CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-287
Drug:	Alfuzosin HCl ER (10 mg) tablets
Sponsor:	Sanofi Synthelabo
Date of Submission:	12/12/02, 05/22/03
Type of Submission:	Response to approvable letter
Reviewer:	Venkateswar R. Jarugula, Ph.D.

I. EXECUTIVE SUMMARY

NDA 21287 for alfuzosin extended release tablets was issued an approvable letter on October 5, 2001. The approvable letter stated that the effect of maximum recommended doses of CYP3A4 inhibitor (ketoconazole) on alfuzosin needs to be evaluated. In addition, the letter also stated that the effect of alfuzosin on cardiac repolarization needs to be further evaluated.

In response, sponsor provided two clinical pharmacology studies in the current submission. These were a drug interaction study with 400 mg of ketoconazole, which is the maximum recommended dose and a QT evaluation study with alfuzosin 10 mg and 40 mg doses and moxifloxacin 400 mg as an active control (a drug that is known to cause QT prolongation).

The issues regarding the effect of alfuzosin on cardiac repolarization and the clinical significance were discussed by Cardiorenal Drugs Advisory committee in a public meeting held on May 29, 2003. The following are the major points expressed by the AC members:

- At present there is no one single method of QT correction that is considered most appropriate to evaluate the drug effects.
- Holter bin method has advantages since it circumvents formal corrections for heart rate. However, this method needs further validation.
- In the absence of definitive/quantitative link between the QT interval and the clinical outcomes, it is unclear how much QT increase is a clinical concern.
- The committee concluded that the effect of alfuzosin on QT interval is not clinically significant because the QT increase with alfuzosin was less than that for moxifloxacin (active control), and there is extensive post marketing experience for alfuzosin from other countries with no events of torsade de pointe.
- The committee recommended that the results of QT evaluation study be reported appropriately in the labeling.

RECOMMENDATION

The resubmission of NDA 21287 for alfuzosin extended release tablets is acceptable from Clinical Pharmacology and Biopharmaceutics perspective.

Summary of Clinical Pharmacology and Biopharmaceutics findings:

Coadministration of potent CYP3A4 inhibitor, ketoconazole (400 mg repeated dosing) increased the Cmax and AUC of alfuzosin by 2.3 and 3.2 fold, respectively. Due to the concerns regarding increased incidence of adverse events and increase in QT interval at higher doses, the labeling should contraindicate coadministration of alfuzosin ER with potent CYP3A4 inhibitors such as antifungal agents (e.g. ketoconazole) and protease inhibitors (e.g. ritonavir).

Based on the results of the two drug interaction studies with ketoconazole, there was about 110% increase in AUC of alfuzosin with 200 mg ketoconazole dose and 200% increase in AUC with 400 mg ketoconazole dose indicating the dose dependent inhibitory effects of ketoconazole.

Mean increases in corrected QT (QTc) with alfuzosin and moxifloxacin, active control from Study PDY5105 are listed in the following table.

Mean QT/QTc change in msec (95% CI) from baseline at Tmax (relative to placebo)

Drug/ Dose	Uncorrected QT	Corrected QT (QTc)				Holter Monitor
		Bazett method	Fridericia method	Population method	Individual method	
Alfuzosin 10 mg	-5.8 (-10.2,-1.4)	10.2 (3.9,16.6)	4.9 (0.9, 8.8)	1.8 (-1.4, 5.0)	1.8 (-1.3, 5.0)	0.4 (-1.8, 2.6)
Alfuzosin 40 mg	-4.2 (-8.5.0.2)	13.9 (5.8, 22.0)	7.7 (1.9, 13.5)	4.2 (-0.6, 9.0)	4.3 (-0.5, 9.2)	2.5 (0.4, 4.7)
Moxifloxacin 400 mg	6.9 (2.3,11.5)	15.7 (10.8,20.6)	12.7 (8.6,16.8)	11.0 (7.0,15.0)	11.1 (7.2,15.0)	6.9 (4.8,9.1)

The magnitude of QT increase observed with alfuzosin depended on the correction method used. Mean QTc increase with Bazett was highest and the mean increase with Fridericia was higher than with individual and population methods and also with Holter monitor method. With all methods, the effect on QT was lower with alfuzosin than with moxifloxacin. According to the Cardiorenal Advisory Committee meeting dated 5/29/03, there is no one single method of QT correction that is considered most appropriate to evaluate the drug effects.

There is dose-related increase in QTc with all methods indicating that the effect on QT is most likely attributable to the drug. QT prolongation appears to increase with increase in plasma concentrations of alfuzosin for certain individuals, again raising the question whether there is risk related to high concentrations of the drug.

The following labeling recommendations regarding Clinical Pharmacology section were agreed upon during the labeling negotiations with the sponsor:

Steady state accumulation ratio was changed from 1.6 (reported in the original NDA) to a range of 1.2 to 1.6 based on the pooled pharmacokinetic data on 10 mg dose included in the submission dated 5/22/03.

Uroxatrol should not be coadministered with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritnovair) because the exposure to alfuzosin is significantly increased.

Uroxatrol should be contraindicated in patients with moderate to severe hepatic impairment since the exposure was increased three to four fold compared to normal subjects. Since no pharmacokinetic study was conducted in patients with mild hepatic impairment, caution should be exercised when Uroxatrol is administered in these patients.

There was about 50% increase in systemic exposure to alfuzosin following administration of Uroxatrol in patients with mild, moderate or severe renal impairment. However, subgroup analysis of phase III studies showed that the safety profile including vasodilatory adverse events in mild, moderate renal insufficiency patients is similar to that in patients with patients with normal renal function. Therefore, a precaution in these patients is not necessary. Since the number of patients with severe renal impairment in Phase III studies is limited, an appropriate caution is proposed.

The results of the QT evaluation study (PDY5105) should be reported in the Clinical Pharmacology section of the labeling and a precaution regarding the coadministration of Uroxatrol and the other drugs known to prolong QT interval and in patients with congenital long QT syndrome should be included in the label.

Question Based Review

What is the maximum inhibitory effect of ketoconazloe (at 400 mg daily dose) on the pharmacokinetics of alfuzosin?

Drug interaction with ketoconazole

A drug interaction study with alfuzosin 10 mg and ketoconazole 200 mg per day was submitted with the original NDA (please refer to the Review of original NDA). In the current submission, to ensure maximum inhibition with ketoconazole, sponsor provided another drug interaction study (INT5056) with ketoconazole 400 mg per day.
This was a single-center, open-label, non-randomized, two-period crossover study in 12 healthy male Caucasian subjects (age: 19 to 39 years) with following treatments:
Period 1: On Day 1, a single dose of alfuzosin ER tablets 10 mg.
Period 2: from Day 1 Day 8, 400 mg of ketoconazole per day. On Day 7 a single dose of alfuzosin ER tablet (10 mg) coadministered with ketoconazole.

Both alfuzosin (1x10 mg ER tablet) and ketoconazole (2x200 mg tablets) were administered with 200 mg non-carbonated water around 8 A.M., 5 minutes after the end of a high fat breakfast. On Day 1 of period 1 and on Day 7 of Period 2, no meal was given to subjects until dinner.

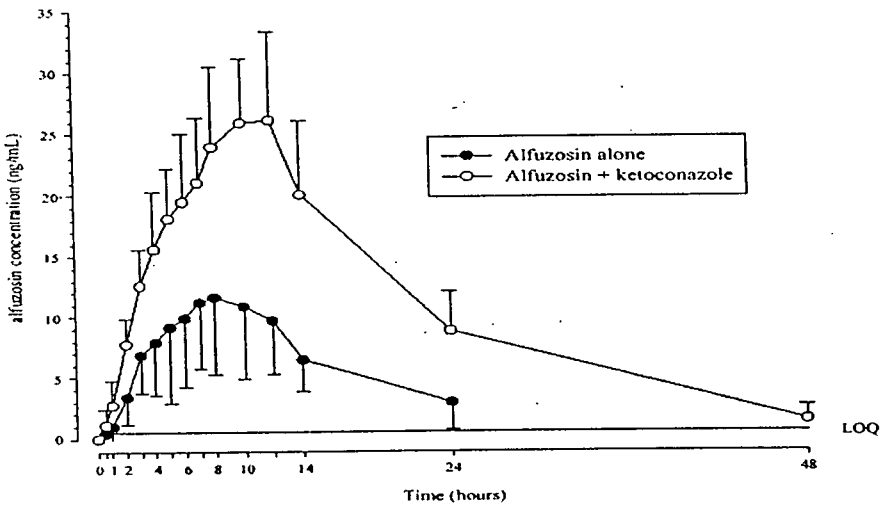

Figure 1. Mean (SD) alfuzosin plasma concentrations following a single administration of alfuzosin 10 mg ER alone or coadministered on Day 7 with ketoconazole 400 mg per day (n=12)

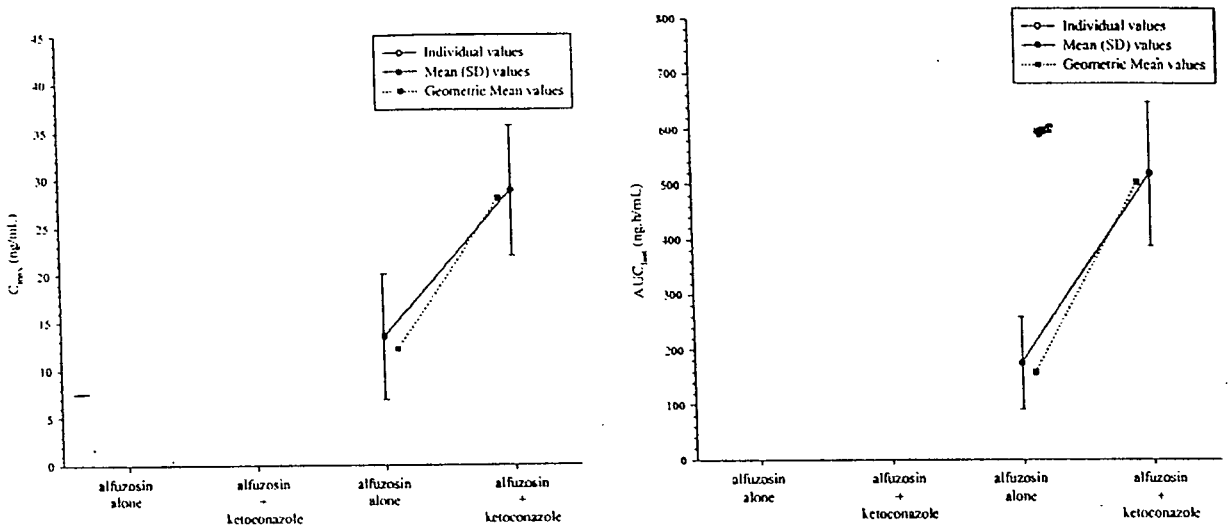

Figure 2. Individual, mean (SD) pharmacokinetic parameters following single dose administration of alfuzosin with and without coadministration of ketoconazole 400 mg.

Table 1. Mean (SD) pharmacokinetic parameters of alfuzosin following single dose administration of alfuzosin 10 mg with or with coadministration of 400 mg ketoconazole (n = 12).

PK Parameter	Alfuzosin alone	Alfuzosin +Ketoconazole	Ratio [90% CI] or p value
C_{max} (ng/ml)	13.5 (6.6)	28.8 (6.8)	2.31 [1.90 – 2.80]
AUC_{last} (ng.h/ml)	175.2 (83.3)	517.9 (130.1)	3.18 [2.68 – 3.76]
AUC (ng.h/ml)	189.9[b] (85.6)	543.3 (138.6)	2.97 [2.54 – 3.48][b]
T_{max} (h)[a]	8.0	10.0	P=0.33
$t_{1/2}$ (h)	7.6[b] (3.0)	8.8 (2.7)	P=0.02[b]

[a] : median values (min – max); [b] : n = 11

The study results showed that repeated administration of ketoconazole 400 mg daily for 8 days increased the C_{max}, AUC_{last} and AUC of alfuzosin by 2.3, 3.2 and 3.0 fold, respectively. The individual PK parameters also show the similar degree (same trend) of interaction for all subjects in the study.

A previous drug interaction study (INT4285) with 7 days of repeated daily dosing of 200 mg ketoconazole showed that C_{max}, AUC_{last} and AUC of alfuzosin were increased by 2.1, 2.5 and 2.1 fold, respectively.

When the results of these two studies are compared, there was about 110% increase in AUC of alfuzosin with 200 mg ketoconazole dose and 200% increase in AUC with 400 mg ketoconazole dose indicating the dose dependent inhibitory effects of ketoconazole.

Adverse events and Safety evaluation:

The number of subjects who experience at least 1 treatment emergent adverse event (TEAE) was higher after co-administration of ketoconazole and alfuzosin on Day 7 of period 2 (n=6) than after alfuzosin alone on Day 1 of Period 1 (n=2). The most frequent TEAE observed was headache. There were no deaths or serious AEs during the study. One discontinuation due to thrombocytopenea was reported 1 hour after single dose administration of alfuzosin alone and this was reported as preexisting condition not related to the study treatment.

Vital signs (heart rate, systolic and diastolic blood pressure) and ECG were measured 1 h before dosing and 8 h after dosing of alfuzosin on Day 1 period and Day 7 of Period 2. It should be noted that the ECG were automatically measured.

No significant difference was noted between alfuzosin alone and alfuzosin + ketoconazole arms for vital signs parameters. Notably, there was one subject each in both arms with supine systolic blood pressure ≥140 mmHg and with an increase versus baseline ≥20 mmHg.

There was one subject with corrected QT (QTc) increase versus baseline of 33 msec with an associated heart rate increase of 13 bpm after alfuzosin alone administration and two subjects with delta QTc (increase versus baseline) of 40 msec and 50 msec following the combination of alfuzosin + ketoconazole along. The heart rate increases in these subjects were 13 bpm and 17 bpm respectively.

It should be noted the sample size and the measurement of times of the safety parameters in study were not adequate to determine the effects on the safety parameters such as vital signs and ECG.

Because of the significant pharmacokinetic drug interaction noted in the two studies mentioned above, the labeling should recommend contraindication for coadministration alfuzosin with potent CY3A4 inhibitors such as antifungal drugs (e.g. ketoconazole) and protease inhibitors (e.g. ritonavir).

How does alfuzosin affect the cardiac repolarization at the recommended and supratherapeutic dose?

Effect of alfuzosin on QT interval:

In response to the FDA's approvable letter, sponsor submitted a QT evaluation study (PDY5105) in the current submission. This study is similar in design to the previously submitted study in the original NDA. The major difference is that this study included moxifloxacin as a positive control.
Briefly study PDY5105 was a randomized, double-blind, placebo-controlled, 4-way crossover single dose study with the following treatments:

- Placebo
- Alfuzosin 10 mg (which the recommended therapeutic dose)
- Alfuzosin 40 mg (which covers the exposure expected with maximum CYP3A inhibition with ketoconazole)
- Moxifloxacin (serving as active control)

45 healthy white male subjects of age 19 to 45 years completed the study. QT interval was measured by two methods: 12-lead ECG and Holter monitor.

For 12 Lead-ECG method, baseline ECG was defined as the mean of 3 measurement at time zero of each treatment. Baseline ECGs for Holter monitor method were obtained from 7hr through 11 hr following placebo administration on Day 2 run-in period. QT interval and blood samples for measurement of alfuzosin concentrations were measured for over 30 hours following dosing.

For 12-lead ECG, Change in QT/QTc from baseline at the time of individual peak concentration (Tmax) and also at 7 through 11h window corresponding to the range of expected Tmax.

For Holter Monitor method, the change in QT interval between treatment and baseline was analyzed for each subject during 7 through 11 hrs following dosing. For this analysis, QT intervals classified in the following RR bins were used:

- 1000 msec RR bin corresponding to heart rate of 60 beats per minute
- Largest sample size RR bin
- Average of all RR bins

The QT interval is inversely related to heart rate. To determine the effect of drug on intrinsic duration of QT interval independent of associated heart rate changes, various methods of QT interval corrections are generally used. The sponsor has used the following methods to correct the measured QT interval from 12-Lead ECG recordings:

1. Bazett's correction ($QTcB = QT/RR^{1/2}$)
2. Fridericia's correction ($QTcF = QT/RR^{1/3}$)
3. Population-specific correction ($QTcN = QT/RR^{B}$)
4. Subject-specific correction ($QTcNi = QT/RR^{Bi}$)

Bazett and Fridericia methods of correction are commonly used methods.
For the population-specific correction method, the relationship between QT and RR-interval was assessed by fitting the Day 3 placebo on-treatment period data (12 recordings per subject) to the log-transformed power model: Log QT = Log A + B Log RR + error.

For the subject-specific correction method, the relationship between QT and RR-interval was assessed by fitting the Day 3 placebo on-treatment period data and Day 2 run-in placebo data of each period (55 recordings per subject) to the log-transformed power model: Log QT = Log Ai + B Log RR + error.

The resulting estimated B value (the exponent in the correction formula) for the population- specific method was 0.23767 and the mean estimated Bi value for individual-specific method was 0.24060 (range: 0.19939 – 0.28717) as opposed to a value of 0.33 for the Fridericia correction method.

The purpose of the QT correction methods is to make the measured QT intervals independent of heart rate (RR intervals). Ideally after applying the correction method, the slope of QTc versus RR interval should be horizontal (zero slope). The relationship between uncorrected QT and RR intervals and corrected QT and RR intervals using the various correction methodologies for all subjects on placebo is shown in Figure's 3 and 4, respectively.

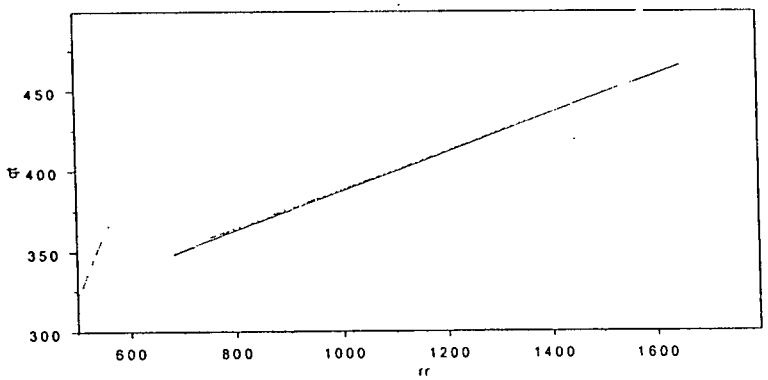

Figure 3. Uncorrected QT for all subjects on placebo versus RR interval

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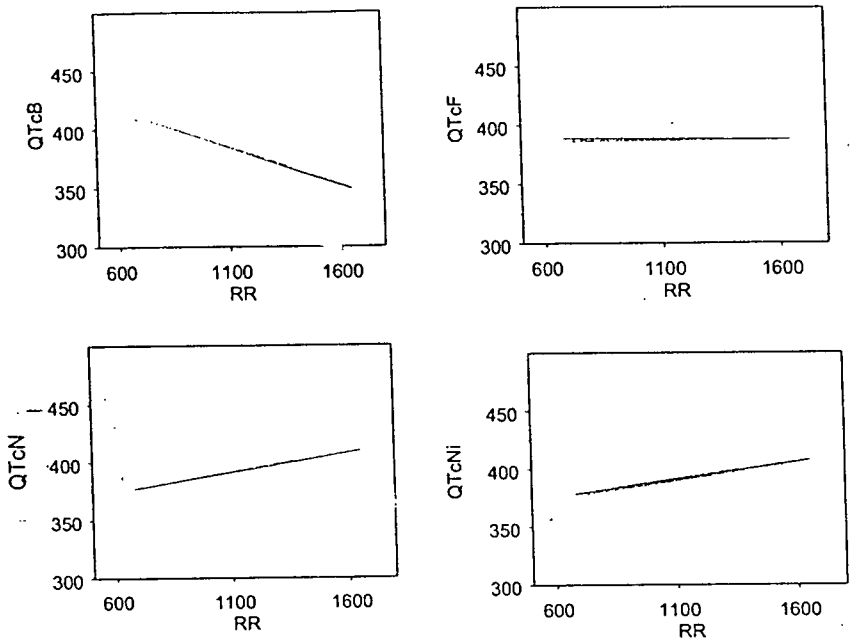

Figure 4. Relationship between corrected QT and RR intervals for various methods of correction for all subjects on placebo (Bazett: QTcB, Fridericia: QTcF, population: QTcN and subject-specific: QTcNi)

As expected, the uncorrected QT is positively correlated with RR interval. To evaluate these correction methods, a comparison of QTc (corrected QT) vs RR for different methods of correction are shown in this slide. All subjects' baseline and placebo QTc data (on Y-axis) were plotted against RR interval (on x-axis) for different methods of correction: Bazett, Fridericia, population and individual methods. The slope in each plot is obtained by linear regression of the pooled data and does not take into account the individual subject's correlation.

Based on the regression of pooled data, Fridericia method yields slope closer to zero (-0.002) than any other method including population (0.03) and individual correction (0.03) methods. However, this approach has limitation and it does not take into consideration that the data points from with in an individual may be correlated. To address this issue, slopes of QTc Vs RR were estimated for each individual separately and these are shown in Figure 5.

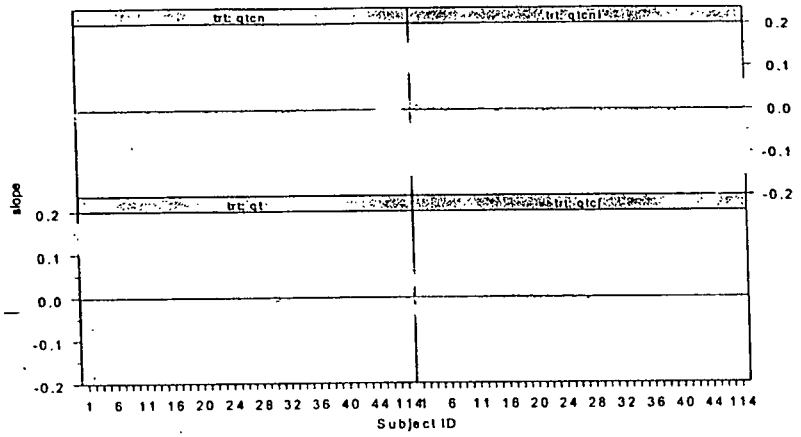

Figure 5: Slopes of QT versus RR relationship for each individual subject before correction (trt:qt) and after Fridericia (trt:qtcf), population specific (trt:qtcn) and subject-specific (trt:qtcni) correction methods.

The individual slope analysis is similar to what sponsor has reported on the correction methods (submission dated 5/22/03). When the data is analyzed at the individual subject level, the individual and population correction methods yielded slopes closer to zero than the Fridericia method. The mean slope for individual and population methods are 0.001 and 0.002 compared to Fridericia with mean slope of -0.04.

Therefore the evaluation of these methods depends on how the QTc versus RR data are analyzed. Pooling all subjects' data and looking at QTc versus RR relationship on a population basis without considering the individual correlation may give different results than when the individual correlation is explored. The reason why a positive slope is noted for population and individual correction methods in Figure 2 when all QTc data are plotted against RR interval may be related to inter- individual differences in the range and distribution of RR intervals.

QT measurements obtained from three recordings from each subject at –1 hr (1 hour before each treatment) on Day 3 of the study constituted the "baseline" QT measurement. To compute QT/QTc change from baseline, the average of the three QT/QTc measurements at –1 hr was subtracted from all the measurements obtained following each treatment. The mean change in QTc (based on Fridericia and subject-specific corrections) from baseline following each treatment are shown in Figure 4 below.

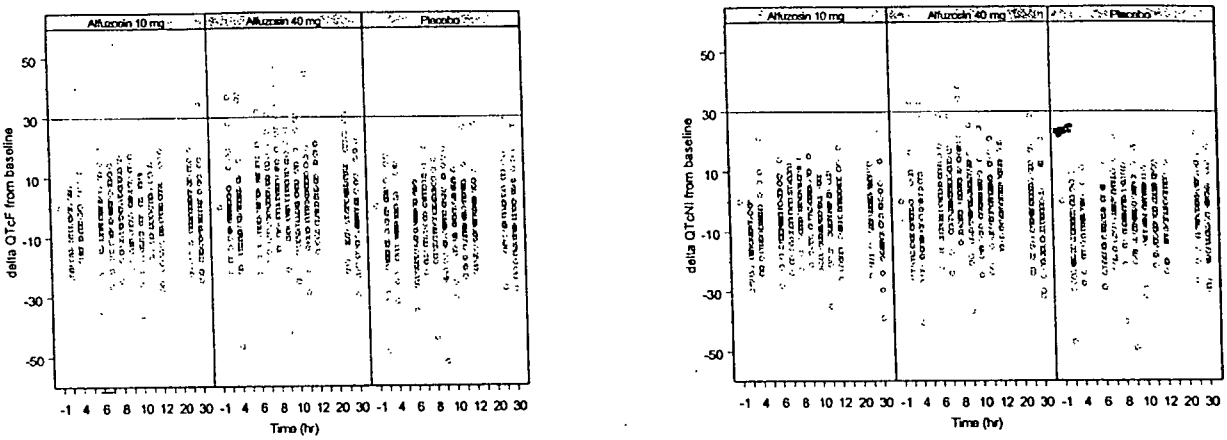

Figure 4. Individual changes in QTc (QTcF and QTcNi) from baseline all observations for all subjects following alfuzosin 10 and 40 mg compared to placebo

[Baseline is defined as average of three measurements at 1 hr before administering each treatment. Note that data points above the reference line at 30 on Y –axis are observations of delta QTc values ≥30 msec. The number of outlier subjects may be different in Table 18 because it tabulates number of subjects

Table 2. 12-Lead ECG: Mean change from baseline at Tmax

ECG Parameter	Treatment	Mean change Vs Placebo	Mean change	Matched Placebo	95% CI	
					Lower Bound	Upper bound
HR (Bpm)	Alfuzosin 10 mg	5.2	5.7	0.6	2.2	8.3
	Alfuzosin 40 mg	5.8	6.9	1.0	3.2	8.4
	Moxifloxacin 400 mg	2.8	2.3	-0.5	1.3	4.2
QT interval (msec)	Alfuzosin 10 mg	-5.8	-13.9	-8.4	-10.2	-1.4
	Alfuzosin 40 mg	-4.2	-10.7	-6.5	-8.5	0.2
	Moxifloxacin 400 mg	6.9	5.5	-1.3	2.3	11.5
Bazett QTc (msec)	Alfuzosin 10 mg	10.2	4.7	-5.3	3.9	16.6
	Alfuzosin 40 mg	13.9	11.9	-2.0	5.8	22.0
	Moxifloxacin 400 mg	15.7	13.4	-2.3	10.8	20.6
Fridericia QTc (msec)	Alfuzosin 10 mg	4.9	-1.5	-6.3	0.9	8.8
	Alfuzosin 40 mg	7.7	4.3	-3.4	1.9	13.5
	Moxifloxacin 400 mg	12.7	10.8	-1.9	8.6	16.8
QTcN (msec	Alfuzosin 10 mg	1.8	-5.0	-6.8	-1.4	5.0
	Alfuzosin 40 mg	4.2	-0.1	-4.3	-0.6	9.0
	Moxifloxacin 400 mg	11.0	9.4	-1.6	7.0	15.0
QTcNi (msec)	Alfuzosin 10 mg	1.8	-4.7	-6.6	-1.3	5.0
	Alfuzosin 40 mg	4.3	0.1	-4.2	-0.5	9.2
	Moxifloxacin 400 mg	11.1	9.4	-1.7	7.2	15.0

Mean changes in corrected QT from baseline at the time of maximum alfuzosin or moxifloxacin plasma concentrations for different methods of correction are presented in Table 3. This table includes sponsor's reported QT interval measurements from

continuous 3-lead Holter monitor during the window of 7 to 11 hours (corresponding to T_{max} of alfuzosin ER tablets) by a selective beat average method.

Table 3. Mean QTc change from baseline at Tmax (corrected for placebo)

Treatment	Fridericia (QTcF)	Population (QTcN)	Individual (QTcNi)	Holter Monitor (Largest sample RR bins)
Alfuzosin 10 mg	4.9	1.8	1.8	0.4
Alfuzosin 40 mg	7.7	4.2	4.3	2.5
Moxifloxacin 400 mg	12.7	11.0	11.1	6.9

As noted in Table 17, the mean changes in placebo corrected QTc for alfuzosin 10 mg (4.9 msec) and 40 mg (7.7 msec) doses based on Fridericia method were almost double those seen with population (1.8, 4.2 msec) and subject-specific (1.8, 4.3 msec) methods. However, for moxifloxacin, the differences in mean change in placebo corrected QTc for these different correction methods are small. This may be because moxifloxacin was associated with smaller increases in heart rate compared to alfuzosin (see Table 16) and consequently different correction methods may have yielded smaller differences in corrected QTc for moxifloxacin.

The mean changes in placebo corrected QTc from baseline with all methods of correction are dose dependent for alfuzosin, with higher change at the 40 mg dose compared to 10 mg. The mean QT interval changes from baseline for the Holter monitor method (as analyzed by the sponsor) were smaller than the 12-lead ECG measurements with various calculated correction methods. However it should be noted that the time course effect on QT was not captures with Holter bin method as the ECGs were classified and averaged according to RR intervals and compared at identical RR intervals. Furthermore, there is limited experience with this method in evaluating the drug effects on QT interval.

The outliers for the different methods of correction (not including the Holter monitor methodology results) are presented below in Table 4.

Table 4. Outliers for corrected QTc interval and change in QTc from baseline

Outlier definition	Number of subjects with at least one outlier value			
	Placebo (N=45)	Alfuzosin 10 mg (N=44)	Alfuzosin 40 mg (N=45)	Moxifloxacin (N=44)
431≤QTcB≥450 msec	1	3	13	5
QTcB≥450 msec	2	1	3	1
QTcB≥500 msec	0	0	0	0
431≤QTcF≥450 msec	3	0	6	5
QTcF≥450 msec	0	0	0	0
QTcF≥500 msec	0	0	0	0
431≤QTcN≥450 msec	3	4	5	7
QTcN≥450 msec	0	0	0	0
QTcN≥500 msec	0	0	0	0
431≤QTcNi≥450 msec	3	4	5	7
QTcNi≥450 msec	0	0	0	0
QTcNi≥500 msec	0	0	0	0
30≤deltaQTcB≥60 msec	5	7	17	14
deltaQTcB≥60 msec	0	1	3	0
30≤deltaQTcF≥60 msec	0	1	9	3
deltaQTcF≥60 msec	0	0	0	0
30≤deltaQTcN≥60 msec	0	0	2	1
deltaQTcN≥60 msec	0	0	0	0
30≤deltaQTcNi≥60 msec	0	0	2	1
deltaQTcNi≥60 msec	0	0	0	0

There were one subject at 10 mg and 9 subjects at 40 mg doses of alfuzosin with the Fridericia method who are outliers at 30≤deltaQTc≥60 msec and there were two subjects at the 40 mg dose of alfuzosin with population and subject-specific methods of correction who were outliers. There were no outliers with placebo.

There were no outliers using a cut-off of delta QTc ≥ 60 msec or QTc≥450 msec with any correction method (except for the Bazett method) or with any treatment.

Relationship between alfuzosin plasma concentrations and QT interval

The relationship between alfuzosin plasma concentrations and the observed QT interval calculated by individual correction method for each subject in the study is illustrated in the following figure.

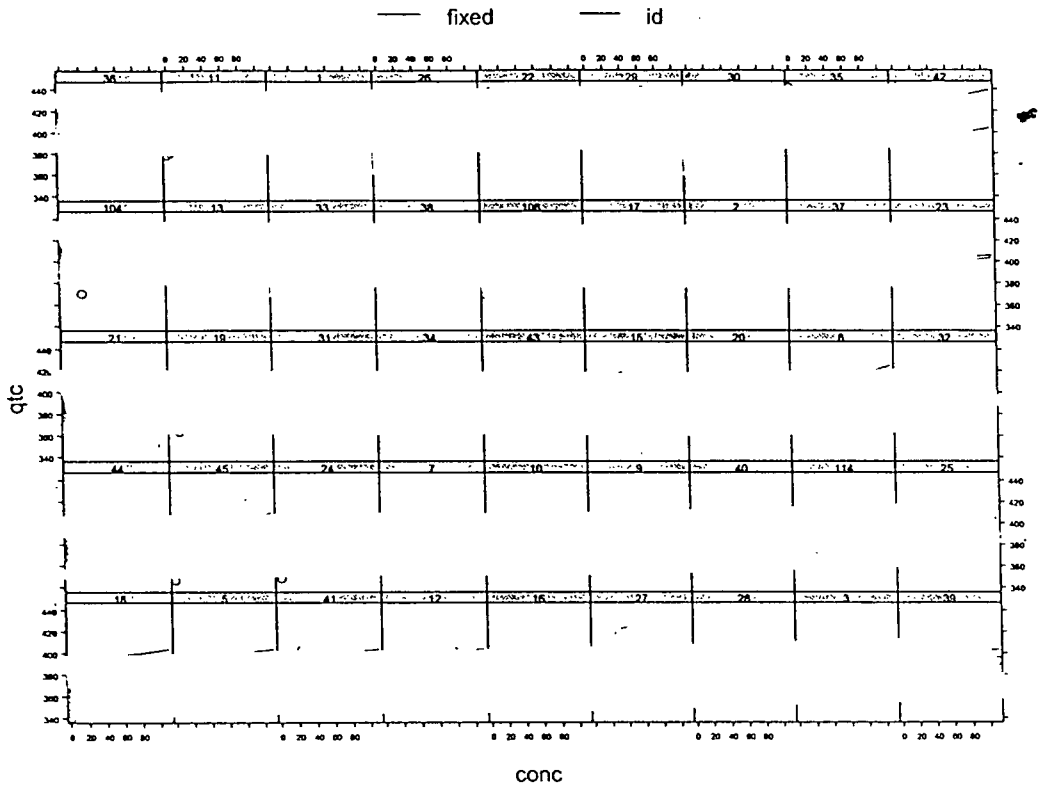

Figure 5. Relationship between alfuzosin plasma concentrations (ng/ml) and the observed QTc (by individual correction method) for each of the 45 subjects in Study PDY5105 (redline: individual trend line, blue line: population trend line).

As can be noted from Figure 5, there were some subjects who had increasing QT intervals with increase in plasma concentrations indicating the effect on QT is concentration dependent at least for some subjects in the study. However, if the data for all subjects is pooled and plotted, the relationship may appear to be shallow.

Based on the results of this study, it can be concluded that

- The magnitude of QT increase observed with alfuzosin depended on the correction method used.
- Mean QTc increase with Bazett was highest and the mean increase with Fridericia was higher than with individual and population methods and also with Holter monitor method.
- There is dose-related increase in QTc with all methods indicating that the effect on QT is most likely attributable to the drug.
- QT prolongation appears to increase with increase in plasma concentrations of alfuzosin for certain individuals, raising the question whether there is risk related to high concentration of the drug.

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/s/

Venkateswar Jarugula
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Ameeta Parekh
6/12/03 07:27:36 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-287 (Response to approvable letter)	Brand Name	Uroxatrol
OCPB Division (I, II, III)	DPE II	Generic Name	Alfuzosin
Medical Division	DRUDP	Drug Class	Alpha-blocker
OCPB Reviewer	Venkat Jarugula	Indication(s)	BPH
OCPB Team Leader	Ameeta Parekh	Dosage Form	ER tablet
		Dosing Regimen	10 mg OD
Date of Submission	12/12/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	5/01/03	Sponsor	Sanofi Synthelabo
PDUFA Due Date	06/12/03	Priority Classification	1S
Division Due Date	05/12/03		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:	X	1		
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	**What is the maximum effect of CYP 3A4 inhibitor (ketoconazole 400 mg per day) on the pharmacokinetics of alfuzosin ER tablets?** **Does alfuzosin ER tablets prolong the QT interval at the anticipated exposures of alfuzosin due to drug interactions?**
Other comments or information not included above	**Sponsor submitted the following two studies to address the deficiencies noted in the approvable letter dated 11/05/01:** **Assessment of pharmacokinetic drug interaction between alfuzosin 10 mg od formulation and ketoconazole 400 mg per day in healthy male subjects (INT5056)** **Effect of supra-therapeutic doses of alfuzosin ER on QT interval, using a rate-independent method, compared to placebo and moxifloxacin in healthy volunteers (PDY5105) { In this study alfuzosin was tested at single doses of 10 and 40 mg).**
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-287, HFD-850 (L.Lesko, S.Huang), HFD-580(Benson, King), HFD-870(Parekh,Hunt, Malinowski)

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/s/

Venkateswar Jarugula
1/31/03 01:28:06 PM
BIOPHARMACEUTICS

Ameeta Parekh
2/4/03 02:57:47 PM
BIOPHARMACEUTICS
concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-287	Brand Name	
OCPB Division (I, II, III)	DPE II	Generic Name	Alfuzosin
Medical Division	DRUDP	Drug Class	Alpha-blocker
OCPB Reviewer	Venkat Jarugula	Indication(s)	BPH
OCPB Team Leader	Ameeta Parekh	Dosage Form	ER tablet
		Dosing Regimen	10 mg OD
Date of Submission	12/8/00	Route of Administration	Oral
Estimated Due Date of OCPB Review	9/8/01	Sponsor	Sanofi Synthelabo
PDUFA Due Date	10/8/01	Priority Classification	1S
Division Due Date	9/8/01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	2	2	
Isozyme characterization:	X	1	1	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	2	2	
multiple dose:	X	3	1	
Patients-				
single dose:	X			
multiple dose:	X	1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	X	1	1	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	
In-vivo effects of primary drug:	X	5	4	
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	X	2	1	
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:				
Phase 2:	X	8	2	
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:		2	2	
Phase 3 clinical trial:	X	1	1	

Population Analyses -				
Data rich:				
Data sparse:	X	1	1	
II. Biopharmaceutics				
Absolute bioavailability:	X	2	1	
Relative bioavailability -				
solution as reference:	X			
alternate formulation as reference:	X	2	1	
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	4	2	
Dissolution:	X	1	1	
(IVIVC):	X	2	2	
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		42	30	
		42+ 62 =104 studies*		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.

QBR questions (key issues to be considered)	What are basic PK (ADME) characteristics of alfuzosin ? How does PK of ER formulation compare with IR formulation? What is the basis for dose-selection? How is exposure-response (efficacy and safety) relationship characterized>? Is there a PK/PD relationship for efficacy and safety parameters? Is Pk altered by various intrinsic and extrinsic factors? IS dose adjustment needed in special populations or with concomitant medications? Is to be marketed formulation bioequivalent to clinical trials formulation?
Other comments or information not included above	Sponsor submitted a BE study conducted under fed conditions and the justification for not conducting a fasted BE study, which included an IVIVC under fasting conditions. The fed BE study, justification provided by the sponsor and IVIVC are review issues. *The NDA also contains 62 early phase I studies (only synopses) on early formulations.
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-287, HFD-850 (L.Lesko, S.Huang), HFD-580(Benson, Farinas), HFD-870(Parekh, Malinowski, Hunt), CDR (B. Murphy)

CP&B Briefing attendees on 9/18/01: Drs. S.Huang, H.Malinowski, M.Mehta, J.Lazor, G.Benson, J.Hunt, A.Parekh, H.Sun, S. Al-Habet, J.Lau, D.Chatterjee, M.Kim, H.Kim, A.Sanchoz, Gardmark, and Ikuko.

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	21-287
Drug:	Alfuzosin HCl ER (10 mg) tablets
Sponsor:	Sanofi Synthelabo
Date of Submission:	12/08/00, 01/17/01, 4/6/01, 8/13/01, 8/28/01, and 9/20/01
Type of Submission:	Original NDA (NME)
Reviewer:	Venkateswar R. Jarugula, Ph.D.

I. EXECUTIVE SUMMARY

A. RECOMMENDATIONS

NDA 2-287 for Alfuzosin 10 mg ER tablets is acceptable from Clinical Pharmacology and Biopharmaceutics perspective. The labeling comments should be communicated to the sponsor as appropriate.

The systemic exposure of alfuzosin is increased by 3 to 4 folds in subjects with moderate and severe hepatic impairment. Consequently, labeling for this drug should indicate contraindication in liver insufficiency.

The exposure of alfuzosin is increased by up to 50% in mild, moderate and severe renal impairment. Since dose related increase in vasodilatory adverse events at 50% higher dose than the recommended dose (10 mg qd) were noted, the label should recommend a caution when the drug is administered in patients with renal impairment.

Potent CYP 450 3A4 inhibitors such as ketoconazole increase the exposure of alfuzosin by more than two fold. Alfuzosin should not be coadministered with potent CYP 450 3A4 inhibitors. Caution should be exercised when alfuzosin is coadministered with moderate or mild inhibitors of CYP 450 3A4.

The proposed dissolution method (USP method II, 0.01 M HCl, 100 rpm) is acceptable. The following dissolution specifications are recommended:

Time	% labeled content dissolved
1 hr	%
6 hr	%
12 h	%
20 h	%

/s/

Venkateswar R. Jarugula, Ph.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader _____

FT signed by Ameeta Parekh, Ph.D., Team Leader _____

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The studies submitted to Section 6 of the NDA have shown the following results:

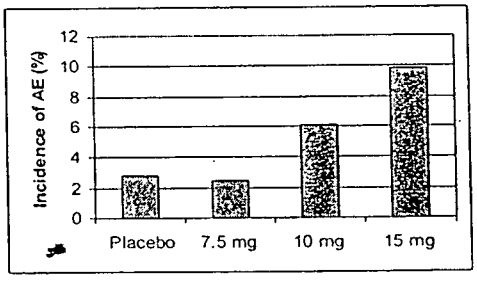
Absorption: Absolute bioavailability of Alfuzosin Geomatrix ER formulation is 49%. The ER formulation releases the drug continually for 20 hrs producing a sustained plasma concentration versus time profile. During the early development of ER formulation, it was found that food increases the bioavailability (both Cmax and AUC) by two-fold. All subsequent studies including the Phase III trials were conducted with food. The labeling for this drug recommends that the drug be taken with meals.
Pharmacokinetics of Alfuzosin ER formulation is dose proportional over the range of 7.5 mg to 40 mg; steady-state is reached after second administration with approximately 1.7 times accumulation in plasma levels.

Distribution: The volume of distribution of alfuzosin is high (3.2 L/kg), indicating it's tissue distribution. Plasma protein binding is around 90%. Drug binds to both albumin and α_1-acid glycoprotein almost to the equal extent.

Metabolism: Alfuzosin is extensively metabolized to inactive metabolites. Major metabolic pathways are oxidation of the tetrahydrofuran ring, O-demethylation and N-dealkylation. CYP 3A4 is the major isozyme responsible for its metabolism. In vitro, alfuzosin does not inhibit or induce CYP 450 enzyme system.

Excretion: Within 7 days after administration of radiolabeled alfuzosin solution, approximately 24% and 69% of the dose administered was excreted in urine and feces, respectively. Approximately 11% of dose administered was excreted as unchanged parent compound in urine. The apparent elimination half-life of ER formulation is 9.1 hours.

Dose-Response: Alfuzosin ER 7.5 mg dose was found not to be superior to placebo for relief of urinary symptoms associated with BPH. 10 mg and 15 mg doses were superior in efficacy compared to placebo. However, 15 mg dose provided no further improvement in efficacy compared to 10 mg dose, which was being recommended for marketing.



The incidence of vasodilatory adverse events increased with increasing doses over 7.5 mg to 15 mg.

Alfuzosin caused dose dependent increase in heart rate corrected QT intervals with a mean increase of 13.2 ms (Bazett's correction) or 7.1 ms (Fridericia's correction) following single administration of 40 mg dose. As expected with α-blockers, there was also dose dependent increase in heart rate.

Parameter	Pairwise comparison	p-value	Mean difference	95% CI UB
Delta HR (bpm)	10 mg vs placebo	0.1011	+0.6	+1.3
	20 mg vs placebo	0.0001	+4.6	+5.4
	40 mg vs placebo	0.0001	+5.8	+6.5
Delta QTcB (ms)	10 mg vs placebo	0.1416	+1.2	+3.0
	20 mg vs placebo	0.0001	+8.5	+10.3
	40 mg vs placebo	0.0001	+13.2	+15.0
Delta QTcF (ms)	10 mg vs placebo	0.2673	+0.5	+1.8
	20 mg vs placebo	0.0001	+3.4	+4.7
	40 mg vs placebo	0.0001	+7.1	+8.4

Intrinsic factors: The systemic exposure of alfuzosin is increased by about 50% in mild, moderate and severe renally impaired subjects compared to normal renal function. Since there is increased incidence of vasodilatory adverse events at 15 mg dose, caution should be exercised when Alfuzosin is administered to patients with renal impairment.

The plasma clearance alfuzosin is reduced by 1/3 to 1/4 in subjects with moderate and severe hepatic impairment compared to that in normal subjects. The labeling proposes to contraindicate in moderate and severe hepatic impairment. Pharmacokinetics in mild hepatic impairment has not been studied. However, the labeling recommends that the physicians should evaluate the risk/benefit in these patients before prescribing alfuzosin. Since, the exposure change in mild hepatic impairment is not known, this condition should also be a contraindication in the label.

Factor	C_{max}	AUC	Label recommendation
Intrinsic factors			
Hepatic	200 to 300% ↑	200 to 300% ↑	Contraindication
Renal	Up to 52% fold ↑	Up to 47% ↑	Caution
Extrinsic factors			
Ketoconazole (potent 3A4 inhibitors)	111% ↑	146%↑	Contraindication
Diltiazem (moderate 3A4 inhibitors)	49% ↑	30% ↑	Caution

Extrinsic factors: Coadministration of Ketoconazole (200 mg qd for 7 days), a potent CYP 3A4 inhibitor, increases the systemic exposure of alfuzosin ER tablets by an average of 2.5 fold. Higher doses of ketoconazole (400 mg: maximum recommended in PDR) might have higher inhibitory effect on alfuzocin metabolism. Moderate CYP 450 3A4 inhibitors, such as cimetidine and diltiazem, resulted in lesser increases in alfuzosin bioavailability (up to 50% increase). Labeling should recommend that coadministration of ketoconazole and other potent inhibitors should be contraindicated. A caution should be exercised when alfuzosin is prescribed to patients who take moderate CYP 3A4 inhibitors.

There was no pharmacokinetic or pharmacodynamic interaction between Alfuzosin, and digoxin.
Coadministration of alfuzosin with warfarin resulted in lower prothrombin times (on average 7% lower) compared to warfarin alone administration. But the sample size of the study is small (n=6).
There was no pharmacokinetic interaction between alfuzosin and atenolol (beta-blocker) and hydrochlorthiazide (diuretic).

Biopharmaceutics: The to be marketed formulation is bioequivalent to the clinical trials formulation under fed conditions. Even though a bioequivalence study was not conducted under fasting conditions, Sponsor has submitted an adequate IVIVC using the in vivo absorption data under fasted conditions proving that the commercial formulation is bioequivalent to the clinical formulation under fasted conditions also.

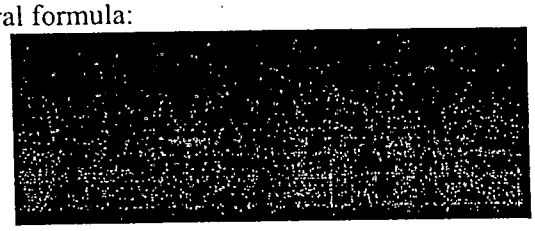
VI. Clinical Pharmacology and Biopharmaceutics Review

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product

Physico-chemical properties

- Structural formula:



- Molecular Weight: 425.92
- Molecular Formula: $C_{19}H_{27}N_5O_4 \cdot HCl$
- IUPAC name: (R,S)-N-[3-[4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino] propyl]tetrahydro-2-furancarboxamide hydrochloride
- —
- —
- Aqueous solubility at various pH levels

Alfuzosin hydrochloride is readily soluble in water (>10%). Its solubility over a range of pH levels is given in Table 1.

Table 1 - Solubility at Various pH Levels

pH	Solubility (mg/mL)
2.2	176
5.98	172
6.60	235
7.20	243
7.22	234
7.37	179
7.73	109
8.49	20

FORMULATION

Alfuzosin ER tablet is three-layer tablet, with the drug substance in a matrix layer between two inactive layers (figure1). The three layer tablet is round and convex. The layers are colored successively: yellow, white, and yellow.

Figure 1. Three layered Geomatrix ER tablet of alfuzosin

Table - Unit Formula for Alfuzosin Hydrochloride ER 10 mg Tablet

Ingredient	Quantity per Unit	Function
First Layer (Outer-Inactive		
Hydroxypropyl methylcellulose		
Hydrogenated castor oil		
Ethylcellulose		
Yellow ferric oxide		Coloring agent
Silicon dioxide [a]		
Magnesium stearate		
Alcohol	q.s.	
Purified water [b]	q.s.	
Second Layer (Inner-Active)		
Alfuzosin hydrochloride	10.00 mg	Active substance
Mannitol, USP		
Hydroxypropyl methylcellulose		
Povidone		
Microcrystalline cellulose		
Silicon dioxide [a]		
Magnesium stearate		
Alcohol	q.s.	
Purified water [b]	q.s.	
Third Layer (Outer-Inactive)		
Hydroxypropyl methylcellulose		
Hydroxypropyl methylcellulose		
Hydrogenated castor oil		
Povidone		
Yellow ferric oxide		Coloring agent
Silicon dioxide [a]		
Magnesium stearate		
Alcohol	q.s.	

b) Eliminated during process.

What is the proposed mechanism of action?

Alfuzosin, quinazoline derivative, is a selective α_1-adrenoceptor antogonist.
The pathophysiology of intravesical obstruction secondary to BPH includes both anatomical and functional factors. The anatomical obstruction arises from the physical enlargement of the prostate whereas the functional obstruction arises from the dynamic constrictor tone of the prostate. The prostate is enervated by both the sympathetic and parasympathetic branches of the autonomic nervous system. α_1-adrenoceptor subtypes are abundant in the proximal urethra and bladder neck but sparse in the bladder body. Thus α_1-blockers such as alfuzosin reduce sympathetic tone at the prostate level and urethra and relieve the symptoms of urinary obstruction in BPH patients.

Three α_1-blockers are currently marketed in the Unites States of America for BPH: terazocin, doxazocin and tamsulocin. Alfuzosin has been approved as immediate release (2.5 mg IR tablets tid) and sustained release (SR: 5 mg bid) in 1987 and 1993, respectively, in European market and, subsequently in 87 countries worldwide. Alfuzosin extended release (ER) tablets, the subject of current NDA, was also approved recently in European market. Thus extensive safety and efficacy information is available for this drug.

What is the proposed indication and dose?
The indication sought for alfuzosin is treatment of the signs and symptoms of benign prostatic hyperplasia. The recommended dose is 10 mg ER tablet once a day to be administered with meals.

B. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Typically International Prostate Symptom Scores (IPSS) scores and peak urinary flow rate are the primary endpoints measured in clinical trials for drugs used in BPH. Sponsor measured these two primary end points in pivotal phase III studies.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to IV. F, Analytical Section; if no, describe the reasons)

Yes. Alfuzosin, the parent compound was measured in all the pharmacokinetic studies. The metabolites are not measured since they are not active and not found in plasma to a measurable extent. Since, both enantiomers are equally active with respect to their affinity to α_1-adrenoceptors, sponsor measured the pharmacokinetics of R and S isomers in one study (refer to enantiomeric disposition).

What are the basic pharmacokinetic characteristics of Afluzosin?
How does pharmacokinetics of extended release formulation compare with immediate release formulation?
Is the dose selected for ER justified by pharmacokinetic comparison with IR formulation?

1) Pharmacokinetics (ADME)

a. Absorption
Alfuzosin was rapidly absorbed and peak concentrations of alfuzosin reached within 1 hour following the administration of immediate release tablets of 2.5 mg tid.

Absolute Bioavailability
Absolute bioavailability of alfuzosin following oral administration of 5 mg as capsules or solution compared to 5mg intravenous infusion was 64% (SD: 13).

The absolute bioavailability of alfuzosin ER tablets was determined in study 98-00242 by comparing the bioavailability following single dose administration of 10 mg ER formulation and intravenous infusion of 5 mg alfuzosin over 30 minutes. In this study the effect of high fat meal on the pharmacokinetic profile 10 mg ER formulation was also investigated. This was an open, label, randomized (partially), three period crossover study in 18 healthy male Caucasian subjects aged 50 to 65 years. The following three treatments were administered with a one week washout period between treatments.

Treatment A: Intravenous infusion of 5 mg alfuzosin hydrochloride over 30 minutes, at 5 minutes after a high fat dinner (58 g fat, 57 g carbohydrates, 40 g protein).
Treatment B: Alfuzosin hydrochloride 10 mg Geomatrix formulation (batch #PDV03-01A1), single oral administration 5 minutes after a high fat dinner (58 g fat, 57 g carbohydrates, 40 g protein).
Treatment C: Alfuzosin hydrochloride 10 mg Geomatrix formulation (batch #PDV03-01A1), single oral administration in fasting state.

Table 3. Mean (SD) Pharmacokinetic parameters of alfuzosin

Dose	Tmax (h)	Cmax (ng/ml)	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	T1/2 (h)	CL (L/h)	Vd (L/kg)
5 mg IV	0.5	105 ± 19	197 ± 72	205 ± 76	6.3 ± 0.9	27 ± 7.6	3.2 ± 1.1
10 mg fed	9.6±2.9	12.3±6.6	195 ± 101	224 ± 120	10 ± 2.6		
10 mg fasting	11.6±4.0	10.9±3.8	176 ± 61	203 ± 62	10.7±3.3		

The absolute bioavailability of 10 mg ER formulation under fed condition is approximately 50 %. Following infusion, alfuzosin has a clearance rate of around 27 L/h and volume of distribution of 3 L/kg. Oral administration of 10 mg ER formulation with high fat meal had resulted in slightly (around 10%) higher Cmax and AUC compared to fasting administration.

This result is in contrast to three other food effect studies, which showed a two fold increase in Cmax and AUC with food.

b. Distribution

The mean (SD) volume of distribution of alfuzosin following intravenous administration (over 25 minutes) as 3.2 (1.1) L/Kg indicating extensive tissue distribution of the drug.

Plasma protein binding of alfuzosin (determined by equilibrium dialysis method) was determined as 90% in one study over concentration range of 14 to 265 ng/ml and as 74 to 82% in another study over a wide concentration rage of 5 to 5000 ng/ml. In both the studies, protein binding was independent of concentration. The mean fraction of alfuzosin bound to human plasma albumin and α_1-acid glycoprotein was 68.2 (0.3)% and 52.5 (1.5%), respectively.

The blood/plasma ratio alfuzosin was found to be 0.82 and was relatively constant over the dosing interval. The distribution of alfuzosin in prostate tissue/blood in patients with BPH was 2.4 following repeated administration of 5 mg SR formulation.

c. Metabolism and Excretion

Based on the in vitro and in vivo metabolism studies, the following metabolic pathways were identified:

- Oxidation of the tetrahydrofuran ring, resulting in the formation of SL80.0306 and SL80.0363.
- O-demethylation of the dimethoxyquinazoline ring, resulting in the formation SL80.0037 and SL80.0018.
- N-dealkylation of the aliphatic chain, resulting in the formation of SL79.0723 and SL79.0724.
- N-demethylation of alfuzosin, resulting in the formation of SL85.0090.
- Hydroxylation of the parent compound, resulting in the formation of Met-A; Met-B and Met-D.

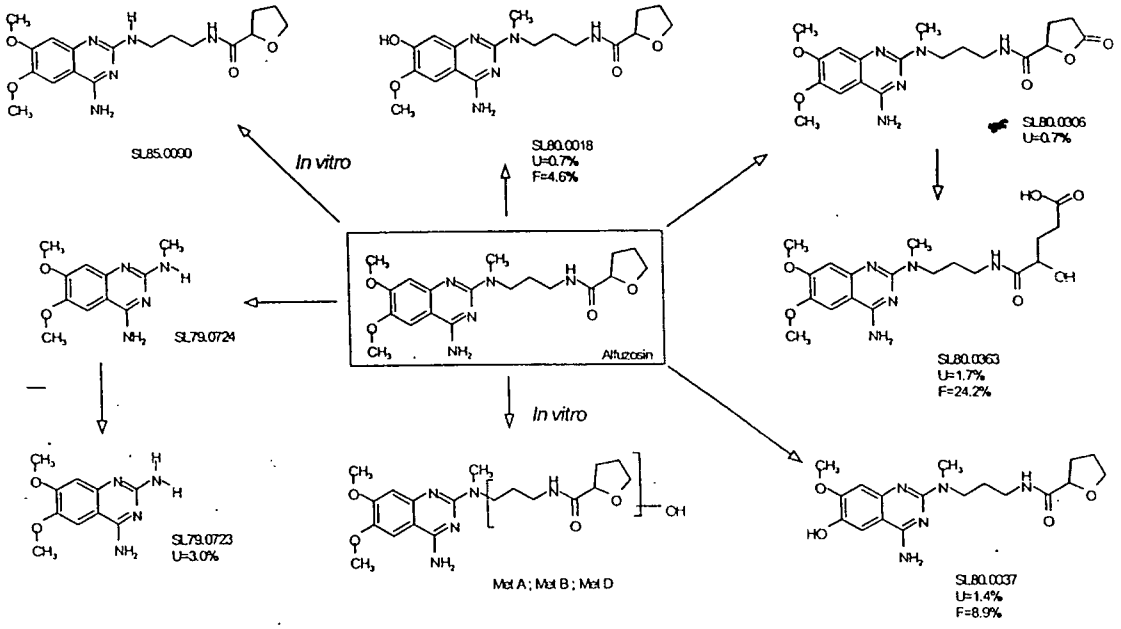


Figure 2. Metabolic Pathways of Alfuzosin

The two metabolic pathways identified *in vitro* in human liver microsomes i.e., hydroxylation and N-demethylation (yielding Met A, Met-B, Met-D and SL85.0090) were not identified *in vivo*. Conversely, the O-demethylated metabolites (SL80.0018 and SL80.0037) which accounted for 15% of the dose *in vivo*, were only found as traces of SL80.0037 in vitro in human liver microsomes.

In vitro metabolism

Study #00-00071-EN-00 characterized the CYP450 isozymes responsible for metabolism of alfuzosin by following methods:

- Incubation of alfuzosin with a pool of human microsomes in the presence of known selective chemical inhibitors
- Incubation of alfuzosin with c-DNA expressed enzymes
- Incubation of alfuzosin with primary cultured human hepatocytes in presence of ketoconazole, quinidine, and furafylline as inhibitors

The potential of alfuzosin to inhibit CYP 450 isozymes (1A2, 2A6, 2C9, 2C19, 2D6, and 3A4) was investigated in this study by monitoring the following activities: phenacetin O-deethylase, coumarin 7-hydroxylase, diclofenac 4'-hydroxylase, (S)-mephentoin 4'-hydroxylase, (+/-)-bufuralol 1'-hydroxylase and testosterone 6β-hydroxylase in the presence of various alfuzosin concentrations.

The major in vitro biotransformation pathways identified are shown above (figure 1).

Over the concentration range of 0- 400 µM, the metabolism of alfuzosin in human liver microsomal fraction was weak. The overall intrinsic clearance (Vm/Km) was low (1.7 µl/min/mg microsomal protein).

Incubation of alfuzosin (20 µM and 400 µM concentrations for 1 hour) with C-DNA expressed enzymes and human microsomes in presence of known selective inhibitors showed that CYP 3A4 is the primary enzyme responsible for the biotransformation of alfuzosin. Ketoconazole (at 3 µM) significantly inhibited (by 87%) the in vitro metabolism of alfuzosin (incubation of 1 µM). CYP 1A2 also played a minor role in the metabolism of alfuzosin.

Alfuzosin (over 1 to 100 µM incubation concentrations) had no inhibitory effect on CYP isozymes 3A4, 2D6, 2C19, 2A6, and 1A2. Additionally, SL80.0363, which is the major in vivo metabolite (13-26% of the oral dose in man) did not inhibit CYP 3A4 activity.

In vivo metabolism of alfuzosin was investigated in two mass balance studies. In study report #85-00037, 10 mg radiolabeled alfuzosin was administered as a IR capsule to 3 healthy young volunteers (1 female and 2 male), where as in study report #00-00150, 5 mg radiolabeled dose was administered as a solution to 4 healthy middle aged male volunteers.

Table 4- Quantitative Evaluation of ^{14}C-Alfuzosin and Metabolites in Urine After a Single Oral Administration of 5 mg or 10 mg of Radiolabeled ^{14}C-Alfuzosin in Healthy Volunteers. Mean (SD) Value Expressed as Percentage (%) of the Administered Dose.

	85-00037 (capsule) 10 mg (n=3, 2 Males and 1 Female) Urinary Collection: 0-13 h	**00-00150 (solution) 5 mg (n=4, Males) Urinary Collection: 0-24 h**
Total radioactivity	17.3 (7.1)	19.4 (6.8)
Alfuzosin	4.1 (1.6)	7.6 (5.5)
SL80.0037	1.4 (0.7)[a]	1.2 (0.6)[a]
SL80.0018	0.7 (0.6)[a]	3.0 (1.3)[a,b]
SL80.0363	1.7 (0.4)	1.2 (0.5)
SL80.0306	0.7 (0.4)	-
SL79.0723	3.0 (2.8)	-
Non-identified peaks	5.7 (1.6)	1.1 (0.8)
Total unchanged + metabolites	17.2 (7.1)	14.2 (7.8)
Radioactivity not identified	0.0	5.2 (2.3)

[a] As glucuronide (totally or mainly)
[b] Including traces of alfuzosin N-glucuronide.

Table 5 - Quantitative Evaluation of ^{14}C-Alfuzosin and Metabolites in Feces After a Single Oral Administration of 5 mg or 10 mg of Radiolabeled ^{14}C-Alfuzosin in Healthy Volunteers. Mean (SD) Value Expressed as Percentage (%) of the Administered Dose

	85-00037 10 mg (n=3, 2 Males and 1 Female) Fecal Collection: 0-45 h	00-00150 5 mg (n=4 Males) Fecal Collection: 0-144 h
Total radioactivity	79.5 (7.3)	69.0 (8.5)
Alfuzosin	35.0 (12.3)	28.7 (18.3)
SL80.0037	8.9 (1.1)	9.9 (3.8)
SL80.0018	4.6 (2.4)	1.6 (0.5)
SL80.0363	24.2 (2.6)	11.5 (6.5)
Non identified peaks	6.6 (2.9)	1.4 (1.7)
Total unchanged + metabolites	79.3 (7.5)	53.2 (12.2)
Radioactivity not identified	0.0	15.9 (3.7)

Table 6- Mean (SD) Percentage of the Total Radioactivity Excreted in Urine and Feces After a Single Oral Administration of Radiolabeled ^{14}C-Alfuzosin in Healthy Volunteers

Fluid Sampled	85-00037 (V48 P115) 10 mg (n=3, 2 Males and 1 Female) [a]	00-00150 (V85 P40) 5 mg (n=4 Males) [b]
Urinary excretion	20.6 (8.1)	24.0 (8.4)
Fecal excretion	83.9 (8.3)	69.0 (8.5)
Total excretion	104.5 (3.8)	93.0 (1.1)

[a] Collected over 5 days.
[b] Collected over 7 days.

Based on the results of these studies, alfuzosin is extensively metabolized. Approximately 20 to 24% of dose administered is excreted in the urine and about 70 to 85% is excreted in the feces. More than 90% of the renal and fecal excretion occurred within 24 hours and 48 to 72 hours, respectively. The metabolite profile in plasma was invetsigated in study # 00-00150. The majority of the radioactivity in plasma was accounted for by unchanged alfuzosin at all times. The radioactivity in most of the plasma samples was not sufficient to allow accurate quantitation of the metabolites. However, in the plasma sample of one subject, at 1hour post-dosing, glucuronide conjugates of alfuzosin, SL80.0037, and SL80.0018 were detected. Unchanged alfuzosin accounted for 4 to 8% of the total dose in urine (in 24 hours) and 29 to 35% of the total dose in feces. Thus about 1/3 of the dose is eliminated from the body as unchanged drug.

Only one of the metabolites of alfuzosin had an affinity for α_1-adrenoceptors that was less than 1/3 of alfuzosin itself. This metabolite (SL 80.0306) was found in very low quantities in human urine and not detected in the plasma. All other metabolites, including the primary metabolite (SL 80.0363) were essentially inactive (see Preclinical review).

The elimination half-life following intravenous administration of alfuzosin was 6.3 hours and following repeated oral administration of IR 2.5 mg tablets was 7.1 hours.

2. Pharmacokinetics of Extended Release Tablets

a. Relative Bioavailability and Dose selection

During the early development of this formulation, it was found that food increases the bioavailability by two fold (see Food effect section of the review). Therefore, all subsequent studies including safety and efficacy trials were conducted with food.

Relative bioavailability of 10 mg ER formulation (administered with evening meal) in comparison to 2.5 mg IR formulation given three times a day was determined in 18 healthy middle aged male subjects in study #97-00926. The mean plasma concentrations and pharmacokinetic parameters of alfuzosin are shown in the following Figure and Table, respectively.

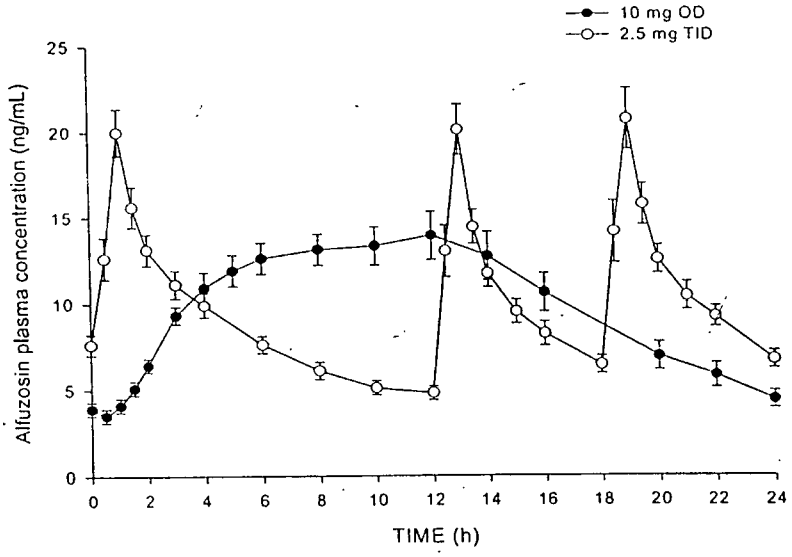


Figure 3. Mean alfuzosin plasma concentration-Time profiles following repeated administration of 10 mg ER formulation and 2.5 mg IR formulation

Table 7 - Mean (SD) Pharmacokinetic Parameters of Alfuzosin 10 mg Extended Release-Tablet OD and Alfuzosin 2.5 mg Immediate-Release Tablet Thrice Daily on Day 5 After a Repeated Administration in 18 Healthy middle-aged Male

Parameters	10 mg Extended-release Tablet (A)	2.5 mg Immediate-Release Tablet (B)	Ratio Estimate (A/B) [90% Confidence Interval]
C_{max} (ng/mL)	16.6 (5.5)	1: 20.2 (6.0) 2: 20.7 (6.3) 3: 21.6 (8.1)	0.82[b] [0.71-0.94]
t_{max} (h)	9.0[a]	1: 1.0[a] 2: 1.0[a] 3: 1.0[a]	NA
AUC_{0-24} (ng.h/mL)	238 (74)	233 (63)	1.01 [0.91-1.12]

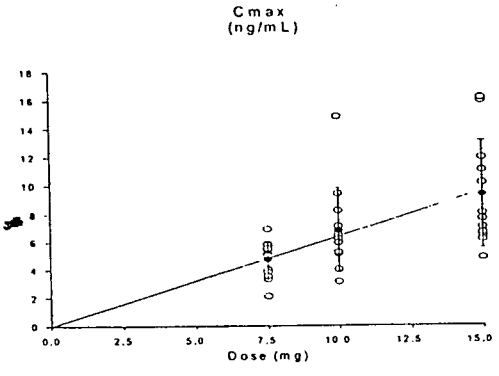
NA = Not applicable
[a] Median value
[b] Comparison versus the C_{max} value obtained after the first dose.

The ER formulation of 10 mg once a day provides equivalent systemic exposure of alfuzosin (uncorrected for dose) when compared to 2.5 mg IR formulation administered three times a day. As expected, peak concentrations from 10 mg ER tablets are lower than those from 2.5 mg IR tablets.

An earlier pharmacokinetic study showed that the relative bioavailability of 7.5 mg ER formulation was 81% compared to 2.5 mg IR given three times a day. Based on phase III clinical data, 7.5 mg dose was found not significantly superior to placebo (ALFOD Study), and no additional benefit was observed with 15 mg when compared to 10 mg dose in two additional studies (ALFOTAM and ALFUS). Therefore, sponsor proposed 10 mg dose for marketing. Selection of 10 mg dose appears reasonable based on the comparison of systemic exposure to that of IR dosage form (see Dose –Response section).

b. Dose Proportionality

The pharmacokinetics of ER formulation is dose proportional in the range of 7.5 to 30 mg. Two studies included the assessment of dose proportionality: study 97-00257 (7.5 mg, 10 mg, 15 mg) and study 97-00725 (7.5 mg, 15 mg, 22.5 mg and 30 mg).



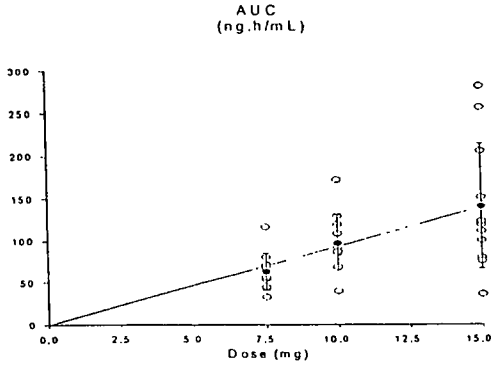


Figure 4 - Individual and Mean (SD) Values of C_{max} and AUC_{0-24} as Function of the Dose of Alfuzosin Extended-Release Tablet in 12 Healthy Young Male Volunteers [Report no. 97-00257]

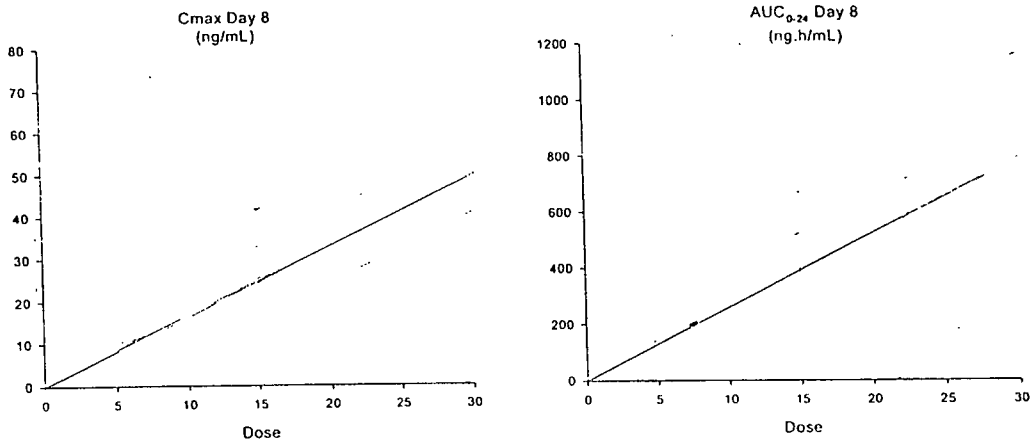


Figure 5- Individual and Mean (SD) Values of C_{max} and AUC_{0-24} Obtained on Day 8 as Function of the Multiple-Dose of Alfuzosin 7.5 mg Extended-Release Tablet in Four Groups of 9 Healthy Middle-aged Male Volunteers [report no. 97-00725]

In the second study, the Cmax and AUC of 15 mg dose were higher than anticipated based on dose proportionality. Except for this deviation, the two studies showed that the pharmaokinetics of alfuzosin ER tablets was dose proportional in the range of 7.5 to 30 mg.

c. Variability in Pharmacokinetics

Single Dose PK

The mean pharmacokinetic parameters obtained from four single dose studies of ER formulation are summarized in the following table and figure.

Table 8 - Mean Values (SD) of Alfuzosin Pharmacokinetic Parameters in Healthy Middle-aged Male Volunteers After a Single Dose of 10 mg Alfuzosin Extended-Release Tablet

Alfuzosin Pharmacokinetic Parameters	10 mg Extended-release tablet				
	98-00986[b] n=8 Batch PDV03-04A1	98-00242[c] n=18 Batch PDV03-01A1	00-00152[d] n=8 Batch PDV05-01A1	99-00291[e] n=24 Batch PDV03-01A1	Pooled n=58
T_{max} (h)	5.0[a]	9.5[a]	8.5[a]	10.0[a]	9.0[a]
C_{max} (ng/mL)	13.1 (5.4)	12.3 (6.6)	13.1 (3.3)	14.7 (8.2)	13.5 (6.8)
AUC (ng.h/mL)	227 (90)	224 (120)	210 (58)	225 (114)	223 (105)
$T_{\frac{1}{2}}$ (h)	10.3 (4.7)	10.0 (2.6)	7.2 (1.6)	8.0 (1.9)	8.8 (2.8)

[a] Median value
[b] report no 98-00986 (V70 P58)
[c] report no 98-00242(V64 P52)
[d] report no 00-00152(V87 P47)
[e] report no 99-00291(V74 P43)

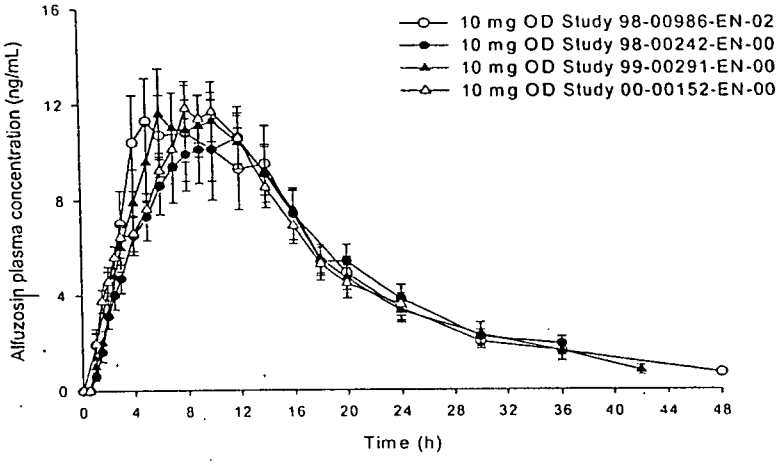


Figure 6 - Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles in Healthy Middle-aged Male Volunteers After a Single Administration of 10 mg Alfuzosin Extended-Release Tablet

The pharmacokinetics of 10 mg ER tablets appears to be similar across the different studies. The inter subject variability associated with the PK parameters is about 50% for both Cmax and AUC. However the variability in elimination half-life is less (approximately 30%). Thus absorption of ER tablets is more variable than the elimination, consistent with most controlled release formulations.

Multiple dose PK

Mean plasma concentrations of alfuzosin pooled from two studies with repeated administration of 10 mg ER tablets is given below.

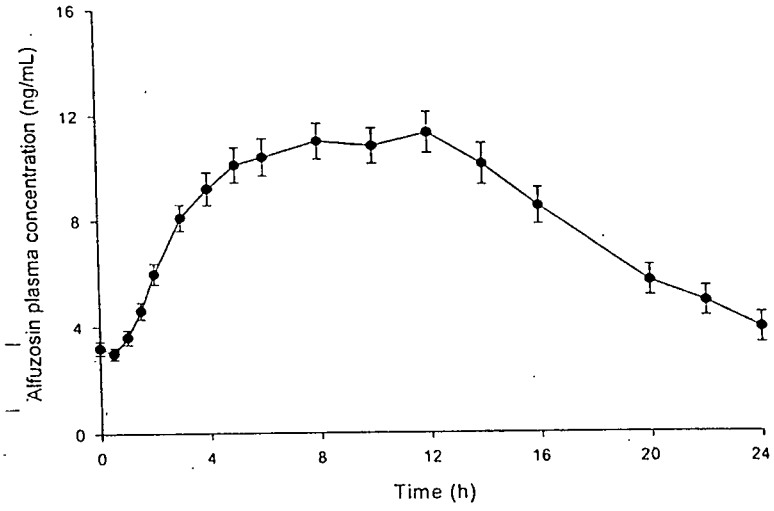


Figure 7- Mean (SEM) Alfuzosin Plasma Concentration-Time Profiles Obtained on Day 5 in 42 Healthy Middle-aged Male Volunteers After a Repeated Administration of Alfuzosin 10 mg Extended-Release Tablet [Report nos. 97-00926 and 00-00025]

The plasma alfuzosin levels reached steady state after two days of dosing and the levels at steady state were 1.6-1.7 times higher than after single dose administration.

Pharmacokinetics of enantiomers

Pharmacokinetic profile of enantiomers was determined following multiple dosing of 10 mg ER tablets for 5 days in 16 healthy middle aged volunteers. The plasma concentrations of R-isomer were higher than those of S isomer with AUC ratio of 1.35. The apparent elimination half-life of R isomer was slightly higher than that of S isomer.

Sponsor reported that the R and S enantiomers of alfuzosin have similar affinity to α_1-adrenoceptors. Both enantiomers are equipotent in inhibiting contractile response of smooth muscles in isolated trigone and urethra (see preclinical review). Therefore, sponsor measured only racemate in all other pharmacokinetic studies.

Pharmacokinetics in patients