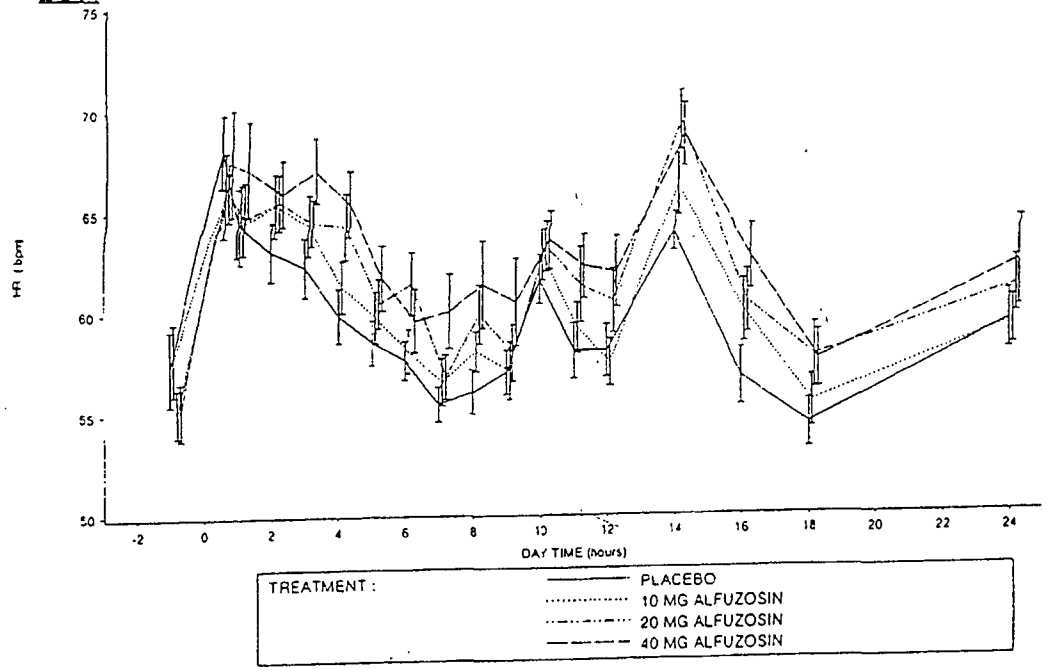
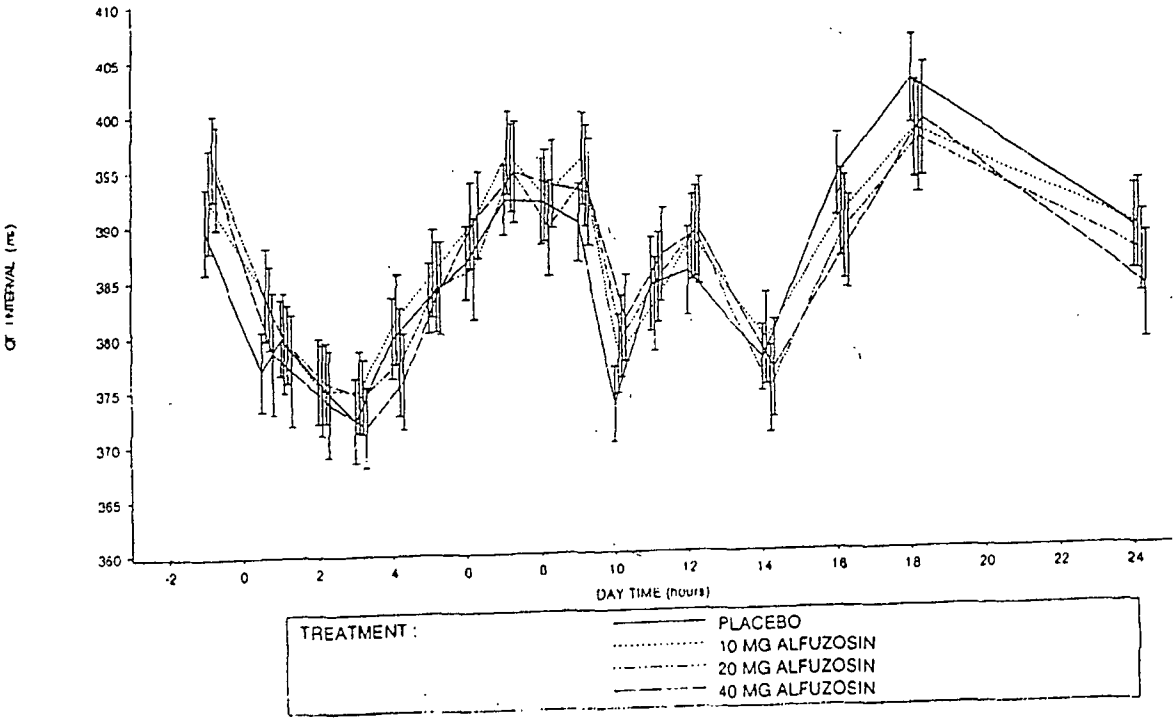
14.3.5.2 Mean data

ECG:



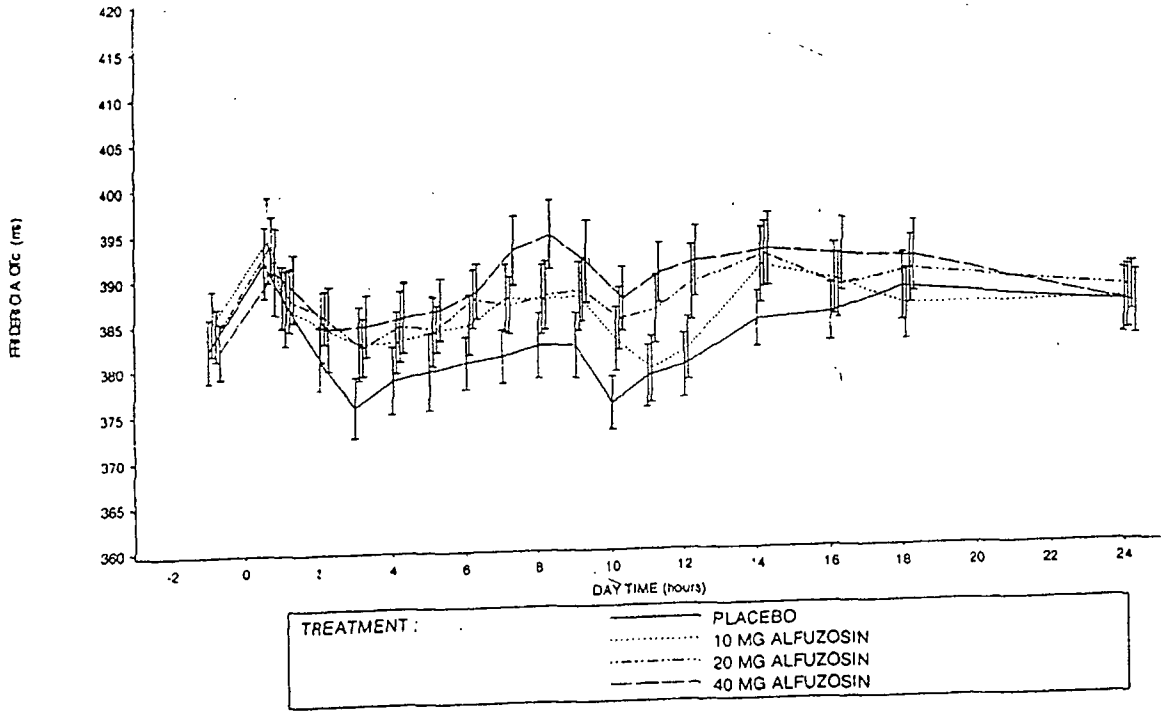
Ref.: Appendix 16.2.9.1.11.1

Figure (14.3.5.2) 1 - Mean HR +/- (SEM) (Manual Reading)



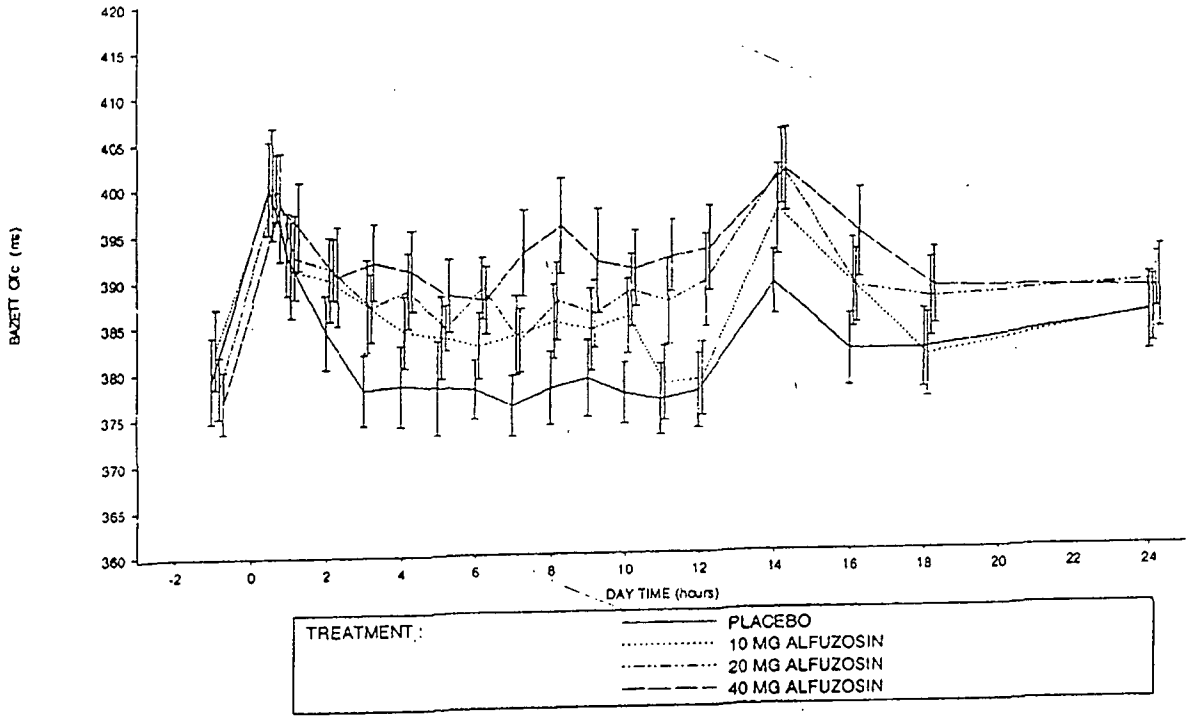
Ref.: Appendix 16.2.9.1.11.5

Figure (14.3.5.2) 4 - Mean QT Interval +/- (SEM) (Manual Reading)



Ref.: Appendix 16.2.9.1.11.7

Figure (14.3.5.2) 6 - Mean Fridericia QTc +/- (SEM). (Manual Reading)



Ref.: Appendix 16.2.9.1.11.6

Figure (14.3.5.2) 5 - Mean Bazett QTc +/- (SEM) (Manual Reading)

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Safety Update Review

See Integrated Review of Safety, pages 17-23 of the Medical Officer Review #2, dated June 12, 2003.

PS
6/12/03

NDA 21-287
Alfuzosin Hydrochloride

Safety Update Review

See Appendix G of the Clinical Review

NDA 21287 Amendment #36 Complete response to Approvable Action

Date submitted: December 12, 2002
Date received: December 12, 2002
Review completed: June 3, 2003

Medical Officer Review

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

Marcea Whitaker, MD
Medical Officer
/S/

George Benson, MD
Urology Team Leader
/S/

Donna Griebel, MD
Deputy Director, DRUDP
/S/

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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 daily should be "approved" for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia". The drug's QT prolonging effects do not appear to be clinically significant. The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Alfuzosin hydrochloride extended-release (ER) is an alpha$_1$-adrenergic receptor antagonist proposed for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)". The recommended dose is the 10 mg alfuzosin ER formulation once daily. Other approved alpha$_1$-adrenergic receptor antagonists for the treatment of BPH are Hytrin® (terazosin), Cardura® (doxazosin), and Flomax® (tamsulosin).

The immediate-release formulation of alfuzosin (2.5 mg TID) has been marketed in foreign markets since 1987. The sustained-release formulation (5 mg BID) and extended-release formulations (10 mg QD) have been approved in foreign markets since 1993 and 1999, respectively.

The original NDA, submitted December 8, 2000, contained 3 pivotal Phase III studies (ALFUS, ALFOTAM, and ALFORTI) using the 10 mg ER formulation. The NDA also contained an additional Phase III trial (ALFOD) using the 7.5 mg ER formulation. ALFUS was conducted in the United States and the remaining 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.

The original NDA contained two deficiencies that were outlined in the "approvable" letter dated October 5, 2001:

1) 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."

2) "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."

Amendment #36 (Complete response to approvable action) was submitted by the sponsor on December 12, 2002, to address these deficiencies. The amendment contains data from two Phase I studies, PDY 5105 and INT 5056, a QT study and a ketoconazole study, respectively. Both protocols had been submitted to the agency previously and were found to be acceptable. Trial PDY 5105 was a Phase I, single-center, 4-way crossover, randomized, double-blinded, double-dummy, placebo-controlled study in 48 healthy volunteers. Trial INT 5056 was a Phase I, single-center, open-labeled, non-randomized, two-period pharmacokinetic study using 400 mg of ketoconazole in 12 healthy male subjects.

B. Efficacy

The improvement in IPSS is clinically and statistically significant across all three pivotal trials submitted with the original NDA using the 10 mg alfuzosin ER formulation. Q_{max}, a more variable endpoint, achieved statistical significance in 2 of the 3 trials and trended toward significance in the third. Although there are insufficient data to directly compare alfuzosin with the other alpha-blockers, improvement in IPSS and Qmax seen with alfuzosin 10 mg ER appears comparable to results reported for the other alpha$_1$-adrenergic blocking agents currently approved for the treatment of symptoms of benign prostatic hyperplasia.

No new efficacy information was submitted in the complete response to the "approvable" action.

C. Summary of submitted studies

i) QT interval: Clinical trial PDY 5105 -"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"

A Holter-monitoring analysis method was used as the primary endpoint for this study. The results are shown below in Table 1 and compare QT changes for alfuzosin 10 mg, alfuzosin 40 mg and moxifloxacin 400 mg.

Results:

- Moxifloxacin at therapeutic dose (400 mg) increased the mean QT interval by 6.6 – 7.0 msec at all endpoints (p=0.0001).
- Alfuzosin 10 mg produced a mean increase in QT interval of 0.1-0.4 msec over placebo.
- Alfuzosin 40 mg produced a mean increase in QT of 2.0-2.9 msec.

- 95% CI width was approximately 5 msec for all comparisons.
- The sponsor believes that these results confirm that alfuzosin does not cause a meaningful increase of the QT interval.

Table 1. Holter-monitoring method:
QT change comparing alfuzosin 10 mg, 40 mg and moxifloxacin

Holter-Monitoring Endpoints	Treatment	P-Value	Mean Difference vs Placebo (msec)	Mean change (msec)	Placebo (msec)	95% CI	
						Lower Bound	Upper Bound
1000 msec RR Bin	Alfuzosin 10 mg (n = 36)	0.9694	0.1	-2.3	-2.2	-2.5	2.6
	Alfuzosin 40 mg (n = 35)	0.0278	2.9	0.8	-2.2	0.3	5.5
	Moxifloxacin 400 mg (n = 37)	0.0001	7.0	4.8	-2.2	4.4	9.6
Largest Sample-Size RR Bin	Alfuzosin 10 mg (n = 41)	0.7017	0.4	-2.0	-2.4	-1.8	2.6
	Alfuzosin 40 mg (n = 45)	0.0197	2.5	0.2	-2.4	0.4	4.7
	Moxifloxacin 400 mg (n = 43)	0.0001	6.9	4.5	-2.4	4.8	9.1
Average of All RR Bins	Alfuzosin 10 mg (n = 42)	0.9547	0.1	-2.2	-2.2	-1.9	2.0
	Alfuzosin 40 mg (n = 45)	0.0484	2.0	-0.1	-2.2	0.0	3.9
	Moxifloxacin 400 mg (n = 43)	0.0001	6.6	4.4	-2.2	4.6	8.6

Source: Sponsor tables (11.4.1.1)1 and (15.2.1)

Secondary endpoints were 12-lead ECG methods with calculations of QTc Bazett, QTc Fridericia, QTcN and QTcNi. QTcN and QTcNi represent population-specific and subject-specific analyses, respectively, based on the QT/RR data relationships. Results are shown below in Table 2.

Table 2. 12-lead ECG: Change in HR, QT and QTc from baseline to Cmax:
Comparing alfuzosin 10 mg, 40 mg and moxifloxacin 400mg versus placebo

ECG Parameters	Treatment	P-Value	Mean Difference vs Placebo	Mean Difference	Matched Placebo	95% CI	
						Lower Bound	Upper Bound
HR (bpm)	Alfuzosin 10 mg	0.0013	5.2	5.7	0.6	2.2	8.3
	Alfuzosin 40 mg	0.0001	5.8	6.9	1.0	3.2	8.4
	Moxifloxacin 400 mg	0.0005	2.8	2.3	-0.5	1.3	4.2
QT interval (msec)	Alfuzosin 10 mg	0.0115	-5.8	-13.9	-8.4	-10.2	-1.4
	Alfuzosin 40 mg	0.0590	-4.2	-10.7	-6.5	-8.5	0.2
	Moxifloxacin 400 mg	0.0045	6.9	5.5	-1.3	2.3	11.5
Bazett QTc (msec)	Alfuzosin 10 mg	0.0023	10.2	4.7	-5.3	3.9	16.6
	Alfuzosin 40 mg	0.0012	13.9	11.9	-2.0	5.8	22.0
	Moxifloxacin 400 mg	0.0001	15.7	13.4	-2.3	10.8	20.6
Fridericia QTc (msec)	Alfuzosin 10 mg	0.0171	4.9	-1.5	-6.3	0.9	8.8
	Alfuzosin 40 mg	0.0102	7.7	4.3	-3.4	1.9	13.5
	Moxifloxacin 400 mg	0.0001	12.7	10.8	-1.9	8.6	16.8
QTcN (msec)	Alfuzosin 10 mg	0.2709	1.8	-5.0	-6.8	-1.4	5.0
	Alfuzosin 40 mg	0.0819	4.2	-0.1	-4.3	-0.6	9.0
	Moxifloxacin 400 mg	0.0001	11.0	9.4	-1.6	7.0	15.0
QTcNi (msec)	Alfuzosin 10 mg	0.2456	1.8	-4.7	-6.6	-1.3	5.0
	Alfuzosin 40 mg	0.0804	4.3	0.1	-4.2	-0.5	9.2
	Moxifloxacin 400 mg	0.0001	11.1	9.4	-1.7	7.2	15.0

Source: Appendix Table A.5 and A.6 merged.

Results:

At C_{max}: Comparison of moxifloxacin vs placebo

- Moxifloxacin produced a statistically significant QT interval increase at C_{max} in comparison with placebo with conventional formulae (Bazett 15.7 msec and Fridericia 12.7 msec).
- Similar but smaller increases versus placebo were found using QTcN and $QTcN_i$ (11.0 and 11.1 msec, respectively).

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

- QTcF showed a mean change of 4.9 msec for alfuzosin 10 mg and 7.7 msec for alfuzosin 40 mg over placebo.
- QTcB showed a mean change of 10.2 msec for alfuzosin 10 mg and 13.9 msec for alfuzosin 40 mg over placebo.
- The sponsor believes that QTcB and QTcF calculations are inappropriate due to the increase in heart rate observed with alfuzosin (mean of 5 to 6 bpm). The sponsor believes that the heart rate inappropriately drove the QTcB and QTcF increases. QTcN and QTcNi corrections were developed to better correct for the confounding heart rate effect.
- QTcN and QtcNi increases versus placebo were 1.8 msec for alfuzosin 10 mg.
- QTcN and QtcNi increases versus placebo were approximately 4 msec for alfuzosin 40 mg.

Sponsor's conclusions:

1. The sponsor believes that QTcB and QTcF calculations "overcorrect" for increases in heart rate observed with alfuzosin (mean of 5 to 6 bpm). QTcN and QTcNi corrections were developed to better correct QT for the confounding HR effect.
2. An increase in QTc based on Bazett's and Fridericia's formulae is found for moxifloxacin comparable to values reported in the literature, thus demonstrating the sensitivity of the trial.
3. A QT increase of about 7 msec seen with moxifloxacin at the therapeutic dose is found using the Holter-monitoring method. This demonstrates that the Holter-monitoring method is sensitive and can detect moderate drug-induced increases of QT interval.
4. Using the Holter method, the therapeutic dose of alfuzosin (10 mg) produces no significant change in the QT interval. At 4 times the therapeutic dose (40 mg), alfuzosin produces QT changes of no more than 2.9 msec.
5. Pharmacokinetic data was also obtained and showed mean C_{max} and AUC values increases by 4.3- and 4.6-fold, respectively, when alfuzosin 10 mg is compared with alfuzosin 40 mg. The data is consistent with dose proportionality and linear pharmacokinetics. Mean C_{max}, AUCs, $t_{1/2}$ and median t_{max} of moxifloxacin were consistent with the literature.

Reviewer's Comments:
(1) Based on the available data, alfuzosin exhibits a measurable QT prolonging effect of 4.9 msec (for alfuzosin 10 mg) and 7.7 msec (for alfuzosin 40 mg) with a dose response when corrected with standard Fridericia formula. When individual/population correction methods (QTcN/QTcNi) are used, the QT prolonging effect is reduced to 1.8 msec.
(2) Further analysis by the clinical pharmacology reviewer included plotting slopes for uncorrected QT vs RR interval. For the population and individual correction methods, the slopes are closer to zero when compared to the Fridericia correction method. This analysis suggests, in this data set, that population and individual methods may more accurately correct the QT interval for heart rate than does the Fridericia method.
(3) At the to-be-marketed alfuzosin dose (10 mg), the QTc appears to increase by <5 msec compared to placebo (using Fridericia or individual corrections). This level of increase, in the opinion of this reviewer, constitutes a low and acceptable risk for arrhythmia.
(4) The Cardiovascular and Renal Advisory Committee voted unanimously (14-0) that the data did not "demonstrate a clinically relevant QT prolongation associated with alfuzosin".
(5)Alfuzosin's QT prolonging effect does not appear to be clinically significant. The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

ii) ketoconazole: Study INT 5056, "Assessment of pharmacokinetic drug interaction between alfuzosin 10 mg qd formulation and ketoconazole 400 mg per day in healthy male subjects."

Repeated administration of ketoconazole 400 mg daily for 8 days increased the C_{max} of alfuzosin (10 mg single dose) by 2.3-fold. Repeated administration of ketoconazole 400 mg daily for 8 days increased the AUC_{last} and AUC by 3.2 and 3.0-fold, respectively. Terminal half-life $t_{1/2}$ increased by 1.16-fold.

D. Dosing

The recommended dose is the 10 mg alfuzosin ER formulation once daily.

Reviewer's Comment:
The change in 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.
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. In my opinion, the 10 mg dose is the appropriate to-be-marketed formulation.

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 insufficient to make meaningful conclusions concerning racial differences.

Geriatric issues: In the clinical trials submitted with the original NDA, 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 older and younger patients. In a pharmacokinetic assessment during Phase 3 clinical studies in BPH patients, the Cmax was 13.4 in patients over 75 years of age and 9.7 in patients between 65 and 74, compared with 10.9 in those patients less than 65 years 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 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.

Reviewer's Comment: The section on "Patients with Renal Impairment" in the label should be revised to reflect this increase in adverse events rate.

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. In the opinion of this reviewer, alfuzosin should be contraindicated in patients with all degrees of hepatic insufficiency.

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.

Clinical Review

I. Introduction and Background

A. Proposed Drug

Alfuzosin hydrochloride extended-release (ER) is an alpha$_1$-adrenergic receptor antagonist proposed for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia (BPH)." The recommended dose is 10 mg alfuzosin ER formulation once daily. Other approved alpha$_1$-adrenergic receptor antagonists for the treatment of BPH are Hytrin® (terazosin), Cardura® (doxazosin), and Flomax® (tamsulosin).

At the time of the original NDA submission the preferred trade name was Uroxatral. On December 16, 2002, the sponsor submitted a request to change the trade name to [redacted] This request has been reviewed by DMETS and DDMAC, and the proposed name, [redacted] was not recommended because of "sound-alike" and "look-alike" similarities with other drugs. At the time of completion of this review, the tradename issue had not been settled.

B. Milestones in Product Development

The original NDA was submitted on December 8, 2000. Two deficiencies of the NDA were outlined in the "approvable" letter dated October 5, 2001:

1) 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."
2) "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."

Amendment #36 was submitted by the sponsor on December 12, 2002, to address these deficiencies. The amendment contained data from two Phase I studies, PDY 5105 and INT 5056, a QT study and a ketoconazole study, respectively. Both protocols had been submitted to the agency previously and were found to be acceptable. These actions were conveyed via regulatory letters on September 16, 2002, and May 1, 2002, respectively.

C. Active Issues

1) QT interval

The sponsor had previously submitted data in protocol PKD4532 using 10 mg, 20 mg, and 40 mg of alfuzosin and in protocol PCALF96US1 using a dose range of 7.5 mg to 30 mg of alfuzosin. As stated in the original 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 10 msec.'" And, "heart rate, QTcB, and QTcF are significantly increased from baseline for the 20 and 40 mg doses compared to placebo." In essence, the division believed that there was insufficient data to determine whether alfuzosin has a clinically significant 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 heart rate 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 standard correction formulas.

2) Ketoconazole

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

D. Foreign Approval

The immediate-release formulation (2.5 mg TID) has been marketed in foreign markets since 1987. The sustained-release formulation (5 mg BID) and extended-release formulations (10 mg QD) have been approved in foreign markets since 1993 and 1999, respectively.

II. Human Pharmacokinetics and Pharmacodynamics

Data from Original NDA review

C_{max} 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:

A) Ketoconazole (200 mg) increases the alfuzosin C_{max} 2-fold and the AUC 2.5-fold. The reviewer agreed with the clinical pharmacology recommendation that ketoconazole and other potent CYP3A4 inhibitors should be "contraindicated."
B) The C_{max} of alfuzosin is increased 1.5-fold in patients with mild, moderate, and severe renal insufficiency. The reviewer agreed 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."

Additional data from newly completed studies PDY 5105 and INT 5056:

A. Study PDY 5105 (QT study)
Mean C_{max} and AUC values increased by 4.3- and 4.6-fold, respectively, when alfuzosin 10 mg was compared with alfuzosin 40 mg. The data was consistent with dose proportionality and linear pharmacokinetics. Mean C_{max}, AUCs, $t_{1/2z}$ and median t_{max} of moxifloxacin were consistent with the literature.

B. Study INT 5056 (ketoconazole study)
Repeated administration of ketoconazole 400 mg daily for 8 days increased the C_{max} of alfuzosin (10 mg single dose) by 2.3-fold. Repeated administration of ketoconazole 400 mg daily for 8 days increased the AUC_{last} and AUC by 3.2 and 3.0-fold, respectively. Terminal half-life ($t_{1/2}$) increased by 1.16-fold.

III. Description of Clinical Data and Sources

The following materials were reviewed: 1) cardiac safety profile; 2) Study INT 5056 and cover letter; 3) Study PDY 5105; 4) draft package insert; and 5) patient package insert; 6) update of integrated safety summary; 7) 3-month safety update (10/1/02-12/31/02); 8) 15-day safety reports; and DMETS and DDMAC proprietary name review consultation.

IV. Integrated Review of Efficacy (see review of original NDA submission)

A. Efficacy Conclusions

The results of the three Phase 3 Trials were reported in the original NDA in which the 10 mg alfuzosin ER dose showed statistically significant improvement in both primary endpoints (International Prostate Symptom Score [IPSS] and maximum urinary flow rate [Qmax]). Although there are insufficient data to directly compare alfuzosin with the other alpha-blockers, the magnitude of improvement appears similar to that seen with currently approved $alpha_1$- adrenergic blocking agents approved for the treatment of the symptoms of BPH.

B. Approach to Review of Efficacy

The sponsor originally submitted four 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 three Phase 3 studies evaluated the 10 mg alfuzosin ER dose and two of the three trials also evaluated a 15 mg alfuzosin ER dose. Each of the four 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 of the original NDA review). 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 used in the 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 three 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: 1) 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 <350 cc. Exclusion criteria included patients with diseases known to affect lower urinary tract function and the use of alpha-adrenergic blocking agents, androgens,

antiandrogens, 5 alpha-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 (Qmax). (In ALFORTI, Qmax 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 (alfuzosin dose of 7.5 mg/day), 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 10mg N=170	placebo N=147	alfuzosin 10mg N=136	placebo N=150	alfuzosin 10mg 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 in 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 12 cc/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 trended toward significance in the third.

No new efficacy information was submitted in the complete response to the "approvable" action.

V. Integrated Review of Safety

A. QT study

Clinical trial PDY 5105 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" was reviewed. (See Appendix A for full review.)

1) A Holter-monitoring anaylsis method was used as the primary endpoint for this study. The results are shown below in Table 4.

Results:

- Moxifloxacin at therapeutic dose (400 mg) increased the QT interval by 6.6 – 7.0 msec at all endpoints (p=0.0001).
- Alfuzosin 10 mg produced changes in the QT interval of 0.1-0.4 msec.
- Alfuzosin 40 mg produced a QT change of 2.0-2.9 msec.
- 95% CI width was approximately 5 msec for all comparisons.
- Conclusion: The sponsor believes that these results confirm that alfuzosin does not cause a meaningful increase of the QT interval.

Table 4 Holter-monitoring method:
QT change comparing alfuzosin 10 mg, 40 mg and moxifloxacin 400 mg

Holter-Monitoring Endpoints	Treatment	P-Value	Mean Difference vs Placebo (msec)	Mean change (msec)	Placebo (msec)	95% CI	
						Lower Bound	Upper Bound
1000 msec RR Bin	Alfuzosin 10 mg (n = 36)	0.9694	0.1	-2.3	-2.2	-2.5	2.6
	Alfuzosin 40 mg (n = 35)	0.0278	2.9	0.8	-2.2	0.3	5.5
	Moxifloxacin 400 mg (n = 37)	0.0001	7.0	4.8	-2.2	4.4	9.6
Largest Sample-Size RR Bin	Alfuzosin 10 mg (n = 41)	0.7017	0.4	-2.0	-2.4	-1.8	2.6
	Alfuzosin 40 mg (n = 45)	0.0197	2.5	0.2	-2.4	0.4	4.7
	Moxifloxacin 400 mg (n = 43)	0.0001	6.9	4.5	-2.4	4.8	9.1
Average of All RR Bins	Alfuzosin 10 mg (n = 42)	0.9547	0.1	-2.2	-2.2	-1.9	2.0
	Alfuzosin 40 mg (n = 45)	0.0484	2.0	-0.1	-2.2	0.0	3.9
	Moxifloxacin 400 mg (n = 43)	0.0001	6.6	4.4	-2.2	4.6	8.6

Source: sponsor tables (11.4.1.1) 1 and (15.2.1)1

Secondary Endpoints were 12-lead ECG methods with calculations of QTc Bazett, QTc Fridericia, QTcN and QTcNi. QTcN and QTcNi represent population-specific and subject-specific analyses, respectively, based on the QT/RR data relationships ($QTcN= QT/RR^{B}$, $QTcNi= QT/RR^{Bi}$). Results are shown below in Table 5.

Table 5: 12-lead ECG: Change in HR, QT and QTc from baseline to Cmax:
Comparing alfuzosin 10 mg, 40 mg and moxifloxacin 400mg versus placebo

ECG Parameters	Treatment	P-Value	Mean Difference vs Placebo	Mean Difference	Matched Placebo	95% CI	
						Lower Bound	Upper Bound
HR (bpm)	Alfuzosin 10 mg	0.0013	**5.2**	5.7	0.6	2.2	8.3
	Alfuzosin 40 mg	0.0001	**5.8**	6.9	1.0	3.2	8.4
	Moxifloxacin 400 mg	0.0005	**2.8**	2.3	-0.5	1.3	4.2
QT interval (msec)	Alfuzosin 10 mg	0.0115	**-5.8**	-13.9	-8.4	-10.2	-1.4
	Alfuzosin 40 mg	0.0590	**-4.2**	-10.7	-6.5	-8.5	0.2
	Moxifloxacin 400 mg	0.0045	**6.9**	5.5	-1.3	2.3	11.5
Bazett QTc (msec)	Alfuzosin 10 mg	0.0023	**10.2**	4.7	-5.3	3.9	16.6
	Alfuzosin 40 mg	0.0012	**13.9**	11.9	-2.0	5.8	22.0
	Moxifloxacin 400 mg	0.0001	**15.7**	13.4	-2.3	10.8	20.6
Fridericia QTc (msec)	Alfuzosin 10 mg	0.0171	**4.9**	-1.5	-6.3	0.9	8.8
	Alfuzosin 40 mg	0.0102	**7.7**	4.3	-3.4	1.9	13.5
	Moxifloxacin 400 mg	0.0001	**12.7**	10.8	-1.9	8.6	16.8
QTcN (msec)	Alfuzosin 10 mg	0.2709	**1.8**	-5.0	-6.8	-1.4	5.0
	Alfuzosin 40 mg	0.0819	**4.2**	-0.1	-4.3	-0.6	9.0
	Moxifloxacin 400 mg	0.0001	**11.0**	9.4	-1.6	7.0	15.0
QTcNi (msec)	Alfuzosin 10 mg	0.2456	**1.8**	-4.7	-6.6	-1.3	5.0
	Alfuzosin 40 mg	0.0804	**4.3**	0.1	-4.2	-0.5	9.2
	Moxifloxacin 400 mg	0.0001	**11.1**	9.4	-1.7	7.2	15.0

Source: Appendix Table A.5 and A.6 merged.

Results:

At C_{max}: Comparison of moxifloxacin vs placebo

- Moxifloxacin produced a statistically significant QT interval increase at C_{max} in comparison with placebo with conventional formulae (Bazett 15.7 msec and Fridericia 12.7 msec).
- Similar but smaller increases versus placebo were found using QTcN and $QTcN_i$, (11.0 and 11.1 msec, respectively).

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

- QTcF showed a mean change of 4.9 msec for alfuzosin 10 mg and 7.7 msec for alfuzosin 40 mg.
- QTcB showed a mean change of 10.2 msec for alfuzosin 10 mg and 13.9 msec for alfuzosin 40 mg.
- The sponsor believes that QTcB and QTcF calculations are inappropriate due to the increase in HR observed with alfuzosin (mean of 5 to 6 bpm). The sponsor believes that the heart rate inappropriately drove the QTcB and QTcF increases. QTcN and QTcNi corrections were developed to better correct the confounding heart rate effect.
- QTcN and QtcNi increases versus placebo were 1.8 msec for alfuzosin 10 mg.
- QTcN and QtcNi increases versus placebo were approximately 4 msec for alfuzosin 40 mg.

Sponsor's conclusions:

1. The sponsor believes that QTcB and QTcF calculations "overcorrect" for increases in heart rate observed with alfuzosin (mean of 5 to 6 bpm). QTcN and QTcNi corrections were developed to better correct QT with confounding heart rate effect.
2. An increase in QTc based on Bazett's and Fridericia's formulae is found for moxifloxacin comparable to values reported in the literature, thus demonstrating the sensitivity of the trial.
3. A QT increase of about 7 msec seen with moxifloxacin at the therapeutic dose is found using the Holter-monitoring method. This demonstrates that the Holter-monitoring method is sensitive and can detect moderate drug-induced increases of QT interval.
4. Using the Holter method, the therapeutic dose of alfuzosin produces no significant change in the QT interval. At 4 times the therapeutic dose, alfuzosin produces QT changes of no more than 2.9 msec.

Reviewer's Comments:

(1) Based on the available data, alfuzosin exhibits a measurable QT prolonging effect of 4.9 msec (for alfuzosin 10 mg) and 7.7 msec (for alfuzosin 40 mg) when corrected with standard Fridericia formula. When individual/population correction methods (QTcN/QTcNi) are used, the QT prolonging effect is reduced to 1.8 msec (for alfuzosin 10 mg) and a maximum of 4.3 msec (for alfuzosin 40 mg). All three methods exhibit a dose-response relationship.

(2) Further analysis by the clinical pharmacology reviewer included plotting slopes for uncorrected QT vs RR interval. For the population and individual correction methods, the slopes are closer to zero when compared to the Fridericia correction method. This analysis suggests, in this data set, that population and individual methods may more accurately correct the QT interval for heart rate than does the Fridericia method.
(3) At the to-be-marketed alfuzosin dose (10 mg), the QTc appears to increase by <5 msec compared to placebo (using Fridericia or individual corrections). This level of increase, in the opinion of this reviewer, constitutes a low and acceptable risk for arrhythmia.
(4) The Cardiovascular and Renal Advisory Committee voted unanimously (14-0) that the data did not "demonstrate a clinically relevant QT prolongation associated with alfuzosin".
(5) Alfuzosin's QT prolonging effect does not appear to be clinically significant. The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

B. Update of integrated safety summary

1. Introduction and patient exposure

The sponsor has developed three alfuzosin-containing oral dosage regimens that are marketed (foreign) for use in benign prostatic hyperplasia (BPH). The immediate-release (IR) formulation is a 2.5 mg tablet for tid dosing. The sustained-release (SR) formulation is a 5 mg tablet for bid dosing. The IR and the SR formulations of alfuzosin were first approved for use in BPH in the European market in 1987 and 1993, respectively. The more recently developed extended-release (ER) formulation of alfuzosin, utilizing a patented Geomatrix® system technology that allows for QD administration, was first approved in Europe on 10 September 1999, and is the intended formulation to be marketed in the United States. Since the first launch of alfuzosin 2.5 mg IR formulation on October 3, 1988, and until September 30, 2002, the estimated number of therapy-days of alfuzosin (all formulations) is [redacted] This update provides safety information obtained with all 3 formulations from **June 1, 2001, to September 30, 2002,** inclusively. The remainder of the safety information was submitted in the original NDA.

2. Listing of studies (see Table 6)

The sources of safety data in this submission (amendment #36) include two Phase I trials, one completed Phase III trial, 3 ongoing Phase III trials, 8 completed Phase IV trials, one special study, 5 observational studies/post-marketing surveys and one unsponsored study from Germany.

Table 6. Listing of studies submitted in current safety update

Study Name	Description	No. of patients treated w/alfuzosin (or enrolled)	Deaths	SAEs	Discontin-uations
Completed Phase I studies					
INT 5056	Interaction between alfuzosin 10 mg and ketoconazole 400 mg	13	—	---	1
PDY5105	QT study comparing alfuzosin 10 mg, 40 mg, moxifloxacin 400 mg and placebo	45	—	---	---
Completed Phase III Study					
ALFAUR Part I	Alfuzosin 10 mg vs placebo BPH w/ urinary retention	238	—	5	5
Ongoing blinded Phase III studies					
ALFAUR Part II	Alfuzosin 10 mg vs placebo secondary prevention of urinary retention	(169)	3	7	3
ALTESS	Long-term efficacy and safety of alfuzosin 10 mg	(1296)	3	10	6
ALFAURUS	Alfuzosin 10 mg vs placebo management of urinary retention	(189)	---	47	21
Completed Phase IV studies previously reported but subsequently unblinded*					
ALFRENOA*	Alfuzosin 5 mg bid vs serenoa repens 160 mg	131	—	5	13
ALPOST*	Alfuzosin 5 mg BID, efficacy post surgery	130	—	1	9
ALBITAM*	Alfuzosin 5 mg bid vs tamsulosin 0.4 mg bid, efficacy and safety	12	–	1	3
ALFLOW*	Alfuzosin effect on uroflowmetry	86	—	1	3
ALFLOW EXT*	Alfuzosin effect on uroflowmetry	150	---	8	7
AMBALF*	Alfuzosin 5 mg bid, 2.5 mg tid vs placebo	20 (5 mg) 17 (2.5 mg)	—	2	7
TERALBI	Alfuzosin vs terazosin	127	---	2	13
ALTIBIEXT	Alfuzosin 5 mg long-term efficacy	39	—	1	2
Special study					
ALFIRST	Alfuzosin 10 mg	47	---	---	2
Observational studies and post-marketing surveys					
ALFONE	Open-label, alfuzosin 10 mg	5289	13	179	[redacted]
TOSCANE	Open-label, alfuzosin 10 mg (Netherlands)	1702	2	5	[redacted]
M UROX 102	Alfuzosin 10 mg (Germany)	1751	---	1	[redacted]
L_8349	Alfuzosin 2.5, 5, 10 mg in Filopino patients (Phillipines)	1125	---	1	[redacted]
RESTHARN AWB	Residual urine volume –5 mg qd, 5 mg bid (Germany)	1694	—	1	[redacted]
German study	*Alfuzosin 5 mg, 10 mg*	*unknown*	*1*	*10*	[redacted]
Spontaneous Reporting			*2*	*62*	[redacted]

*For the Phase IV studies, 6 studies were unblinded and mentioned in the 4-month safety update, 2 studies were unblinded and reported during the 7-month safety update but some new cases of discontinuations were identified during this reference period.

3. Deaths

Table 7. By-patient listing of deaths from ongoing blinded Phase III studies

Source	Patient ID	Age (years)	Daily regimen	Time to onset	MedDRA preferred term
ALFAUR-II	27780390	81	Alfuzosin 10 mg OD or Placebo	D133 [a]	Pneumonia NOS, outcome: death (about 4 months after last intake)
ALFAUR-II	44640488	82	Alfuzosin 10 mg OD or Placebo	D37 [a]	Cardiac arrest, outcome: death (15 days after last intake)
ALFAUR-II	45020890	86	Alfuzosin 10 mg OD or Placebo	D126 [a]	Death NOS (22 days after last intake)
ALTESS	616003005	65	No Drug [b]	Not applicable	Renal cell carcinoma stage unspecified, outcome: death
ALTESS	124002030	66	Alfuzosin 10 mg OD or Placebo	D235	Colon cancer NOS, outcome: death (about 2 months after last intake)
ALTESS	616007042	70	Alfuzosin 10 mg OD or Placebo	D81/D141	Gastric cancer NOS / Death NOS

NOS, Not otherwise specified [a] during post-study period [b] during run-in period Source Table (3.2.1)1 ISS, page 20.

No deaths were reported in the completed Phase I and Phase III studies or special study. Six deaths were reported in ongoing Phase III studies in AUR (Table 7). No CRFs are presented for these studies which remain blinded. Fifteen deaths were reported in observational studies (Table 8) and 2 deaths were reported in spontaneous reporting (Table 9).

Table 8. By-patient listing of deaths from observation studies and post-marketing surveys

Case reference	Patient ID	Age (yrs)	Alfuzosin Formulation Daily regimen	Time to onset	MedDRA preferred term
ALFONE-BR020004	ALFONE- BR020004	74	ALFUZOSIN 10 mg OD	26 days	Myocardial infarction
ALFONE-CO180018	ALFONE-CO180018	63	ALFUZOSIN 10 mg OD	67 days	Cerebrovascular accident (h/o prior TIA, HTN)
ALFONE-DK039926199	ALFONE DK0399260199	78	ALFUZOSIN 10 mg OD	303 days	Dyspnea NOS, cardiac disorder NOS
ALFONE-FR04180842-2	ALFONE- FR04180842	67	ALFUZOSIN 10 mg OD	4 months	Lung cancer stage unspecified (excl metastatic tumors to lung)
ALFONE-FR10542151	ALFONE- FR10542151	74	ALFUZOSIN 10 mg OD	91 days	Renal failure acute post hip arthroplasty
ALFONE-FR10883519	ALFONE- FR10883519	68	ALFUZOSIN 10 mg OD	213 days	Cerebral haemorrhage (NIDDM, possible HTN)
ALFONE-FR11492848	ALFONE- FR11492848	76	ALFUZOSIN 10 mg OD	15 months	Cerebrovascular accident (h/o CVA, HTN)
ALFONE- FR14763069-2	ALFONE- FR14763069	78	ALFUZOSIN 10 mg OD	458 days	Myocardial infarction (h/o HTN, DM, severe aortic stenosis)
F01200200018	ALFONE- DKUNK0107	69	ALFUZOSIN 10 mg OD	109 days	Death NOS[a] (found dead at home)
F01200200134	ALFONE- RU070135	70	ALFUZOSIN 10 mg OD	181 days	Sudden death[b] (found dead at home)
F02200200006	ALFONE- FR12220372	62	ALFUZOSIN 10 mg OD	10 months	Myocardial infarction (h/o CAD, HTN)
F02200200017	ALFONE-FR01230617	72	ALFUZOSIN 10 mg	276 days	Respiratory failure, abdominal strangulated hernia, peritonitis
F02200200042	ALFONE-FR14562929	74	ALFUZOSIN 10 mg	604 days	Cardiac arrest[c] (h/o CVA, HTN, died suddenly in the street)
TOSCANE-0260593	TOSCANE-00260593	53	ALFUZOSIN 10 mg	UNK	Metastases to liver (primary colon cancer)
TOSCANE-0711237	TOSCANE-0711237	75	ALFUZOSIN 10 mg	92 days	Myocardial infarction, pneumonia NOS

Source: Table (3.2.1)2 ISS, page 21.

Reviewer's Comments:
1)The non-cancer deaths listed in Table 7 in the ongoing blinded studies are not temporally related to study drug or placebo intake.
2) Three of the deaths listed in Table 8 were "sudden":
a) 69 year-old male who was taking alfuzosin 10 mg/day for 15 weeks was found dead at home. No autopsy was performed and no additional information is available regarding the circumstances of his death. There was no history of hypertension, ischemic heart disease or heart failure. He did have 5 episodes of urinary tract infection within 6 months preceding study inclusion.
b) 70 year-old male who was taking alfuzosin 10 mg/day for 25 weeks was found dead at home. No additional information regarding his death is available. No autopsy was performed. The patient had a known history of myocardial infarction, aortic atherosclerosis, cardiac fibrillation, cardiosclerosis, and hypertension. Concomitant medications were enalapril, hydrochlorthiazide, isosorbide dinitrate and digoxin for 5 years. .
c) 74 year-old male who was taking alfuzosin 10 mg/day for 1 ½ years suddenly died in the street. Cause of death was reported as "cardiac arrest after strong emotion." The patient was not hospitalized and no autopsy was performed. Known history includes cerebrovascular accident treated with celiprolol and hypertension treated with benzapril. No information is available on his recent condition before the event except for a blood pressure of 130/80.

- *Due to the limited amount of information provided, no direct causality of drug to the events can be determined.*

Table 9. By-patient listing of deaths from spontaneous reports

Case reference	Age (years)	Alfuzosin Formulation/ Daily regimen	Date of onset/ Time to onset	MedDRA preferred term
A01200202271	65	ALFUZOSIN 10 mg 10 mg OD	15-SEP-01 1 month	Hepatic disorder aggravated, hepatic cirrhosis NOS, hepatic failure
S/GBALO01016	88	ALFUZOSIN 10 mg UNK	01-JUL-01 UNK	Myocardial ischaemia, fall, fracture NOS

Source: Table (3.2.1)3, ISS, page 21.

4. Serious adverse events:
Table 10 shows the SAEs from all sources submitted with the amendment.

Table 10. Overview of number of patients with SAEs, including deaths during the reference period: All available sources

Source	Number of patients with SAEs					
	Placebo	Alfuzosin ER 10 mg OD	Alfuzosin ER 15 mg OD	Alfuzosin SR 5 mg BID	Alfuzosin IR 2.5 mg TID	Unspecified
Completed Phase I studies	0	0	NA	NA	NA	NA
Completed Phase III study	2	2[a]	NA	NA	NA	NA
Ongoing Phase III studies	64[b]		NA	NA	NA	NA
Special study	0	0	NA	NA	NA	NA
Completed Phase IV studies	0	NA	NA	0	0	NA
Observational studies and post-marketing surveys	NA	185	NA	2	0	NA
Spontaneous reports	NA	29	NA	12	8	13

[a] One additional SAE was reported in the alfuzosin group in the 4-month safety update when the study was still blinded.
[b] Since the blind has not been broken; it is not known whether the patients received alfuzosin or placebo. Source: Table (3.2.2)1, ISS, page 22.

Completed Phase I/Phase III: No SAEs were reported in completed Phase I studies. In the completed Phase III study, 4 SAEs were observed in ALFAUR-I during the reference period (June 1, 2001 to September 30, 2002). Two of the 4 patients received alfuzosin 10 mg and reported hemorrhoids and a catheter-related infection. The two patients receiving placebo reported UTI and a catheter-related infection. Sixty-four patients in ongoing Phase III studies reported SAEs.

Ongoing Phase III:
The ongoing Phase III study remains blinded.

Completed Phase IV Studies: There were six Phase IV studies that were unblinded during the reference period (ALFRENOA, ALFPOST, ALBITAM, ALFLOW, ALFLOWEXT, AMBALF). The SAEs reported in these studies for alfuzosin 2.5 mg bid or 5 mg bid were arthrosis (3), inguinal hernia (2), angina pectoris (1), myocardial infarction (1), dizziness (1), nausea (1), renal calculus (1), gastric carcinoma (1), micturition frequency (1), genital edema (1), hematuria (1), pyelonephritis (1), penis disorder (1), UTI (1), and urinary retention (1).

Observational Studies:
In the 9,253 patient reports from observational studies and post-marketing surveys, there was one case of death NOS, one case of cardiac death and one case of sudden death. The narratives for these cases are listed in section B.3 under deaths.

Reviewer's comment: Overall for SAEs, there were no new safety concerns identified.

Spontaneous Reports:
The most common serious adverse events during *spontaneous reporting* for all formulations ( ) were syncope (71), hypotension NOS (61), malaise (20), orthostatic hypotension (23), gait abnormality (17), and dizzness (15).

Special Studies/Other:
No SAEs were reported in the special study (ALFIRST). The German study had 1 death due to pulmonary edema and 10 out of the remaining 10 events were related to syncope, orthostatic hypotension, or hypotension.

5. Treatment-emergent adverse events:

Study INT5056: After co-administration of alfuzosin and ketoconazole, there were 6 cases of headache, 2 cases of nausea, and 1 case of hot flushes. After alfuzosin alone, there was 1 case of vagal malaise and 1 case of thrombocytopenia.

The case of thrombocytopenia occurred in a 22 year-old male with history of mild pollen allergy. His baseline platelet count was 152 Giga/L (normal range 151- 399

Giga/L). One hour following his first alfuzosin dosing and 3 hours between lab draws, the platelet count dropped from 119 to 90 Giga/L. The hemoglobin dropped slightly from 8.4 to a nadir of 8.18 mmol/L (normal range approximately 8.07 to 10.8 mmol/L). The hematocrit was relatively stable at a borderline of 0.39 % (normal 0.40 to 0.53%) Further lab testing showed the platelet count rising to 126, then back to the 119 Giga/L baseline.

There was one report of elevated CK of 793 U/L.

Reviewer's Comment: The case of thrombocytopenia shows a decrease in the platelet count in a 22 year-old male subject with incomplete recovery by the end of the study. No additional information is available. No temporal relationship exists between study drug intake and the event and his pre-dose platelet count was low at 119 Giga/L.

Study PDY5105: Thirteen subjects experienced mild to moderate hypotension with alfuzosin with a dose-effect relationship (three subjects at 10 mg and 10 subjects at 40 mg). Other AEs were dizziness (n=4), headache (n=4), and malaise (n=4).
Study ALFAUR-Part I: In the alfuzosin group, 8.4% of patients reported at least 1 TEAE including hypotension (n=8), infection (n=3), constipation (n=2), dizziness (n=2), hematuria (n=2), diarrhea (n=1), dyspepsia (n=1), hemorrhoids (n=1), nausea (n=1), abdominal pain (n=1), vasovagal attack (n=1), anorexia (n=1), hypokalemia (n=1), abnormal urine (n=1), iron deficiency anemia (n=1), pyrexia (n=1), asthma (n=1), other [medical device discomfort] (n=2). This is compared with 13.1% in the placebo group.
Study ALFIRST: 19.1% of study participants experienced a TEAE. The AE's include dizziness (n=3), headache (n=3), rash (n=2), constipation (n=1), paresthesias (n=1), increase BUN (n=1), and an increase in SGOT (n=1) compared to 10.6% in placebo. No additional details are provided.

6. Syncope:
There were no syncopal episodes reported in the completed, placebo-controlled trials (two Phase I and one Phase III).

7. Discontinuations:

Table 11 shows an overview of discontinuations from all available sources. In the completed phase I studies, one study patient was discontinued due to worsening of pre-existing thrombocytopenia (Study INT5056, see reviewer's comment on page 22). In the completed Phase III study, one patient in the treatment group experienced hemorrhoids and another experienced a catheter-related infection. One additional discontinuation due to a non-SAE was reported in the alfuzosin group in the 4-month safety update when the study was still blinded but this information was not included in this report. In the ongoing Phase III studies, 30 discontinuations due to AEs were reported and include GI distress (8), dizziness

(4), infection (2), syncope due to hypotension SBP 40mm Hg (1), dementia (1), prostate cancer (1), SOB (1), exacerbation of chronic bronchitis (1), aortic stenosis (1), DKA (1), lymphoid granulomatosis (1), sinus congestion (1), lightheaded (1), AST/ALT > 3x ULN (1), CVA (1), duodenal ulcer (1), UTI (1), acute MI (1), and angina (1). These studies remain blinded.

Table 11. Overview of discontinuations due to adverse events during the reference period: All available sources

Source	Placebo	Number of discontinuations due to AEs		
		Alfuzosin ER 10 mg OD	Alfuzosin SR 5 mg BID	Comparative drug[d]
Completed Phase I studies	0	1	NA	NA
Completed Phase III study	1	3[a]	NA	NA
Ongoing Phase III studies		30[b]	NA	NA
Special study	1[c]	0	NA	NA
Completed Phase IV studies	1	0	12	9

[a] One additional discontinuation due to non-SAE was reported in the alfuzosin group in the 4-month safety update when the study was still blinded.
[b] Since the blind has not been broken, it is not known whether the patients received alfuzosin or placebo.
[c] One additional discontinuation due to AE was reported in the placebo run-in period in the 7-month safety update
[d] Terazosin 10 mg OD or tamsulosin 0.4 mg OD Source table (3.3)1 p. 41 ISS.

The 3-month safety update covering the period October 1, 2002, to December 31, 2002, was reviewed. Overall, the update did not raise any unexpected safety concerns. The findings are consistent with the original ISS.

- The update contained completed Phase III ALFUR II, ongoing blinded Phase III study, observational studies, post-marketing surveys and spontaneous reports.
- In completed Phase III , TEAEs listed were included in the original NDA assessment of 4 pivotal trials – UTI, headache, and pharygitis were most common.
- No new deaths were reported. However, there were 3 deaths that were previously blinded in AURII , 2 of the deaths were in the alfuzosin treatment group. The patients suffered from pneumonia and cardiac arrest both occurring at least 2 weeks after last study drug intake.
- Eight new deaths were reported among the ongoing Phase III, observational studies, post-marketing surveys and spontaneous reporting. The causes of death were small cell lung cancer, colon cancer, pulmonary fibrosis, bronchopneumonia, MI+CVA, cardiac death, prostate cancer and CVA. This study remains blinded.

Recent 15-day CRF submissions dated December 20, 2002, through April 4, 2003, have been reviewed. Of the 29 cases reported, there were 3 noteworthy cases. A 74 year-old male on treatment for 2 ½ months (ALFONE) experienced sudden death; autopsy was unrevealing. A 57 year-old male on treatment (L-8508 urinary tract symptom trial) for 19 days had general weakness and was diagnosed with a cardiac arrhythmia requiring pacemaker. The type of arrhythmia was not mentioned. A 78 year-old male on treatment for unknown duration (not included in clinical trials) experienced 5 episodes of syncope.

VI. Use in 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 insufficient to make meaningful conclusions concerning any racial differences.

Geriatric issues: In the clinical trials submitted with the original NDA, 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 older and younger patients. In a pharmacokinetic assessment during Phase 3 clinical studies in BPH patients, the C_{max} was 13.4 in patients over 75 years of age and 9.7 in patients between 65 and 74, compared with 10.9 in those patients less than 65 years 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 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.

Reviewer's Comment: The section on "Patients with Renal Impairment" in the label should be revised to reflect this increase in adverse events rate.

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. In the opinion of this reviewer, alfuzosin should be contraindicated in patients with all degrees of hepatic insufficiency.

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.

VII. Conclusions and Recommendations

Conclusions:
A. QT Study (PDY 5105)

Based on the available data, alfuzosin 40 mg (4-times the to-be-marketed dosage) exhibits a measurable QT prolonging effect of 7.7 msec using standard Fridericia correction. QTcN and QTcNi appear to be valid corrections and are based on population and individualized corrections. When applied to alfuzosin, the QT prolonging effect is reduced to 1.8 for alfuzosin 10 mg (for both QTcN and QTCNi). For alfuzosin 40 mg, the QT effect is 4.2 and 4.3 msec, for QTcN and QTCNi, respectively, and shows a positive dose-response. Further analysis by the clinical pharmacology reviewer included plotting slopes for uncorrected QT vs RR interval. For the population and individual correction methods, the slopes are closer to zero when compared to the Fridericia correction method. This analysis suggests, in this data set, that population and individual methods may more accurately correct the QT interval for heart rate than does the Fridericia method.

The Holter-monitoring method is a novel, rate-independent process which further minimizes the effect of alfuzosin on QT interval.

In summary, the QTc of alfuzosin 10 mg appears to increase by <5 msec compared to placebo. This level of increase in the opinion of this reviewer, constitutes a low and acceptable risk for arrhythmia.

B. Ketoconazole Study (INT 5056)

Repeated administration of ketoconazole 400 mg daily for 8 days increased the C_{max} of alfuzosin (10 mg single dose) by 2.3-fold. Repeated administration of ketoconazole 400 mg daily for 8 days increased the AUC_{last} and AUC by 3.2 and 3.0-fold, respectively. Terminal half-life ($t_{1/2}$) increased by 1.16-fold.

Recommendation:
In the opinion of this reviewer, from a clinical perspective, alfuzosin hydrochloride 10 mg extended-release (ER) tablets taken once daily should be "approved" for the indication "treatment of the signs and symptoms of benign prostatic hyperplasia". The drug's QT prolonging effects do not appear clinically significant. The risks associated with the use of this drug are acceptable and can be managed adequately with labeling.

Recommended labeling changes:

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 Qmax) should be included.
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 200 mg increases the alfuzosin Cmax 2-fold and the AUC 2.5-fold, and ketoconazole 400 mg increases the alfuzosin Cmax 2.3-fold and the AUC 3.0-fold, ketoconazole and other potent CYP3A4 inhibitors should be "contraindicated." Information concerning moderate CYP3A4 inhibitors should be added to the "Precautions" section of the label.

Addendum: A Cardiovascular and Renal Advisory Committee was held on May 29, 2003. The Advisory Committee concluded:

(1) The single dose QT study was sufficient since steady state levels were reached. Multiple dose studies are, in general, superior.

(2) The Advisory Committee could not make a recommendation as to whether C_{max} or AUC was the most important pharmacokinetic parameter affecting the QT interval.

(3) All possible correction methods should be explored because the Advisory Committee was uncertain as to which method was most accurate.

(4) Moxifloxacin is an adequate positive control.

(5) The committee voted unanimously (14-0) that the data did not "demonstrate a clinically relevant QT prolongation associated with alfuzosin".

Addendum: The label was discussed with the sponsor via teleconference on June 11th and 12th, 2003. The following major label changes were agreed upon:
(1) The effect of alfuzosin on the QT interval was included in the "Clinical Pharmacology" and "Precautions" sections. Actual values of QT prolongation (in msec) were included for uncorrected QT and the Fridericia, population-specific and subject-specific methods.
(2) Alfuzosin should be contraindicated in patients with moderate or severe hepatic insufficiency.
(3) Alfuzosin should not be co-administered with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole and ritonavir.
(4) A section on patients with mild, moderate, or severe renal insufficiency was included in the "Precautions" section.
(5) Moderate CYP3A4 inhibitors will be deleted from the "Precautions" section.
(6) The sponsor accepts an approval action with the tradename UROXATROL™.
(7) In addition, the sponsor has agreed to a Phase IV commitment to include a study to evaluate the impact on QT interval prolongation of combining a phosphodiesterase-5 inhibitor with alfuzosin at steady-state drug levels. The timeline will be as follows:

(a) Draft protocol submission within six months of the approval date
(b) Study initiation within 12 months of the approval date

(c) Submission of Clinical Study Report within 20 months of the approval date

From a medical officer perspective, there are no outstanding issues with NDA 21-287.

VIII. Appendices

Appendix A

Clinical Trial PDY 5105: "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." The study was conducted between May 6, 2002, and August 16, 2002, in France.

A.1 Objectives: The primary objective was to assess the effect on the QT interval of the ECG using Holter-monitoring following alfuzosin 10 mg, 40 mg, placebo, and moxifloxacin 400 mg. The secondary objectives were 1) to evaluate the change from baseline of QTc, corrected by Bazett (QTcB), Fridericia (QTcF), a population-specific formula (QTcN), and a subject-specific formula (QTcNi) following administration of single doses of alfuzosin 10 mg, 40 mg, and moxifloxacin 400 mg at C_{max} using the 12-lead ECG; 2) to document systemic exposure after single doses of alfuzosin 10 mg, 40 mg, and moxifloxacin 400 mg; and 3) to assess safety.

A.2 Design and Conduct Summary: The protocol was a Phase I, single-center, 4 way-crossover, randomized, double-blinded, double-dummy, placebo-controlled study. Each period consisted of a 2-day run-in placebo period (Day 1 and Day 2) followed by a single-dose day (Day 3) with a washout of 5 to 9 days between successive periods. Therapeutic (10 mg) and supratherapeutic (40 mg) doses of alfuzosin were used and the QT interval was measured with both 12-lead ECGs and Holter monitors. Moxifloxacin was used as a "positive control."

A.3 Study Population: The study population consisted of 48 healthy Caucasian men between the ages of 18 and 50 years with BMI between 18-30kg/m^2 who met the inclusion and exclusion criteria.

Table A.1 - Summary of subject characteristics [Taken from sponsor table (11.1)1]

Parameter		Results
Number of subjects		48
Age (years)	Mean (Range)	27 (19-45)
Weight (kg)	Mean (Range)	74.08 (55.9-93.6)
Height (cm)	Mean (Range)	177.6 (162-192)
BMI (kg/m^2)	Mean (Range)	23.49
Gender		Male (100%)
Race		Caucasian (100%)

A.4 Inclusion/Exclusion Criteria:

A.4.1 Inclusion Criteria: Inclusion criteria included 1) Caucasian men between the ages of 18-50 years; 2) body weight < 90 kg with a body mass index between 18-30 kg/m^2 ; 3) certified healthy by comprehensive clinical exam; 4) nonsmoker or ≤ 5 cigarettes/day; 5) Normal blood pressure and heart rate at the screening visit after 10 minutes in supine position, (90≤SBP≤140, 50≤DBP≤90); 6) Normal 12-lead ECG (120≤PR≤210 msec, QRS ≤120 msec, QTcB ≤440 msec). Incomplete right-bundle-branch block was accepted if QRS ≤120 msec. 7) Normal 24-hour Holter as follows: (a) Sinus pauses ≤2.5 seconds during the day and ≤3 seconds at night; (b) Minimum hourly HR ≥45 bpm during the day and ≥40 bpm at night; (c) Isolated premature ventricular complexes (PVCs) ≤10 per hour and <100 per 24 hours; (d) No ventricular tachycardia ≥3 PVCs; 8) Laboratory tests within the normal range or within the acceptable range. Transaminases and creatinine were to be strictly within the normal range. 9) Good intravenous access; 10) Written informed consent form signed; 11) Covered by health insurance system and in compliance with the recommendations of national law in force relating to biomedical research.

A.4.2 Exclusion Criteria: Exclusion criteria included 1) Presence or history of clinically relevant cardiovascular, pulmonary, gastrointestinal, renal, metabolic, hematological, neurological or psychiatric disease, any acute infectious disease, or signs of acute illness; 2) Frequent headaches and/or migraines, recurrent nausea, and/or vomiting (more than twice a month); 3) Symptomatic hypotension (whatever the decrease of BP) or asymptomatic postural hypotension, defined by a decrease in SBP equal to or greater than 20 mmHg after 2 minutes when changing from the supine to the standing position; 4) Subjects undergoing dental care within the last month; 5) Presence or history of drug allergy or severe allergic disease; Specifically, no allergy to alfuzosin, moxifloxacin, or fluoroquinolone antibiotics. 6) Any medication including over-the-counter medication received within 2 weeks prior to the drug administration, or within 6 times the elimination half-life, except occasional use of paracetamol; 7) Administration of enzyme-inducing drugs within the prior 2 months or enzyme-inhibiting drugs within the prior 2 weeks. 8) History or presence of drug abuse or alcohol consumption abuse >40 g per day; 9) Subjects who had undergone general anesthesia within 3 months prior to the study; 10) Excessive consumption of beverages containing xanthine bases (coffee, tea, or cola more than 6 cups or glasses per day) or smoking more than 5 cigarettes or equivalent per day; 12) Inability to abstain from smoking, alcohol or intensive muscular effort or sport competition during hospitalization; 13) Loss of greater than 400 mL of blood, or blood donation within the prior 3 months; 14) Inability to complete the required post-treatment washout period from a previous clinical trial; 15) Inability to communicate or cooperate with the Investigator because of a language problem, poor mental status, impaired cerebral status, or likely to be non-cooperative during the study; 16) Long-term dietary practices (e.g., vegetarians or with special dietary habits); 17) Positive HBsAg or Anti-HCV Ab; 18) HIV positive; 19) Positive results of screen for drugs of abuse in urine (amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, or opiates); 20) Not easily reachable in case of emergency.

Reviewer's comment: The inclusion and exclusion criteria are acceptable.

A.5 Study characteristics:

A.5.1 Randomization:
Subjects were randomized to one of four sequences in the chronological order of entry into the study with respect to a pre-established randomization list prepared by sponsor.

A.5.2 Treatment:

Table A.2 illustrates the sequence of study treatments.

Table A.2 - Sequence of study treatments [Taken from sponsor table (9.1)1]

Sequence	Period 1	Period 2	Period 3	Period 4
1	A	D	B	C
2	B	A	C	D
3	C	B	D	A
4	D	C	A	B

A = placebo; B = alfuzosin 10 mg; C = alfuzosin 40 mg; D = moxifloxacin 400 mg

At each period, subjects received 4 tablets (alfuzosin and/or placebo-alfuzosin) at 8:00 A.M. and 1 capsule (moxifloxacin or placebo-moxifloxacin) at 2:00 P.M. to match the time of peak concentration. The duration of the study was 8 weeks.

A.5.3 Monitoring information:

Informed Consent – An informed consent was signed prior to the screening period.

Vital sign assessment – Supine readings were measured after 10 minutes of rest. Upright readings were measured after 2 minutes of standing. Heart rate was measured for 1 minute immediately following supine BP. Baseline assessment during the screening visit and readings on days 1-3 of each period predose and at hours T7 and T11 on days 2, 3 were obtained in the supine and upright positions. BP readings at T24, T30 on day 4 were recorded in the supine position only.

Standard 12-lead ECG- ECGs were done at baseline on screening visit and during each period as follows:

- on day 1 at T0, T4, and T12 hours
- on day 2, at T0 (3 successive ECG at 5 minute intervals), and at T2, T4, T6, T7, T8, T9, T10, T11, T12 hours
- on day 3, at T0, T2, T4, T6, T7, T8, T9, T10, T11, T12 hours
- on day 4, at T24 and T30 hours

24-hour Holter monitoring – 24-hour Holter-monitoring was obtained at the screening visit and on days 2 and 3.

Lab monitoring -Serology for HepB, HepC, HIV, urine drug screen, alcohol breath test, urinalysis, CBC, chemistry panel (to include chem 7, metabolic labs, lfts, ck), alfuzosin and moxifloxacin levels were obtained.

A.6 Study restrictions

Activity restrictions: Subjects were hospitalized during the dosing periods and discharged during the washout periods. Subjects were required to remain supine or semi-recumbent for 12 hours on day 2 after placebo administration and in the supine position for 24 hours on day 3 after drug/placebo. Subjects were not allowed to sleep during hours 0-12 after drug administration on days 2 and 3 and were to be awake during the recording of all 12-lead ECGs. Light exercise of the legs was scheduled at T9h for 10 minutes on days 2 and 3 to allow heart rate to increase >80 bpm.

Dietary restrictions: Subjects received the "standard FDA high-fat, high-protein breakfast" followed by dinner 11-12 hours later on days 2 and 3.

Medication restrictions: Subjects were not permitted to take any medication except paracetamol within 2 weeks prior to Day 1 until end of study.

A.7 Primary and secondary endpoints

The primary endpoints were the Holter assessments of 1000 msec RR bin, the largest sample-size RR bin, and the average of all RR bins. The secondary endpoints are the corrected QT interval variables using the following formulas: $QTcB = QT/RR^{1/2}$ (Bazett), $QTcF = QT/RR^{1/3}$ (Fridericia), $QTcN = QT/RR^{B}$ (population-specific), and $QTcN_i = QT/RR^{Bi}$ (subject-specific).

A.8 Pharmacodynamic assessment

There was central reading of the Holter and 12-lead ECGs in a blinded manner. Data was processed separately for Day 2 and Day 3. The run-in placebo assessment (Day 2) was considered baseline for comparison with Day 3.

A.8.1 Holter methods

The holter device used was a 3-lead Holter digital device [redacted] Data was processed by a single expert cardiologist in a blinded manner through the use of validated software, WinAtrec®, and occurred in the following 3 steps. (Ninety-six to 98% of the recorded complexes were readable.)

Step 1. RR interval measurement

Each RR interval was measured using automatic reading with validation of QRS complex recognition. For each treatment period of each subject, the median RR was obtained.

Step 2. Classification of ECG complexes into 10msec RR groups ("bins")

Each complex was stored automatically into groups of 10 msec width according to the preceding RR interval duration.

Step 3. Averaging of complexes and measurements of QT intervals

Within each bin, complexes (n≥50) were electronically averaged to obtain 1 averaged complex. QT length was measured from the start of the QRS complex to the return to baseline of the deflection produced by ventricular repolarization (T-wave).

A.8.2 12-lead ECG methods

The ECG device used was the _____

Electrode placements on the skin were marked with ink for reproduciblity. Each ECG consisted of a 10-second recording. A standardized methodology was used on the digitized ECG waveforms with computerized-assisted, manual on-screen measurements. The tangent method or the overlapped averaged template were the two methods used for determination of HR and QT interval. The standard approach was the tangent method.

A.9 Pharmacokinetic assessment:

Blood sampling of 6 ml were taken in lithium heparinate Vacutainers at specified times. Plasma concentrations of alfuzosin and moxifloxacin and the real sampling times were used to perform a noncompartmental analysis using validated in-house software.

A.10 Withdrawals, compliance, and protocol violations:

A.10.1 Withdrawals: 45 subjects were planned for the study, with a total of 48 subjects included. Two subjects withdrew from the study after run-in placebo administration on Day 1. One subject withdrew after the run-in period placebo administration on Day 2. These 3 subjects were replaced. Therefore, the safety analysis for the run-in placebo population included 48 subjects and the active treatment analysis included 45 subjects.

A.10.2 Compliance: Compliance was verified by mouth inspection and drug plasma levels.

A.10.3 Protocol violation: There was one dosing irregularity in period 3 in which the treatment for 2 subjects were switched. Subject 033 received the treatment for subject 034 and subject 034 received the treatment for subject 033. The data from that period for the 2 subjects were not used for the pharmacodynamic and pharmacokinetic analyses.

Table A.3– Overall summary of subject disposition [Taken from sponsor table (10.1)1]

Status	SEQ 1*	SEQ 2	SEQ 3	SEQ 4	Total
Included	11	12	14	11	48
Randomized	11	12	14	11	48
Treated (Study Treatment)	11	11	12	11	45
Treated (Placebo Run-in)	0	1	2	0	3
Completed Study Treatment Period	11	11	12	11	45
Discontinued	0	1	2	0	3

*See Table A.2 for explanation of sequences

A.11 Results:

A.11.1 Pharmacodynamic Results: Holter-monitoring

The results of the Holter monitoring method are shown in the below table.

Table A.4 Holter-monitoring method: QT change comparing alfuzosin 10 mg, 40 mg and moxifloxacin [Taken from sponsor tables (11.4.1.1) 1 and (15.2.1)1]

Holter-Monitoring Endpoints	Treatment	P-Value	Mean Difference vs Placebo (msec)	Mean change (msec)	Placebo (msec)	95% CI	
						Lower Bound	Upper Bound
1000 msec RR Bin	Alfuzosin 10 mg (n = 36)	0.9694	0.1	-2.3	-2.2	-2.5	2.6
	Alfuzosin 40 mg (n = 35)	0.0278	2.9	0.8	-2.2	0.3	5.5
	Moxifloxacin 400 mg (n = 37)	0.0001	7.0	4.8	-2.2	4.4	9.6
Largest Sample-Size RR Bin	Alfuzosin 10 mg (n = 41)	0.7017	0.4	-2.0	-2.4	-1.8	2.6
	Alfuzosin 40 mg (n = 45)	0.0197	2.5	0.2	-2.4	0.4	4.7
	Moxifloxacin 400 mg (n = 43)	0.0001	6.9	4.5	-2.4	4.8	9.1
Average of All RR Bins	Alfuzosin 10 mg (n = 42)	0.9547	0.1	-2.2	-2.2	-1.9	2.0
	Alfuzosin 40 mg (n = 45)	0.0484	2.0	-0.1	-2.2	0.0	3.9
	Moxifloxacin 400 mg (n = 43)	0.0001	6.6	4.4	-2.2	4.6	8.6

Reviewer's Comment: The sponsor should clarify why the number of patients analyzed varies between treatment groups.

- Moxifloxacin at therapeutic dose (400 mg) increased the mean QT interval by 6.6 – 7.0 msec at all endpoints (p=0.0001).
- Alfuzosin 10 mg produced a mean increase in the QT interval of 0.1-0.4 msec over placebo.
- Alfuzosin 40 mg produced a mean increase in the QT of 2.0-2.9 msec.
- 95% CI width was approximately 5 msec for all comparisons.
- The sponsor believes that these results confirm that alfuzosin does not cause a meaningful increase of the QT interval.

A.11.1.2 Pharmacodynamic Results:12-lead ECG results

Data were analyzed for time C_{max} and over the T7-T11 hours window. Table A.5 below shows the change from baseline for moxifloxacin at C_{max}. Table A.6 shows the change from baseline to C_{max} for alfuzosin. The change in QTc for the time T7 through T11 exhibited the same trend with the correction factors as the data from C_{max}.

At C_{max}: Comparison of moxifloxacin vs placebo

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

Table A.5 - Change from baseline to Cmax: Moxifloxacin 400mg
[Taken from sponsor tables (11.4.1.2)1 and (15.2.2)1]

ECG Parameter	p-Value	Mean difference vs placebo	Mean change	Matched placebo	95% CI	
					Lower Bound	Upper Bound
HR (bpm)	0.0005	2.8	2.3	-0.5	1.3	4.2
QT interval (msec)	0.0045	6.9	5.5	-1.3	2.3	11.5
Bazett QTc (msec)	0.0001	15.7	13.4	-2.3	10.8	20.6
Fridericia QTc (msec)	0.0001	12.7	10.8	-1.9	8.6	16.8
QTcN (msec)	0.0001	11.0	9.4	-1.6	7.0	15.0
QTcNi (msec)	0.0001	11.1	9.4	-1.7	7.2	15.0

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

- QTcF showed a mean change of 4.9 msec for alfuzosin 10 mg and 7.7 msec for alfuzosin 40 mg over placebo.
- QTcB showed a mean change of 10.2 msec for alfuzosin 10 mg and 13.9 msec for alfuzosin 40 mg over 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). The sponsor believes that the HR drove the QTcB and QTcF changes.
- QTcN and QtcNi values increased 1.8 msec for alfuzosin 10 mg over placebo (p=0.2).
- QTcN and QtcNi values increased approximately 4 msec for alfuzosin 40 mg over placebo (p=0.08).

Table A.6 12-lead ECG: Change from baseline to Cmax: Alfuzosin 10 mg and 40 mg versus placebo
[Taken from sponsor tables (11.4.1.2)2 and (15.2.2)1]

ECG Parameters	Treatment	P-Value	Mean Difference vs Placebo	Mean change	Matched placebo	95% CI	
						Lower Bound	Upper Bound
HR (bpm)	Alfuzosin 10 mg	0.0013	5.2	5.7	0.6	2.2	8.3
	Alfuzosin 40 mg	0.0001	5.8	6.9	1.0	3.2	8.4
QT interval (msec)	Alfuzosin 10 mg	0.0115	-5.8	-13.9	-8.4	-10.2	-1.4
	Alfuzosin 40 mg	0.0590	-4.2	-10.7	-6.5	-8.5	0.2
Bazett QTc (msec)	Alfuzosin 10 mg	0.0023	10.2	4.7	-5.3	3.9	16.6
	Alfuzosin 40 mg	0.0012	13.9	11.9	-2.0	5.8	22.0
Fridericia QTc (msec)	Alfuzosin 10 mg	0.0171	4.9	-1.5	-6.3	0.9	8.8
	Alfuzosin 40 mg	0.0102	7.7	4.3	-3.4	1.9	13.5
QTcN (msec)	Alfuzosin 10 mg	0.2709	1.8	-5.0	-6.8	-1.4	5.0
	Alfuzosin 40 mg	0.0819	4.2	-0.1	-4.3	-0.6	9.0
QTcNi (msec)	Alfuzosin 10 mg	0.2456	1.8	-4.7	-6.6	-1.3	5.0
	Alfuzosin 40 mg	0.0804	4.3	0.1	-4.2	-0.5	9.2

A.11.1.3 **Sponsor Conclusions:** Pharmacodynamic

- An increase in QTc based on Bazett's and Fridericia's formulae is found for moxifloxacin comparable to values reported in the literature, thus demonstrating the sensitivity of the trial.
- A QT increase of about 7 msec by moxifloxacin, at the therapeutic dose, is found using the Holter-monitoring method. This demonstrates that the Holter-monitoring method is sensitive and can detect moderate drug-induced increases of QT interval.
- Using the Holter method, the therapeutic dose of alfuzosin (10 mg) produces no significant change in the QT interval. At 4 times the therapeutic dose (40 mg), alfuzosin produces QT changes of no more than 2.9 msec.

A.11.2 Pharmacokinetic results:

Table A.7 shows the pharmacokinetic parameters for the study drugs.

Table A.7 Plasma pharmacokinetic parameters after a single oral administration of alfuzosin 10 mg, alfuzosin 40 mg and moxifloxacin 400 mg. [Taken from sponsor table (11.5.1.2)1]

	Pharmacokinetic Parameters Mean (SD) – CV%				
Drug/Dose	C_{max} (ng/mL)	t_{max} [a] (h)	AUC_{last} (ng.h/mL)	$t_{1/2z}$ (h)	AUC (ng.h/mL)
Alfuzosin 10 mg N = 44	11.2 (4.5) - 40	7.0 (2.0 – 16.0)	176 (71) - 40	11.7 [b] (4.4) - 38	193 [c] (71) - 37
Alfuzosin 40 mg N = 45	48.6 (21.0) - 43	9.0 (2.0 – 16.0)	747 (277) - 37	12.3 [d] (6.8) - 55	898 [e] (375) - 42
Moxifloxacin 400 mg N = 44	3724 (849) - 23	2.0 (0.97 – 5.0)	38267 (6105) - 16	11.6 (1.5) – 13	45789 [f] (7708) - 17

[a] Median (range)
[b] n = 42 Minimum of 3 points used for the estimation of λ Z
[c] n = 23 Other values not calculable or with extrapolated portion of AUC >30%
[d] n = 43 Minimum of 3 points used for the estimation of λ Z
[e] n = 29 Other values not calculable or with extrapolated portion of AUC >30%
[f] n = 15 Other values not calculable or with extrapolated portion of AUC >30%

A.11.3 Sponsor conclusions:

- Mean C_{max} and AUC of alfuzosin increased with dose (4.3- and 4.6-times, respectively). The data were consistent with dose proportionality and linear pharmacokinetics.
- Mean C_{max} , AUCs, $t_{½z}$ and median T_{max} of moxifloxacin observed in this study after a single oral administration of 400 mg per day were in agreement with those described in the literature.
- Median T_{max} was 2.0 for moxifloxacin, 7.0 and 9.0 hours for alfuzosin 10 mg and 40 mg, respectively. This validated the T7 through T11h window prospectively chosen for the Holter-monitoring analysis.
- No relationship was found between QT changes and alfuzosin plasma concentration.

A.12 Safety:

A.12.1 Extent of exposure:
Treatment with active study drug per patient: 3 days (2 days of alfuzosin and 1 day of moxifloxacin). Due to the reported error between 2 patients, one patient received 2 doses of alfuzosin 10 mg in consecutive periods and one patient received 2 doses of moxifloxacin 400 mg in consecutive periods.

A.12.2 Serious adverse events:
No deaths or SAEs due to AE were reported during the study.

A.12.3 Treatment-emergent adverse events (TEAEs)
The TEAEs are summarized in the table below.

Table A.8 Summary of number of subjects with at least 1 treatment emergent adverse events- [Taken from sponsor table (12.2.2)1]

TEAE	Placebo n= 45	Alfuzosin 10 mg n=44	Alfuzosin 40 mg n=45	Moxifloxacin 400mg n=44
Total (% of patients)	2.2%	9.1%	28.9%	4.5%
Hypotension, postural		3	10	
Dizziness	1		4	
Headache		1	3	
Malaise			1	
Diarrhea				1
Rash				1
Total subjects	*1*	*4*	*13*	*2*

Reviewer's Comment: In the above sponsor table (12.2.2)1), the tabulation of the total subjects for the 40 mg dose of alfuzosin is incorrect. The sum should be 18 not 13 out of 45. The total percentage should be 40% versus the reported 28.9%.

Mild to moderate postural hypotension was reported with alfuzosin with an apparent dose-effect relationship. The sponsor believed that this was due to alpha blockade with exacerbation by the prolonged supine position. The one episode of malaise occurred after alfuzosin 40 mg and during blood sampling and was of moderate intensity.

A.12.4 Premature discontinuation due to adverse event:
There was no discontinuation due to AE during the study.

A.12.5 Lab abnormalities:
One subject had an abnormal total bilirubin, already present at baseline. Four patients had a decrease in hemoglobin by 2 grams/dl from baseline.

A.12.6 Special safety issues- QT interval effects:

12-Lead ECG

- Ten subjects had a total of 12 PCSAs (potential clinical significant abnormality) of QTcB or delta QTcB. The sponsor defines "potentially clinically significant

abnormalities" as: 1) for QTC absolute values: "prolonged" is > 450 msec in men and > 470 msec in women and "borderline" is 431-450 msec in men and 451-470 msec in women and 2) for increase in QTc versus baseline for both men and women: "prolonged" is > 60 msec and "borderline" is 30-60 msec. In all cases, large concomitant increases in HR were observed. These abnormalities were not found when using other formulae (QTcF, QTcN, and QTcNi) to calculate the QT in case of HR >60 bpm.

- Three subjects had QTcB over 450 msec after 40 mg alfuzosin administration.
- Three subjects had delta QTcB over 60 msec after 40 mg administration.
- One subject had QTcB over 450 msec and delta QTcB over 60 msec after 10 mg alfuzosin administration.
- Three subjects had QTcB over 450 msec (1 after moxifloxacin 400 mg administration and 2 after placebo administration).

Holter monitoring

- The safety monitoring by the 24-hour Holter-monitoring method did not reveal changes in supraventricular or ventricular rhythm or abnormal beat frequency during treatment with alfuzosin or moxifloxacin. Specifically, there were no changes in the frequency of PVC's, and no sinus pauses occurred when the placebo run-in day (Day 2) and the treatment day (Day 3) were compared.
- Four brief episodes of nonsustained ventricular tachycardia out of 174 placebo run-in periods were recorded, and no episode of ventricular tachycardia during the alfuzosin or moxifloxacin treatment days was found.

A.13 Reviewer's assessment of Trial PDY5105:

Alfuzosin exhibits a measurable QT prolonging effect of 4.9 msec (for the alfuzosin 10 mg dose) and 7.7 msec (for the alfuzosin 40 mg dose) when corrected with the standard Fridericia formula. The mean QTcN increase over placebo is 1.8 msec for alfuzosin 10 mg and 1.8 msec for alfuzosin 40 mg and the mean QTcNi increase over placebo is 4.2 msec for alfuzosin 10 mg and 4.3 msec for alfuzosin 40 mg. There does appear to be a dose-related increase in QTc across all methods. The FDA "Preliminary Concept Paper on The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" states that "it is difficult to determine whether there is an effect on the mean QT/QTc interval that is so small as to be inconsequential, although drugs whose maximum effect is less than 5 msec at high doses and during co-administration of saturating doses of metabolic inhibitors, have not so far been associated with Torsade de Pointes. Whether this signifies that no increased risk exists for these compounds or simply that the increased risk has been too small to detect is not clear." This would be applicable to results obtained using the population and individual methods, as well as Fridericia's method when isolating the 10 mg alfuzosin dose. Based on the above, I believe that the torsadogenic risk is low to very low.

Appendix B

Clinical Trial INT5056: "Assessment of pharmacokinetic drug interaction between alfuzosin 10 mg qd formulation and ketoconazole 400 mg per day in healthy male subjects." The study was conducted between December 28, 2001, and February 9, 2002, in a single center in France. The principal investigator was Donazzolo Yves.

B.1 Objectives: The primary objectives were 1) to assess the effect of repeated oral doses of 400 mg ketoconazole on the pharmacokinetic profile of a single oral 10 mg dose of alfuzosin (extended-release); and 2) to assess the clinical and biological safety and tolerability of 10 mg alfuzosin qd formulation given alone and co-administered with 400 mg of ketoconazole after repeated daily doses of ketoconazole.

B.2 Design and Conduct Summary: This was a Phase I, single-center, open-labeled, non-randomized, two-period study in 12 healthy male subjects. Period 1 consisted of a single dose day of alfuzosin 10 mg followed by a washout period. Period 2 consisted of 8 days of daily administration of ketoconazole 400 mg. On day 7, a single dose of alfuzosin 10mg was co-administered with the ketoconazole. Subjects were confined during period 1 (days -1 to 2) and period 2 (days 1-9).

B.3 Study Population: The subjects were healthy Caucasian males between the ages of 18 and 40 years with BMI between 18-25.

Table B.1 - Summary of subject characteristics [Taken from sponsor table (11.1)1]

Parameter		Results
Number of subjects		13
Age (years)	Mean (Range)	28.2 (19-39)
Weight (kg)	Mean (Range)	72.55 (61.6-86.0)
Height (cm)	Mean (Range)	176.8 (169-188)
BMI (kg/m^2)	Mean (Range)	23.2
Gender		Male (100%)
Race		Caucasian (100%)

B.4 Inclusion/Exclusion Criteria:

B.4.1 Inclusion Criteria: The inclusion criteria included a) healthy Caucasian males ages 18 to 40 years. b) BMI between 18 and 25 and body weight between 50 and 90 kg. c) Medically normal per history and complete physical; d) Laboratory tests (hematology, chemistry, urine) were within normal laboratory ranges or without clinically relevant abnormalities. e) Normal blood pressure ($90 \leq SBP \leq 140$ mmHg, $50 \leq DBP \leq 90$ mmHg) and heart rate ($45 \leq HR \leq 90$ bpm) after 20 minutes in the supine position. f) Normal 12-lead ECG ($PR \leq 200$ ms, $QRS \leq 110$ ms, $QTc \leq 430$ ms). Incomplete right bundle branch block was accepted. g) Written informed consent given. h) Subject had to be covered by the National Health Care System in compliance with the recommendations of French Law relating to biomedical research.

B.4.2 Exclusion Criteria: The exclusion criteria include a) History or presence of any clinically significant cardiovascular, respiratory, gastrointestinal, hepatic, renal, metabolic, hematologic, neurologic or psychiatric disease. b) Known history of epilepsy, vagal syncope, tachycardia or tremor. c) Symptomatic hypotension whatever the decrease in blood pressure or asymptomatic hypotension defined by a decrease in SBP or DBP greater than 20 mmHg within 5 minutes when changing from the supine to standing position. d) Acute illness within the 2 weeks before the study medication administration. e) Presence or history of any allergic or unusual reaction to drugs in particular hypersensitivity to ketoconazole. f) History of drug dependence. g) History or presence of alcohol abuse. h) Current use of medication. i) Any medication that could interfere with study medication absorption, distribution, metabolism or excretion or could lead to induction or inhibition of microsomal enzymes within 3 months of the screening day. j) Smoking more than 5 cigarettes/day and not able to stop smoking during the inpatient study periods. k) Excessive consumption of beverages containing xanthine (5 cups a-day). l) Positive urine drug screen. m) Positive result for HIV serology. n) Positive result from the hepatitis serology indicating acute or chronic hepatitis B or hepatitis C. o) Any reasonable suspicion that the subject could be unable to meet study requirements for reasons of incompetence or non-compliance. p) Participation in investigational trials or blood donation within 3 months before the screening day. q) Subject who is within the exclusion period of a previous trial in the French National Register.

B.5 Study characteristics:

B.5.1 Treatment

This study consisted of 2 sequential treatment periods separated by a wash-out period.

- Period 1: on Day 1, subjects received a single oral dose of alfuzosin qd formulation (10 mg)
- Period 2: from Day 1 to Day 6 and on Day 8, subjects received a single oral dose of ketoconazole (2x200 mg). On Day 7, subjects received a single oral dose of alfuzosin qd formulation (10 mg) co-administered with a single oral dose of ketoconazole (2x200 mg).

Alfuzosin and ketoconazole were both administered at approximately 8:00 a.m., 5 minutes after the end of a high fat breakfast with 200 ml of non-carbonated water.

B.5.2 Monitoring

Monitoring was performed during the study and included physical examinations and vital signs. Vital signs were recorded during Period 1 (on Day –1 and on Day 1 [1 hour prior to dosing and 8 hours post-dose]), during Period 2 (on Day 1, on Day 6 and on Day 7 [1 hour prior to dosing, and 8 hours post-dose]) and at end-of-study visit. 12-lead ECGs were performed at baseline and twice on alfuzosin dosing days (Period 1: Day 1 and Period 2: Day 7). Laboratory data were collected through hematology and biochemistry measurements. Urinalyses were performed. Patients were screened for hepatitis and HIV.

B.6 Pharmacokinetic assessment:

Alfuzosin plasma concentrations were obtained before dosing and at times 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 48, 72 and 96 hours after alfuzosin dosing on Day 1 of Period 1 and Day 7 of Period 2.

Ketoconazole plasma concentrations were obtained during period 2 on a) Day 1, before dosing; b) Day 7 before dosing and at times 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, and 24 hours after ketoconazole administration; and c) Day 8, 24 hours after ketoconazole administration.

The following pharmacokinetic parameters were determined:

C_{max}: maximum plasma concentration observed
t_{max}: first time to reach C_{max}
t_{lag} :interval between administration time and the sampling time preceding the first concentration above the limit of quantification,
AUC_{last}: area under the plasma concentration versus time curve calculated using the trapeziodal method from time zero to t_{last},
$t_{1/2z}$: terminal half-life
AUC: area under the plasma concentration versus time curve extrapolated to infinity
AUC_{0-24h}: area under the plasma concentration versus time calculated using the trapezoidal method from zero to the real relative time 24 hours

B.7 Withdrawals, compliance and protocol violations:

B.7.1 Withdrawals: One subject withdrew at the end of the first period due to thrombocytopenia (90 Giga/L). Blood testing was performed 1 hour after single administration of alfuzosin on Day 1 of Period 1. Subject had pre-existing thrombocytopenia with baseline of 119 Giga/L. Follow-up platelet counts ranged from 126 to 116 Giga/L with a final reading of 119 Giga/L.

Reviewer's comment: Information provided with the study report shows that the patient with thrombocytopenia had a screening platelet count (Jan. 7, 2002) of 152 Giga/L which is in normal range. Laboratory data taken prior to the first dose of drug (Jan. 11, 2002) showed a drop to 119 Giga/L. A confirmatory level done three hours later and one hour after study drug administration showed a platelet level of 90 Giga/L. The study drug did not have a temporal relationship to the event.

B.7.2 Compliance: Compliance was measured via direct supervision of drug administration and blood sampling for pharmacokinetic evaluation.

B.7.3 Protocol violations: Nine subjects who were included had at least 1 inclusion criterion that was not fulfilled.

B.8 Results:

Table B.2 - Mean values of alfuzosin pharmacokinetic parameters obtained after alfuzosin 10 mg and alfuzosin 10 mg + ketoconazole
[Taken from sponsor table (11.4.1.2)1]

Parameter	Alfuzosin alone		Alfuzosin + ketoconazole		Ratio [90% CI or p value]
	Median	[min-max]	Median	[min-max]	
t_{lag} (h)	0.5		0.0		-
t_{max} (h)	8.0		10.0		p = 0.33
t_{last} (h)	24.0		48.0		-
$t_{1/2z}$ (h)	7.6[b]		8.8		p = 0.02[b]
C_{max} (ng/ml)	13.5		28.8		2.31 [1.90 – 2.80]
AUC_{last} (ng.h/mL)	175.2		517.9		3.18 [2.68 – 3.76]
AUC (ng.h/mL)	189.9[b]		543.3		2.97 [2.54 – 3.48][b]

Sponsor conclusions:

(1) Repeated administration of ketoconazole 400 mg daily x 8 days increased the C_{max} of alfuzosin by 2.3 fold.
(2) Repeated administration of ketoconazole 400 mg daily x 8 days increased the AUC_{last} and AUC of alfuzosin by 3.2 and 3.0, respectively.
(3) t_{max} was statistically unchanged.
(4) $t_{1/2z}$ for alfuzosin was increased by 1.16-fold.

B.9 Safety:

B.9.1 Extent of Exposure

Thirteen subjects received a single dose of alfuzosin 10 mg on Day 1 of Period 1. Twelve subjects received a single administration of ketoconazole (400 mg) from Day 1 to Day 8 of Period 2 including on Day 7 of Period 2 co-administration of a single dose of alfuzosin 10 mg.

B.9.2 Adverse events

There were no deaths or serious adverse events during the study.

After co-administration of alfuzosin and ketoconazole, there were 6 cases of headache, 2 cases of nausea, and 1 case of hot flushes. After alfuzosin alone, there was 1 case of vagal malaise and 1 case of thrombocytopenia (90 Giga/L from baseline of 119 Giga/L).

There was one reported case of elevated creatine kinase of 793 U/L at end of study.

There were no episodes of orthostatic hypotension.

There were no cases of QTc>450 or change from baseline in QTc>60msec.

B.10 Reviewer's assessment of Trial INT 5056:

The co-administration of alfuzosin 10 mg ER on a baseline of ketoconazole 400 mg/ day increases the C_{max} and AUC of alfuzosin 10 mg by 2.3 and 3.2-fold, respectively.

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