid and Placebo in Patients with Symptomatic Benign Prostatic Hyperplasia. Placebo-Controlled , Double-Blind Study, Conducted in 3 Parallel Groups for 3 Months." (Study began May 21, 1997, and ended July 9, 1998)

B.1 Objectives: The aim of this trial was to assess the efficacy and safety of a new formulation of alfuzosin, administered at a dose of 10 mg OD without any dose titration, versus the marketed formulation in Europe (alfuzosin 2.5 mg tid) and placebo for 3 months, in patients with symptomatic BPH.

B.2 Design and Conduct Summary: This was a multicenter, European multinational, randomized, placebo-controlled, Phase 3 trial carried out on a double-blind, double-dummy basis in 3 parallel groups (alfuzosin 10 mg OD, alfuzosin 2.5 mg tid, and placebo). A 28 day single-blind placebo run-in period was followed by an 84 day (3 month) double-blind treatment period. The total duration of the trial for each patient was, therefore, 4 months. Amendment number 3 to the protocol gave patients the option of continuing participation in the trial on an open label basis for an additional 9 months. All patients received alfuzosin 10 mg OD in the 9 month open-label extension regardless of treatment group in the double-blind phase.

The trial consisted of two phases (A and B). Phase A consisted of a single-blind phase during which all patients received placebo (one tablet matching alfuzosin 2.5 mg tid and one tablet matching alfuzosin 10 mg once daily). Phase A began on the day of the Day-28 visit. Phase B consisted of an 84 day double-blind treatment phase during which the patient received either 1) alfuzosin 2.5 mg tid plus placebo alfuzosin 10 mg once daily 2) alfuzosin geomatrix 10 mg once daily plus placebo alfuzosin 2.5 mg tid or 3) placebo alfuzosin 10 mg once daily and placebo alfuzosin 2.5 mg tid. The study was comprised of 6 visits: screening visit (D-28), randomization visit (D0), 3 intermediate visits (D14, D28, and D56), and an endpoint visit at D84.

At screening (D-28), patients underwent hematology and chemistry tests, PSA, and urinalysis. In addition, IPSS, QOL index, Urolife questionnaire, Clinical Global Assessment, uroflowmetry, residual urine, and vital signs were determined.

At all subsequent visits (D0, D14, D28, D56, and D84), a urinalysis, physical examination, uroflowmetry, residual urine, vital signs (supine and after 2 minutes standing), and adverse events were determined.

IPSS, Quality of Life Index, Urolife questionnaire, and alfuzosin blood levels were performed on D0, D28, D56, and D84. The Clinical Global Impression was repeated on D84.

B.3 Study Population: The study population consisted of men aged greater than 50 years with at least a 6 month history of voiding symptoms. Baseline characteristics of the study population are shown in Table B.1.

Table B1. Baseline characteristics of the study population.

	Placebo (n=154)	Alfuzosin 10 mg (N=143)	Alfuzosin 2.5 mg tid (N=150)
Age (mean)	64.2	64.9	64.7
Age (range)	50-85	49-82	50-89
<65 years, N (%)	80 (52%)	68 (48%)	73 (49%)
>65 years, N (%)	74 (48%)	75 (52%)	77 (51%)
Race (Caucasian)	100%	100%	100%
IPSS (mean)	17.8	17.2	16.8
Qmax (cc/sec) (mean)	9.1	9.3	8.8

B.4 Inclusion/exclusion criteria: Inclusion criteria included 1) men > age 50 years 2) symptomatic BPH diagnosed clinically by digital rectal examination complemented (if available) by results of a transrectal ultrasound of the prostate within the preceding 12 months 3) suffering for at least 3 months from voiding disturbances which include day-time frequency, urgency, nocturia, feeling of incomplete emptying, interruption of the stream, impaired quality of the stream, and hesitancy 4) IPSS score of greater than or equal to 13 at D-28 and D0 5) Qmax between 5 and 12 cc/sec with a voided volume of at least 150 cc at D-28 and D0 and 6) residual urine volume of <350 cc at D-28 and D0.

Exclusion criteria included: 1) neurogenic bladder dysfunction 2) urethral stricture 3) bladder neck obstruction 4) acute or chronic prostatitis 5) active urinary tract infection 6) prostate cancer 7) carcinoma of prostate suspected by digital rectal examination or PSA >10 ng/mL, unless prostate biopsies performed in the last 2 years showed no prostate cancer 8) bladder stones 9) gross hematuria 10) previous prostate surgery or other invasive treatment for BPH 11) previous X-ray therapy to the pelvis 12) indwelling catheter 13) previously not improved by an alpha$_1$ blocking agent 14) Parkinson's disease 15) insulin dependent diabetes 16) multiple sclerosis 17) stroke or myocardial infarction in the 5 months prior to D-28 18) unstable angina or severe congestive heart failure 19) AST > 2 X ULN, ALT > 2 X ULN, ALP > ULN, total bililrubin > 2 X ULN, creatinine > 150 umol/L, hemoglobin < 12 g/dL, neutrophils < 1500/ml, or platelets < 150,000/ml 20) history of orthostatic hypotension or syncope or fall in systolic blood pressure of >20 mmHg after 2 minutes in standing position on D-28 or D0 21) patients taking alpha blocker in the month preceding D-28 22) patients taking androgens, anti-androgens, 5 alpha-reductase inhibitors, or LHRH analogues in the 3 months preceding D-28 23) patients who had received tricyclic antidepressants, anticholinergics, sympathomimetics, antihistamines, or plant extracts for BPH within 1 month of D0.

Reviewer's comment: As in trial ALFUS and ALFOTAM, patients with orthostatic hypotension were excluded.

B.5 Primary and Secondary Endpoints:

Primary endpoint: mean change in total IPSS scores at endpoint compared with baseline

Secondary endpoints: peak urine flow rate, mean urine flow rate, IPSS subscores, Quality of Life Index, Urolife scale, and Clinical Global Impression

B.6 Withdrawals, compliance, and protocol violations:

A total of 567 patients were screened and entered the placebo run-in period and 447 patients entered the double-blind treatment phase. The reasons for non-inclusion in the double-blind treatment phase were: 1) Q_{max} out of range of inclusion criteria (45 patients) 2) IPSS < 13 (17 patients) 3) adverse events (7 patients) 4) "biological abnormality" (37 patients) 5) concomitant disease or treatment not authorized (10 patients) 6) voided volume out of range of exclusion criteria (6 patients) 7) other reasons (21 patients). Among the 447 patients, 154 received placebo, 143 received alfuzosin 10 mg OD, and 150 received alfuzosin 2.5 mg tid.

Forty (8.9%) patients withdrew from the study. The most frequent reason for premature discontinuation (in all 3 groups) was adverse events: 3.9% in the placebo group, 5.6% in the alfuzosin 10 mg OD group, and 4% in the alfuzosin 2.5 mg tid group.

The reasons for premature withdrawal from the study are listed in Table B.2.

Table B.2. Reasons for premature withdrawal from the study.

	Placebo (N=154)	Alfuzosin 10 mg OD (N=143)	Alfuzosin 2.5 mg tid (N=150)
Lost to follow-up	0	0	1
Lack of efficacy	1	2	1
Adverse event	6	8	6
Uncooperative	0	1	1
Recovery	0	0	1
Other	3	5	4

Twenty-five randomized patients had 26 major protocol deviations. The majority of the protocol deviations concerned disease severity and BPH symptoms.

B.7 Efficacy analysis:

The primary population for the efficacy analyses was the ITT population. The ITT population included all exposed patients with at least one IPSS evaluation during the double-blind treatment period. The ITT N was 436.

The results of the analysis of the primary endpoint, mean change in IPSS total score at endpoint compared to baseline, are shown in Table B.3.

Table B.3. IPSS total score (mean) – ITT population.

	Placebo	**Alfuzosin 10 mg OD**	Alfuzosin 2.5 mg tid
Day 0	17.7	**17.3**	16.8
Day end	12.8	**10.4**	10.5
Day end – Day 0	-4.9	**-6.9**	-6.4
P versus placebo		**0.002**	0.02

The difference in improvement in the alfuzosin 10 mg OD group versus placebo was achieved by the first post-baseline study visit at 4 weeks and was maintained throughout the study.

Secondary endpoints of most clinical relevance:

1) Data for Qmax is shown in Table B.4.

Table B.4. Changes in Qmax (cc/sec)

	Placebo	**Alfuzosin 10 mg OD**	Alfuzosin 2:5 mg tid
D0 (mean)	9.2	**9.4**	8.7
D end	10.6	**11.7**	11.9
D end – D0	1.4	**2.3**	3.2
P versus placebo		**0.03**	<0.0001

2) Percentage of patients with a > 3 point improvement in IPSS score (see Table B.5.)

Table B.5. Percentage of patients with a > 3 point improvement in IPSS score

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
Change in IPSS score of >3	68%	81%	76%
P versus placebo		0.01	0.14

3)Percentage of patients with a >2cc/sec improvement in Q_{max} (see Table B.6.)

Table B.6. Percentage of patients with a >2cc/sec improvement in Qmax

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
% with >2cc/sec improvement	35%	49%	57%
P versus placebo		0.02	0.0002

4) The Quality of Life Index was significantly improved in the alfuzosin 10 mg OD group compared with placebo. No statistical difference was observed in Urolife between the alfuzosin 10 mg OD dose and placebo.

B.8 Safety analysis

B.8.1 Extent of exposure: The mean duration of exposure is shown in Table B.7.

Table B.7. Duration (mean days) of drug exposure

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
Number of patients	154	143	149
Mean duration of exposure (days)	85	82	84

B.8.2 Serious adverse events:

Deaths: One death was reported during the course of the study. Patient #15640791 was an 80-year-old man treated with alfuzosin 10 mg OD who died after an ENT infection. A relationship to alfuzosin was excluded by the investigator.

Serious adverse events were reported during the treatment period in 6 patients in the placebo group, 3 in the alfuzosin 10 mg OD group, and 2 in the alfuzosin 2.5 mg tid group.

The 3 SAE's in the alfuzosin 10 mg OD group were renal calculus, upper respiratory infection, and cholecystitis. Patient # 15640791 died following an "upper respiratory infection." This patient was thought to have died from meningitis following fracture of the ethmoid following cranial trauma.

Reviewer's comment: The investigators believe that none of these SAE's was related to study drug and the reviewer agrees.

Two SAE's occurred in the alfuzosin 2.5 mg tid group. One consisted of hospitalization for an inguinal hernia and the other (patient #27740674) consisted of syncope and nausea. This second patient had short loss of consciousness 90 minutes after an evening dose of drug. Associated nausea and dizziness lasted for 4 days. Relationship of this episode and study drug is unclear.

B.8.3 Premature discontinuation due to adverse event:

The number of withdrawals due to adverse event was 6/154 in the placebo group, 8/143 in the alfuzosin 10 mg OD group , and 9/149 in the alfuzosin 2.5 mg tid group.

In the alfuzosin 10 mg OD group, the 8 premature discontinuations were due to: hypotension (1), upper respiratory infection (1), influenza-like symptoms (1), renal calculus (1), palpitations (1), cholecystitis (1), increased alkaline phosphatase (1), and thyroiditis (1).

In the alfuzosin 2.5 mg tid group, the 9 premature discontinuations were due to: dizziness (1), postural hypotension (1), syncope (1), gastroesophageal reflux (1), headache (1), orchitis (1), prostatic disorder (1), tachycardia (1), and tinnitus (1).

The cardiovascular or "vasodilatory" events are discussed in section B.8.6: Special safety issues: Cardiovascular events.

B.8.4 Overall adverse events:

Adverse events reported by more than 1% of patients are shown in Table B.8.

Table B.8. Adverse events reported by more than 1% of patients in any treatment group.

	Placebo (N=154)	**Alfuzosin 10 mg OD (N=143)**	Alfuzosin 2.5 mg tid (N=149)
Dizziness	2 (1.3%)	**3 (2.1%)**	7 (4.7%)
Rhinitis	2 (1.3%)	**3 (2.1%)**	4 (2.7%)
Influenza-like symptoms	4 (2.6)	**3 (2.1%)**	2 (1.3%)
Asthenia	2 (1.3%)	**3 (2.1%)**	1 (0.7%)
Headache	1 (0.6%)	**2 (1.4%)**	3 (2.0%)
Pruritis	0	**2 (1.4%)**	1 (0.7%)
Malaise	0	**2 (1.4%)**	1 (0.7%)
Pharyngitis	0	**2 (1.4%)**	0
URI	0	**2 (1.4%)**	0
Renal calculus	0	**2 (1.4%)**	0
Fatigue	2 (1.3%)	**2 (1.4%)**	0
Arthralgia	2 (1.3%)	**2 (1.4%)**	0
Sinusitis	3 (1.9%)	**1 (0.7%)**	1 (0.7%)
Constipation	1 (0.6%)	**1 (0.7%)**	2 (1.3%)
Dry mouth	0	**1 (0.7%)**	2 (1.3%)
Dyspepsia	1 (0.6%)	**1 (0.7%)**	2 (1.3%)
Arthrosis	2 (1.3%)	**1 (0.7%)**	1 (0.7%)
Bronchitis	2 (1.3%)	**1 (0.7%)**	4 (2.7%)
Hypertension	2 (1.3%)	**1 (0.7%)**	0
Arthritis	2 (1.3%)	**1 (0.7%)**	0
Abdominal pain	0	**0**	3 (2.0%)
Urticaria	0	**0**	2 (1.3%)
Postural hypotension	0	**0**	2 (1.3%)
Tachycardia	0	**0**	2 (1.3%)
Dyspnea	2 (1.3%)	**0**	0
Diarrhea	2 (1.3%)	**0**	1 (0.7%)
Tendinitis	2 (1.3%)	**0**	0

B.8.5 Laboratory abnormalities: