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

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

An analysis by the primary medical officer of the clinical trial database revealed four deaths which were clearly unrelated to drug. There was no signal related to heart rate and rhythm disorders. The incidence of adverse events was dose related and different from placebo but mostly related to presumed "vasodilatory" episodes. For example, there was 1/366 (0.3%) cases of syncope in the 7.5 mg dose, 3/690 (0.4%) at the 10 mg dose and 7/707 (1.3%) in the 15 mg dose.

Because of the apparent discrepancies between various QT data analyses presented by the sponsor, a consultation was requested from the Division of Cardiorenal Drug Products

The review of the pre-clinical studies by DCRDP concluded: "Alfuzosin's in vitro elecrophysiologic effects suggest a low risk for repolarization abnormalities. However, while effects on HERG current suggest a low risk, alfuzosin's potency was likely underestimated, and some drugs, e.g. sotalol, and quinolone and macrolide antibiotics weakly inhibit HERG yet prolong QT interval and induce torsade in humans. Additionally, human metabolites were not evaluated." **The primary conclusion of the review of the clinical studies was that "the drug appears to be increasing the corrected QT by perhaps 10 msec."**

DCRDP does not agree with the sponsor's argument that the analysis of the Holter monitor data is superior to the QTcB or QTcF. Finally, although the reported arrhythmia events in Europe since 1987 is small, the consultant believes that "it is hard to know how reassuring this lack of event reporting is."

4.0 RISK/BENEFIT EVALUATION

The evaluation of risk for alfuzosin should take in to account the risk related to the α-antagonist class adverse reactions and risk related to possible cardiac repolarization abnormalities. The analysis of all adverse events in the NDA data base appeared to indicate that alfuzosin's profile is similar to other approved drugs in this class [Hytrin (terazosin) Cardura (doxazosin), Flomax (tamzolosin)] particularly with regard to adverse events related to "vasodilatory" effects (dizziness, syncope, hypotension).

In addition to the evaluations of the routine adverse events and laboratory studies, alfuzosin was aggressively evaluated for QT prolongation. The evaluation involved the following sets of information:

- **In vitro studies to evaluate alfuzosin's potential to disturb cardiac repolarization:**The pharmacology consultant, Dr. John Keorner preliminarily concluded that alfuzosin had a low risk for repolarization abnormalities however information should be provided to support that conclusion

- **Clinical pharmacology studies on alfuzosin's effect on QT interval:** The DCRDP and the sponsor came to disparate conclusions after evaluating the same data regarding alfuzosin's propensity to effect cardiac repolarization in an adverse manner. This dispute is discussed in section 3.1

- **Clinical signals of cardiac repolarization abnormalities in the NDA safety database:** There does not appear to be a signal that would indicate cardiac repolarization abnormality related adverse events after analysis of the NDA database. One could argue that events such as syncope, dizziness and hypotension could be the result of cardiac arrhythmias but they are buried in the noise of the known α-antagonist effects of alfuzosin.

- **Pharmacokinetic studies on alfuzosin:** Renal failure and 3A4 inhibitors may have enough of a effect on the plasma concentration of alfuzosin to reduce the therapeutic index if the effect on QT prolongation is, in fact, dose related.

- **Post-marketing information from countries in which various forms of alfuzosin is registered:** The sponsor argues that there is no post-marketing data in other countries to indicate a increased risk of alfuzosin to causing cardiac arrhythmia. In addition, the sponsor argues, alfuzosin has not been removed from any market. However, it would be very difficult epidemiologically to dissect out information that would indicate cardiac arrhythmia and sudden death caused by alfuzosin in a population of mostly older men on a drug that induces hypotension and it's concomitant adverse events.

5.0 RISK MANAGEMENT ASSESSMENT

Alfuzosin would be the fourth drug in its class to be marketed for the symptoms of BPH. It does not appear to have any efficacy advantage over the already marketed drugs. According to DCRDP there is a signal that alfuzosin has a non-zero risk for causing sudden death secondary to cardiac arrhythmia.

The sponsor may argue that the other alpha-blockers on the market have a similar risk but the risk is not obvious because evaluation of QT prolongation of these products has not been aggressive. However, since the risk of alfuzosin is unknown at best and there is no efficacy advantage, the optimal risk management plan is to prevent marketing of alfuzosin until further information is obtained that would indicate that alfuzosin is at least no more risky than the currently marketed products.

6.0 CONCLUSION AND REGULATORY RECOMMENDATION

I would recommend that alfuzosin is approvalable because of evidence that it causes a dose related prolongation of QT interval and therefore, may adversely affect cardiac repolarization.

This deficiency could be addressed by additional evidence, including clinical pharmacology studies that support the sponsor's contention that alfuzosin does not adversely affect cardiac repolarization.

Daniel A. Shames MD
Deputy director, DRUDP, CDER

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/s/

Daniel A. Shames
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MEDICAL OFFICER

NDA 21-287

Supervisory Medical Officer's Memorandum

From: George S. Benson, MD
Medical Team Leader, DRUDP

To: Flo Houn, MD
Office Director, ODE-3

Through: Donna Griebel, MD
Deputy Director, DRUDP

Date: June 5, 2003

Regarding: Recommendation for regulatory action – NDA 21-287
(complete response to "approvable" action)

Sponsor: Sanofi-Synthelabo Research

Date submitted: NDA originally submitted on December 8, 2000
Approvable action taken October 5, 2001
Complete response to approvable action submitted on December 12, 2002

Drug product: Trade name: Uroxatral (approval pending)
Established name: alfuzosin hydrochloride

Dosage: 10 mg extended release tablet
Route: oral
Dosage regimen: one 10 mg tablet by mouth daily

Drug class: $alpha_1$-adrenergic blocker
Proposed indication: "treatment of the signs and symptoms of benign prostatic hyperplasia"

Related IND's: IND [redacted]

Table of Contents

1. Materials used in conducting the review:

In addition to the material reviewed from the original NDA submission, the following items related to the "complete response to approvable action" were reviewed:

A. Study INT 5056 (ketoconazole study)
B. Study PDY 5105 (QT study)
C. Draft label
D. Draft patient package insert
E. Updated Integrated Summary of Safety
F. Dr. Marcea Whitaker's primary medical review of Trials INT 5056 and PDY 5105, updated Integrated Summary of Safety, 3-month safety update, and 15-day safety reports.
G. Cardiorenal consultation regarding the effect of alfuzosin on the QT interval
H. DMETS and DDMAC proprietary name review consultation
I. DDMAC and DSRCS review of proposed Patient Package Insert

2. Executive Summary

Recommendation:

In my opinion, 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 risks associated with the use of this drug are acceptable and can be adequately managed with labeling.

The reasons for this decision are as follows:

A. The clinical effectiveness of alfuzosin (defined by the appropriate endpoints of American Urologic Association Symptom Index and maximum urinary flow

rate) was demonstrated in three placebo-controlled trials in an appropriate patient population.
B. The overall clinical safety database, collected in adequate controlled and uncontrolled human trials, demonstrates an adverse event profile consistent with the drug's pharmacological effect (alpha-adrenergic blockade) with no other significant safety signals noted.
C. Following the initial review of NDA 21-287, an "approvable" action was taken on October 5, 2001. Two deficiencies were noted:

i) 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."
ii) "Additional pharmacokinetic and pharmacodynamic studies are necessary to determine the effect of maximum doses of inhibitor of CYP450 3A4 isoenzyme (e.g. ketoconazole) on QTc interval."

In the complete response to "approvable" action, the sponsor submitted the results of Trial PDY 5105 to address the QT issue and Trial INT 5056 to address the CYP450 3A4 issue.

Trial PDY 5105 (QT study) is a randomized, double-blinded, placebo-controlled, positive drug (moxifloxacin) controlled, 4-way crossover study which evaluated the effect of alfuzosin 10 and 40 mg, moxifloxacin 400 mg, and placebo on the QT interval. Data were collected by both Holter monitor and 12-lead EKG. 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. Secondary endpoints were the corrected QT interval variables using the following formulas: QTcB= QT/RR1/2 (Bazett), QTcF= QT/RR1/3 (Fridericia), QTcN = QT/RRB (population-specific), and QTcNi = QT/RRBi (subject-specific).

Using the Holter monitoring method (the sponsor's primary endpoint), the mean increase in QT versus placebo ranged from 0.1 to 0.4 msec for alfuzosin 10 mg and from 2.0 to 2.9 msec for alfuzosin 40 mg. Using the 12-lead ECG method, the QTc (Fridericia) showed that the mean increase in QT versus placebo was 4.9 msec for alfuzosin 10 mg and 7.7 msec for alfuzosin 40 mg, the QTcN mean increase in QT versus placebo was 1.8 msec for alfuzosin 10 mg and 4.2 msec for alfuzosin 40 mg, and the QtcNi mean increase in QT versus placebo was 1.8 msec for alfuzosin 10 mg and 4.3 msec for alfuzosin 40 mg.

These 12-lead ECG data determining the relationship between corrected QT and RR intervals for the various methods of correction for all subjects on placebo were also analyzed by the Division's clinical pharamcologists. When the slopes of QT versus RR relationship for each individual patient are plotted versus RR before correction, both the QTcN and the QtcNi corrections appear to more accurately correct the QT interval for heart rate than does the Fridericia

correction formula. Although the most appropriate correction method is not known, when all of the data from the various correction methodologies are considered, the increase in QT seen with alfuzosin 10 is < 5 msec and with alfuzosin 40 mg is < 5 msec for all except Fridericia and Bazett's formulae. (See full review of Trial PDY 5105 in section 4 of this review.)

I believe that the risk of QT interval prolongation is low to very low and acceptable based on the following:

i) The mean QTcN increase over placebo is 1.8 msec for alfuzosin 10 mg and 4.2 msec for alfuzosin 40 mg and the mean QtcNi increase over placebo is 1.8 msec for alfuzosin 10 mg and 4.3 msec for alfuzosin 40 mg. There does appear to be a dose related increase in QTc. The FDA "Preliminary Concept Paper on The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrythmic 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 inconseqeuntial, 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 Torsades 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." Based on the above, I believe that the torsadogenic risk is low to very low.

ii) For alfuzosin, dose of drug above the serum levels reached with maximum metabolic inhibition were reached with the 40 mg alfuzosin dose. In Trial INT 5056, repeated administration of ketoconazole 400 mg daily for 8 days increased the Cmax and AUC of alfuzosin (10 mg single dose) by 2.3 and 3.2 fold, respectively. The pharmacokinetics of alfuzosin are linear.

iii) Outlier analyses showed no patient with either 10 or 40 mg of alfuzosin had a >60 msec increase or a QTc value of > 450 msec in either QTc Fridericia, QTcN, or QtcNi.

iv) No signal for arrhythmogenic (torsadogenic) risk was seen in the controlled and uncontrolled clinical trials.

v) No signal for a torsadogenic risk was found in post-marketing studies and the WHO data base. The post-marketing experience is large. Although I understand the limitations of this analysis, these data are somewhat reassuring.

vi) Although no definitive QT studies are available for other drugs in this class, none of the currently approved alpha1-blockers are known or suspected to prolong the QT interval.

vii) In phase 3 trials, alfuzosin was shown to be a clinically effective drug for the treatment of symptoms of benign prostatic hyperplasia. This is a significant public health problem and I believe that the risk/benefit associated with alfuzosin is acceptable.

Trial INT 5056 (ketoconazole study) evaluated the effect of ketoconazole 400 mg daily administration for 8 days on the pharmacokinetics of alfuzosin (10 mg single dose). Repeated administration of ketoconazole increased the Cmax and

AUC of alfuzosin by 2.3 and 3.0 fold, respectively. The kinetics of alfuzosin are linear. The highest serum levels achieved with potent CYP 3A4 inhibition were, therefore, below the serum concentrations obtained with the 40 mg alfuzosin dose utilized in the QT study.

Because of the dose related prolongation in the QT interval and controversy concerning the various correction methods used for drugs which increase heart rate, this issue was brought to an Advisory Committee (CardioRenal Advisory Committee, May 29, 2003).

Summary of Advisory Committee meeting:

The Advisory Committee was unable to determine which QT correction method most accurately estimated QTc in this data set. The Committee believed (vote of 12 yes, 1 no, and 1 abstain) that Trial PDY 5105 was "adequately designed to evaluate the drug's effect on QT." The Committee voted unanimously (vote of 0 yes and 14 no) to the question "Do these data demonstrate a clinically relevant QT prolongation associated with alfuzosin?" Although the committee believed that there was no "clinically relevant effect on the QT interval," several committee members believed that information concerning the effect of alfuzosin on the QT interval and a description of patients who might be at risk for Torsades be included in labeling.

Summary of most significant proposed labeling changes:

In my opinion, several significant changes should be made to the sponsor's draft label:

i) Information concerning the effect of alfuzosin on the QT interval should be added to the clinical pharmacology section.

ii) The sponsor has proposed a contraindication to the use of alfuzosin in patients with moderate and severe hepatic insufficiency. Because alfuzosin has not been evaluated in patients with mild hepatic insufficiency, I agree with the clinical pharmacology reviewer that alfuzosin should be contraindicted in all patients with hepatic insufficiency.

iii) Because potent CYP 3A4 inhibitors increase the Cmax and AUC of alfuzosin by 2.3 and 3.0-fold respectively, alfuzosin should be contraindicated in patients taking these drugs including ketoconazole and protease inhibitors. A precaution should be added to the label concerning moderate CYP 3A4 inhibitors including diltiazem. The clinical pharmacologist has made both of these recommendations for labeling and I agree.

iv) Since systemic exposure of alfuzosin is increased by 50% in patients with renal insufficiency, the clinical pharmacologist recommended that a precaution

should be added to the label concerning the use of alfuzosin in this group of patients and I agree.

3. **Clinically relevant issues from other discipline's reviews**

3.1 Clinical pharmacology and biopharmaceutics

In his review of the clinical pharmacology data submitted with the original NDA, the clinical pharmacology reviewer found the material submitted by the sponsor to be "acceptable," but specifically noted the following items which will require changes to the draft label:

A. In patients with moderate to severe hepatic impairment, the systemic exposure to alfuzosin is increased by 3 to 4-fold. Such exposure would be predicted to be associated with an unacceptably high incidence of adverse events associated with orthostatic hypotension. In the draft label, the sponsor proposes a contraindication in patients with moderate to severe hepatic impairment and a precaution in patients with mild hepatic impairment to "consider the risks and benefits of administering alfuzosin in this population." The pharmacokinetics of alfuzosin, however, have not been studied in patients with mild hepatic insufficiency. The clinical pharmacology reviewer believes that, since patients with mild hepatic insufficiency have not been specifically studied, that alfuzosin should be contraindicated in patients with all degrees of hepatic insufficiency. The review team changed the proposed contraindication in the draft label to include all degrees of hepatic insufficiency and I agree.

B. The exposure to alfuzosin is increased by up to 50% in patients with mild, moderate, and severe renal impairment. The clinical pharmacology reviewer comments that since a dose-related increase in vasodilatory adverse events was noted at a dose 50% higher than the recommended dose of 10 mg/day that "the label should recommended a caution when the drug is administered in patients with renal impairment." The review team changed the draft label to include this precaution and I agree.

C. Potent CYP 3A4 inhibitors such as ketoconazole (400 mg/day) increase the Cmax and AUC of a single 10 mg dose of alfuzosin by 2.3 and 3.0-fold, respectively. For this reason, the clinical pharmacology reviewer recommends a contraindication for "potent inhibitors of CYP 3A4" and that "caution should be exercised" when alfuzosin is co-administered with moderate inhibitors of CYP 3A4. The review team added these recommendations to the draft label and I agree.

3.2 Non-clinical pharmacology/toxicology:

No additional non-clinical pharmacology/toxicology data were submitted in the complete response to approvable action.

In her final review of the original NDA, the toxicology reviewer found the NDA to be overall "approvable" and noted no clinically relevant deficiencies. Preclinical toxicity was only seen at large multiples of the proposed human exposure and was predominantly related to the drug's pharmacological action.

Although the 2-year carcinogenicity study in mice did not reveal any treatment related tumors, "the doses tested in female mice may not have constituted a maximally tolerated dose." This statement was added to the draft label and I agree with this.

3.3 Biometrics

No additional statistical data were submitted in the complete response to approvable action.

The statistical review of the original NDA submission concludes that "Uroxatral 10 mg once daily prolonged-release formulation was statistically significantly ($p<.01$, adjusting for multiple comparison) superior to placebo in improving the prostate signs and symptoms (IPSS and PFR) in BPH patients." Thus, "the application demonstrates evidence in support of Uroxatral 10 mg OD in the treatment of the signs and symptoms of BPH."

3.4 Chemistry, manufacturing, and controls:

No additional chemistry, manufacturing, and controls data were submitted in the complete response to approvable action.

The chemist's review of the original NDA submission stated that "NDA 21-287 is recommended for approval from the CMC perspective."

Of note, the reviewer believed that there was no difference between and debossed tablets under both room temperature and accelerated conditions during the 6-month stability studies. Thus, the expiration date for the drug product (debossed tablets) in all container/closure systems was set at 24 months based on the stability data for the plain tablets.

At the time of completion of this memorandum, the sponsor has not decided on a tradename for alfuzosin hydrochloride. The tradename Uroxatral was previously approved. The sponsor, however, submitted the tradenames [redacted] for review and consideration. DMETS did not recommend the tradename [redacted] because of safety concerns of confusion of this tradename with other "look-alike/sound alike" products. DDMAC did not recommend the tradename [redacted] because they consider it to be

"overly fanciful." The Division agrees with the DMETS/DDMAC recommendations. The sponsor was notified of this decision. As of June 2, 2003, the sponsor had not decided which tradename they preferred. Uroxatral is currently being re-reviewed by DMETS to determine whether there are safety concerns with this tradename with regard to tradenames which have been approved since their last review of Uroxatral. Chemistry recommends that the NDA be approved pending satisfactory container mock-up labels.

4. Review of QT background, QT (Trial PDY 5105) and ketoconazole (Trial INT 5056) data submitted with the "complete response" to approvable action.

Background: In the original NDA, the 120 Day Update of Integrated Summary of Safety (received on April 6, 2001) contained 5 study reports involving studies to determine the effect of alfuzosin on the QT interval.

The following QT study reports and information were included in the 120 day safety update:
1. Study report for 00-00312-EN-00 ("Effects on the action potential of piglet Purkinje fibers")
2. Study report for 00-00329-EN-00 ("Effects on the herg channel stably expressed in mammalian cell line. Comparison with tamsulosin, doxazosin, prazosin, and terazosin")
3. Study report for INT4285 ("Effect of ketoconazole on alfuzosin blood levels")
4. Study report for PKD4532 ("Effect of supratherapeutic doses of alfuzosin on the ECG")
5. Study report for PCALF96US01 ("Manual reading of QT intervals of ECG from PCALF96US01")

These 5 studies were reviewed as well as the "Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization" included in Addendum 16.1. during the initial NDA review. In PKD4532 (which studied placebo and 10, 20, and 40 mg of alfuzosin), the QTcB was prolonged greater than 60 msec in 2 of 24 placebo patients, in 3 of 24 10 mg alfuzosin patients, in 4 of 24 20 mg alfuzosin patients, and in 4 of 24 40 mg alfuzosin patients. None of the patients had QTcF prolongation of > 60 msec.

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

(Table 1). The consultant concluded: "Heart rate, QTcB, and QTcF are significantly increased from baseline for the 20 and 40 mg doses compared to placebo."

The mean changes in heart rate, QT, QTcB, and QTcF for study 4532 are shown in Table 1.

Table 1. Statistical Analysis of Changes in ECG Parameters from Baseline: Mean (One-sided 95% CI, Upper Bound) Average Difference from Placebo over 0.5 to 24 Hours: Study PKD4532.

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

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

The CardioRenal consultant believed that "the drug appears to be increasing the corrected QT by perhaps 10 msec." The sponsor believed that the Bazett and Fridericia correction formulae over-correct for QTc and that the Holter monitor method more accurately corrects the QT for heart rate than do the other correction methods. The Division believed that there was not sufficient evidence to rule out an effect of alfuzosin on the QT interval and concluded that the "application lacks adequate information, including clinical pharmacology data, to determine whether the product is safe for use because alfuzosin may increase QTc interval" and that "QTc must be measured using an FDA agreed upon validated method."

A. QT Trial PDY 5105: In response to the approvable letter, the sponsor submitted the results of QT Trial PDY 5105. The primary objective of this study was to assess the effect on the QT interval using Holter-monitoring following alfuzosin 10 mg, 40 mg, placebo, and moxifloxacin 400mg. The proposed to be marketed dose of alfuzosin is 10 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 400mg at Cmax using the 12-lead ECG; 2) to document systemic exposure after single doses of alfuzosin 10 mg, 40 mg, and moxifloxacin 400mg; and 3) to assess safety.

The protocol was a single-center, 4 way-crossover, randomized, double-blinded, double-dummy, placebo-controlled study that enrolled 48 healthy Caucasian men between the ages of 18 and 50 years. Therapeutic (10mg) and supratherapeutic (40mg) doses of alfuzosin were evaluated and the QT interval was measured with both 12-lead ECGs and Holter monitors. Moxifloxacin was used as a "positive control." Subjects were randomized to one of four sequences

of drug administration in chronological order of entry into the 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. The duration of the study was 8 weeks.

The Agency concurred with the single dose trial design. The half-life of alfuzosin extended release is approximately 9 hours. Steady state levels, achieved after two days of dosing, are 60-70% higher than levels achieved with a single dose. The inclusion of a dose 4 times higher than that planned for marketing in the clinical trial was intended to cover plasma levels that might be achieved by either CYP 3A4 inhibition or continuous daily dosing. It is possible, however, that this element of the study design would not capture steady state effects in the compartment of interest, the heart, and there is a possibility that clinically relevant QT prolongation could be missed with a single dose study design. The CardioRenal Advisory Committee believed that the trial design was adequate to evaluate the effect of alfuzosin on the QT interval.

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. Standard 12-lead EKG's were performed on Day 1 at T0, T4, and T12, Day 2 at T0 (3successive ECG at 5 minute intervals) and at T2, T4, T6, T7, T8, T9, T10, T11, and T12 and on Day 3 at T0, T2, T4, T6, T7, T8, T9, T10, T11, and T12 (the Tmax of alfuzosin ER is 7 to 11 hours).

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. Secondary endpoints were the corrected QT interval variables using the following formulas: QTcB= QT/RR1/2 (Bazett), QTcF= QT/RR1/3 (Fridericia), QTcN = QT/RRB (population-specific), and QTcNi = QT/RRBi (subject-specific). The agency agreed with the endpoints and to evaluate the QT effects by considering all QT correction methods.

1. Holter methods: The Holter device used was a 3-lead Holter digital device [redacted]. Data were processed by a single expert cardiologist in a blinded manner through the use of validated software, WinAtrec® and occurred in the following 3 steps. (96-98% 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 ($n \geq 50$) 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).

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.

Heart rate correction formulae used for QT were the Bazett's correction (QTcB=QT/RR1/2), the Fridericia correction (QTcF=QT/RR1/3), a population-specific correction formula (QTcN=QT/RRB), and a subject-specific correction formula (QTcNi=QT/RRBi).

3. Holter-monitoring results:

The results of the QT changes using the Holter-monitoring method are shown in Table 2.

Table 2. Holter-monitoring method: QT change comparing alfuzosin 10mg, 40mg 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

4. 12-lead ECG results:

12-lead EKG results for alfuzosin and moxifloxacin with various correction formulae are shown in Tables 3 and 4. (Heart rate increased by 5.2 and 5.8 bpm over placebo at the 10 mg and 40 mg doses of alfuzosin at Cmax.)

Table 3. 12-lead ECG: Change from baseline to Cmax: Alfuzosin 10mg and 40mg 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

Table 4 - 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

5. Outlier analysis:

The outlier analysis based on EKG "potential clinical significant abnormality" is shown in Table 5. 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.

Table 5.

Table (15.4.5) 2 - 12-lead ECG: Summary of counts of post-baseline PCSAs (by treatment analysis) for ECG parameters, analysis with T0 as baseline for each treatment group, by the tangent method

Electrocardiogram PCSA Definition	Subjects With at Least 1 PCSA (By Treatment)/ Evaluable Subjects [1]			
	Placebo (N =45) [2]	Alfuzosin 10 mg (N = 44) [2]	Alfuzosin 40 mg (N = 45) [2]	Moxifloxacin (N = 44) [2]
HR ≤40 bpm & decr. ≥20 bpm versus B	0/45	0/44	0/45	0/44
HR ≥100 bpm & incr. ≥20 bpm versus B	0/45	1/44	0/45	0/44
431 ≤QTcB ≤450 msec	1/45	3/44	13/45	5/44
QTcB > 450 msec	2/45	1/44	3/45	1/44
QTcB > 500 msec	0/45	0/44	0/45	0/44
431 ≤QTcF ≤450 msec	3/45	0/44	6/45	5/44
QTcF > 450 msec	0/45	0/44	0/45	0/44
QTcF > 500 msec	0/45	0/44	0/45	0/44
431 ≤QTcN ≤450 msec	3/45	4/44	5/45	7/44
QTcN > 450 msec	0/45	0/44	0/45	0/44
QTcN > 500 msec	0/45	0/44	0/45	0/44
431 ≤QTcNi ≤450 msec	3/45	4/44	5/45	7/44
QTcNi > 450 msec	0/45	0/44	0/45	0/44
QTcNi > 500 msec	0/45	0/44	0/45	0/44
30 ≤delta QTcB ≤60 msec	5/45	7/44	17/45	14/44
delta QTcB > 60 msec	0/45	1/44	3/45	0/44
30 ≤delta QTcF ≤60 msec	0/45	1/44	9/45	3/44
delta QTcF > 60 msec	0/45	0/44	0/45	0/44
30 ≤delta QTcN ≤60 msec	0/45	0/44	2/45	1/44
delta QTcN > 60 msec	0/45	0/44	0/45	0/44
30 ≤delta QTcNi ≤60 msec	0/45	0/44	2/45	1/44
delta QTcNi > 60 msec	0/45	0/44	0/45	0/44

pgm=SL7704991/PDY5105/CS2/BS/PGM_RPT/ecgrw_aux out=iqesa1.ged 03DEC2002 - 11:36)

PCSA = Potentially Clinically Significant Abnormality (Version 2.0 - April 2002);
decr./incr. = decrease/increase; B = Baseline

[1] Total count of subjects exposed to study drugs (i.e., all subjects who took at least 1 dose of study drug).

[2] Count of subjects evaluable for a given parameter.

Ref.: Appendix 16.2.9.2.2.1

Ten subjects in the placebo, alfuzosin 10 mg, and alfuzosin 40 mg groups had potential clinical significant abnormality (PCSAs - prolonged) of QTcB or delta QTcB. 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 alfuzosin administration.
One subject had QTcB over 450 msec and delta QTcB over 60 msec after 10 mg alfuzosin administration.

Three subjects not treated with alfuzosin had QTcB over 450 msec (1 after moxifloxacin 400 mg administration and 2 after placebo administration).

With regard to QTcF, no patient had a value >450 msec in any treatment group. No patient had a delta QTcF of > 60 msec and 13 patients had a delta QTcF of between 30 and 60 msec (1 with alfuzosin 10 mg, 9 with alfuzosin 40 mg, and 3 with moxifloxacin).

With regard to QTcN, no patient on either dose of alfuzosin had a QTcN >450 msec or a delta QTcN > 60 msec. No patient on either dose of alfuzosin had a QTcNi > 450 msec or a delta QTcNi > 60 msec.

6. Safety data from alfuzosin controlled studies which may signal a risk of QT prolongation

Deaths: There were four deaths in the four major studies submitted to establish the efficacy of alfuzosin and their extension phases. One patient died of an infection following head trauma, two died of cancer (one colon and one stomach), and one died of pneumonia. (One thousand six hundred ninety patients completed one of the three month efficacy studies (1012 took alfuzosin 678 placebo) and 645 patients had taken a dose of 10 mg alfuzosin or higher dose for one year).

Heart rhythm disorders (Table 6):

Table 6. Number of Patients with Heart Rate and Rhythm Disorders in Double-Blind Phase of Major Efficacy Trials

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

In the double-blind and extension phases of the Phase 3 trials combined, there were 130 serious adverse events in 1690 patients (1012 on alfuzosin and 678 on placebo). The majority of these serious adverse events were not thought by the investigator to be related to study medication. There were 10 reports of angina pectoris (0.6%), 3 (0.2%) cerebrovascular disorder, 1 (0.1%) substernal chest pain, 3 (0.2%) coronary artery disorder, 2 (0.1%) fall, 1 (0.1%) hepatocellular damage, 4 (0.2%) myocardial infarction, and 13 (0.8%) syncope. Of these 13 cases of syncope, 1 (0.3%) occurred at the 7.5 mg dose (n=366), 3 (0.4%) at the 10 mg dose (n=690), and 9 (1.3%) at the 15 mg dose (n=707).

7. Relevant post-marketing data to detect a signal for risk of Torsades for alfuzosin:

The sponsor has developed three alfuzosin-containing oral dosage regimens that are marketed 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. Alfuzosin extended release (ER) was first approved in Europe in 1999 and is the intended formulation to be marketed in the United States. Since the first launch of alfuzosin 2.5 mg IR formulation in 1988 until September 30, 2002, the estimated number of therapy-days of alfuzosin (all formulations) is

Adverse event data for alfuzosin from the W.H.O. database is shown in Table 7.

Table 7. Alfuzosin: W.H.O. DATA

A search on 4/2/03 of the World Health Organization's Adverse Event database provided the following data for alfuzosin

Adverse Event	#	Adverse Event	#	Adverse Event	#
Angina pectoris	*17*	**Death**	*2*	*Myocardial infarction*	*16*
Angina pectoris aggravated	*5*	*ECG abnormal specific*	*1*	*Myocardial ischaemia*	*1*
Arrhythmia	*7*	*Extrasystoles*	*2*	*Palpitation*	*30*
Arrhythmia atrial	*1*	*Fibrillation atrial*	*13*	QT prolonged	***0***
Blood pressure fluctuation	*1*	*Fibrillation ventricular*	*3*	*Sudden death*	*3*
Bradycardia	*9*	*Heart murmur*	*1*	*Syncope*	*57*
Cardiac arrest	*1*	*Hypertension*	*5*	*Tachycardia*	*14*
Cardiac failure	*2*	*Hypertension aggravated*	*1*	*Tachycardia supraventricular*	*1*
Cardiac failure left	*2*	*Hypertension intracranial*	*1*	Torsade de Pointes	***0***
Cardiac failure right	*1*	*Hypotension*	*61*	*Vasodilation*	*1*
Convulsions	*1*	*Hypotension postural*	*43*		

B. **Ketoconazole Study (INT 5056)**

Repeated administration of ketoconazole 400 mg daily for 8 days increased the Cmax of alfuzosin (10 mg single dose) by 2.3-fold and the AUC by 3.0-fold. Terminal half-life increased by 1.16-fold.

Conclusions regarding QT (PDY 5105) and ketoconazole (INT 5056) studies:

Ketoconazole (400 mg daily) increases the Cmax and AUC of alfuzosin (10 mg single dose) by 2.3 and 3.0-fold respectively. This worst-case scenario by a potent CYP 3A4 inhibitor demonstrates that the maximal plasma levels achieved by metabolic inhibition are lower than the maximal dose of alfuzosin (40 mg) utilized in the QT study.

Because of the reasons listed in the Executive Summary (page 4 of this review), I believe that the arrhythmogenic risk of alfuzosin is low. There does appear to be a dose related increase in QTc, but, by QTcN, QtcNi, Fridericia, and the Holter methods of correction, is below 5 msec for the 10 mg dose. For the 40 mg dose, the QTc is increased less than 5 msec when correcting by the QTcN, QtcNi, and Holter methods. In my opinion, information concerning alfuzosin's effect on the QT interval should be included in the label and patient package insert

5. Summary Comments Pertaining to Efficacy

No new efficacy data were included in the complete response to approvable action.

I believe that the results of the three adequate and well-controlled Phase 3 clinical trials demonstrate that alfuzosin 10 mg ER tablets given once/day are effective in treating the signs and symptoms of BPH.

The primary efficacy endpoints in the trials were change from baseline in the International Prostate Symptom Score (IPSS) and the peak urinary flow rate (Q_{max}). The IPSS is identical to the American Urologic Association Symptom Index (AUASI). These two endpoints are currently recommended for all drug studies dealing with the symptoms of BPH. (In ALFORTI, improvement in Qmax was a secondary endpoint.) In ALFOD, the 7.5 mg ER dose was not significantly superior to placebo. Because the dose of alfuzosin (ER) was only 7.5 mg in trial ALFOD, this trial was not included in the efficacy analysis (Table 8).

Table 8. 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	1.5 mg tid **10 mg/day** placebo	**10 mg/day**
ALFUS	**157 Uroxatral** 149 drug (15 mg) 158 placebo	**10 mg/day** 15 mg/day placebo	15 mg/day
ALFOTAM	**145 Uroxatral** 142 drug (15 mg) 142 placebo 149 tamsulosin	**10 mg/day** 15 mg/day placebo 0.4 mg/day	15 mg/day

With respect to the IPSS, the mean decreases in total score ranged from –3.6 to –6.9, with a net improvement of approximately 2 points relative to placebo that was consistent across the 3 studies (Table 9).

Table 9. Changes in IPSS scores in the 3 pivotal trials.

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

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

The changes in peak flow rate (Q_{max}) (cc/sec) are shown in Table 10.

Table 10. Changes in Qmax (cc/sec) in the 3 pivotal studies

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

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

Improvement in both IPSS and Q_{max} were achieved by the first post-baseline visit (4 weeks) and the effect was maintained throughout the remainder of the 12 week double-blind treatment phase. The improvement in IPSS is clinically and

statistically meaningful. The change is Q_{max} is modest but statistically significant in ALFUS and ALFORTI and trends toward effectiveness in ALFOTAM. There is minimal data directly comparing alfuzosin to other alpha$_1$-adrenergic receptor blocking agents. The improvements in IPSS and Qmax, however, appear similar to those reported for the other alpha1-adrenergic blocking agents approved for the treatment of symptoms of benign prostatic hyperplasia.

6. Integrated review of safety

Review of safety data submitted with the original NDA. A review of the safety update is included on page 24 of this review.

A. Introduction and Patient Exposure

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

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

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

The number of patients (by treatment group) in the double-blind phase of the 4 pivotal trials are shown in Table 11.

Table 11. Number of Patients in Twelve-Week Double-Blind Portion in 4 Pivotal Studies Combined

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

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

Cardiovascular (vasodilatory) adverse events:

The primary safety concern of alpha1-adrenergic blocking agents is hypotension and the related cardiovascular symptoms of dizziness and syncope.

The number (%) of patients experiencing vasodilatory adverse events in patients in the double-blind phases of the pivotal studies is shown in Table 12.

Table 12. Vasodilatory Adverse Events in Double-Blind Phase of Pivotal Studies

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

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

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

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

Adverse events related to coronary artery disease are shown in Table 13.

Table 13. Number of Patients with Coronary Artery Disease Related Adverse Events

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

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

Serious adverse events: The number of SAE's (including deaths) from the Phase 3 double-blind studies and their extensions is shown in Table 14.

Table 14. Serious Adverse Events From Phase 3 Double-Blind Trials and Their Extension Phases

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

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

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

Overall frequency of adverse events:

The overall frequency of adverse events occurring in >1% of patients in the double-blind portion of the 4 pivotal studies is shown in Table 15.

Table 15. Frequency of Adverse Events Reported by >1% of Patients in Double-Blind Portion of Pivotal Trials.

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	Alfuzosin 10 mg (N=473)	Alfuzosin 15 mg (N=335)
Dizziness	19 (2.8%)	3 (1.5%)	25 (5.3%)	27 (8.1%)
Upper resp. infection	4 (0.6%)	1 (0.5%)	14 (3.0%)	9 (2.7%)
Headache	12 (1.8%)	5 (2.5%)	14 (3.0%)	8 (2.4%)
Flu-like Symptoms	14 (2.1%)	1 (0.5%)	9 (1.9%)	6 (1.8%)
Fatigue	7 (1.0%)	6 (2.9%)	8 (1.7%)	10 (3.0%)
Rhinitis	12 (1.8%)	2 (1.0%)	7 (1.5%)	6 (1.8%)
Impotence	4 (0.6%)	0	7 (1.5%)	4 (1.2%)
Bronchitis	5 (0.7%)	5 (2.5%)	7 (1.5%)	2 (0.6%)
Sinusitis	8 (1.2%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Pain	4 (0.6%)	0	7 (1.5%)	0
Abdominal pain	7 (1.0%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Dyspepsia	7 (1.0%)	3 (1.5%)	6 (1.3%)	1 (0.3%)
Back pain	8 (1.2%)	3 (1.5%)	6 (1.3%)	9 (2.7%)
Inflicted injury	2 (0.3%)	0	6 (1.3%)	3 (0.9%)
Asthenia	5 (0.7%)	0	5 (1.1%)	4 (1.2%)
Constipation	3 (0.4%)	3 (1.5%)	5 (1.1%)	3 (0.9%)
Pharyngitis	2 (0.3%)	2 (1.0%)	5 (1.1%)	3 (0.9%)
Nausea	4 (0.6%)	2 (1.0%)	5 (1.1%)	2 (0.6%)
Somnolence	5 (0.7%)	0	4 (0.8%)	4 (1.2%)
Arthralgia	6 (0.9%)	4 (2.0%)	4 (0.8%)	4 (1.2%)
Diarrhea	10 (1.5%)	2 (1.0%)	3 (0.6%)	3 (0.9%)
Perpheral edema	4 (0.6%)	1 (0.5%)	2 (0.4%)	4 (1.2%)
Hypertension	9 (1.3%)	2 (1.0%)	2 (0.4%)	3 (0.9%)
Urinary tract infection	9 (1.3%)	2 (1.0%)	2 (0.4%)	1 (0.3%)
Arthrosis	2 (0.3%)	3 (1.5%)	2 (0.4%)	0

Long term safety:

In the pooled data from the Phase 3 alfuzosin ER open label extension studies (ALFODEXT, ALFORTIEXT, ALFOTAMEXT, and ALFUSEXT) no previously unidentified adverse events were seen. The incidence of vasodilatory adverse events in the 15 mg group increased in the double-blind plus extension phase compared to the double-blind phase (12.0% versus 9.9%). The incidence in patients treated with the 10 mg dose was essentially the same in the double-blind plus extension phases compared to the double-blind phase (5.8% versus 6.1%). (Table 16) As in the double-blind phase, dizziness was the most frequent vasodilatory adverse event.

Table 16. Patients with at Least One Vasodilatory Adverse Event in the Double-Blind and Double-Blind Plus Extension Phases

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

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

Update of Integrated Summary of Safety

This update provides provided safety information obtained with all 3 formulations from June 1, 2001, to September 30, 2002.The estimated number of therapy-days of alfuzosin (all formulation) until September 30, 2002, is

The sources of safety data in the complete response to approvable (amendment #36) included 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.

No deaths were reported in the completed Phase 1 and Phase III studies or special study. Six deaths were reported in ongoing Phase III studies in acute urinary retention. No CFR's are presented for these studies which remain blinded. Three of these deaths were secondary to cancer (colon, stomach, and kidney), one from pneumonia, one from cardiac arrest (15 days after last study drug intake), and one death NOS (22 days after last study drug intake). In the 15 deaths reported in observational and 2 deaths from spontaneous reporting, no direct causality of drug to the events can be determined.

There were no syncopal episodes reported in the completed, placebo-controlled trials (two phase I and one Phase III trials). Review of the serious adverse events did not reveal any new safety concerns.

Summary of Safety Findings:

The primary safety concern with alpha1-adrenergic blocking agents is hypotension and related symptoms (dizziness and syncope). These symptoms do occur with alfuzosin 10 mg ER, but the incidence is acceptable. Although data concerning direct comparisons with other alpha1 blockers is limited, the

incidence of "vasodilatory" adverse events seen with alfuzosin appear to be similar to other agents in this drug class. The possibility of dizziness, hypotension, and syncope are adequately addressed in the "Warnings" section of the label. A "first-dose" effect does occur with alfuzosin 10 mg ER, but the incidence of adverse events (primarily hypotension and syncope) is low and dose titration does not appear to be warranted.

7. Dosing and administration issues

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

Addendum (June 12, 2003):

Teleconferences with the sponsor were held on June 11, 2003, and June 12, 2003, concerning labeling and tradename issues:

The following conclusions and agreements were reached:

1. The sponsor has chosen Uroxatral as the tradename. There are no outstanding chemistry issues with this decision.
2. The sponsor agreed in principle to a phase 4 commitment to perform a study to evaluate the impact of combining a phosphodiesterase type 5 inhibitor with alfuzosin on QT interval prolongation. The following timeline was accepted by the sponsor:
   a. draft protocol submission within six months of the approval date
   b. study initiation within 12 months of the approval date
   c. submission of the clinical study report within 20 months of the approval date
3. The following label changes were agreed upon:
   a. A section on the effect of alfuzosin on the QT interval was included in the "Clinical Pharmacology" and "Precautions" sections.
   b. A "Contraindication" is included for patients with moderate or severe hepatic insufficiency. A "Precaution" is included for patients with mild hepatic insufficiency.
   c. A "Contraindication" is included for co-administration with potent CYP 3A4 inhibitors, such as ketoconazole, itraconazole, and ritonavir.
   d. A section on patients with mild, moderate, and severe renal insufficiency is included in the "Precautions" section.
4. A section on patients with congentially long QT interval was added to the PPI under "Before taking Uroxatral, tell your doctor:".

The are no further outstanding issues with NDA 21-287.

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

/s/

George Benson
6/12/03 06:08:17 PM
MEDICAL OFFICER
NDA review

Donna Griebel
6/12/03 06:54:27 PM
MEDICAL OFFICER

NDA 21-287

Supervisory Medical Officer's Memorandum

FROM:	Mark S. Hirsch, M.D. Medical Team Leader, HFD-580
TO:	Flo Houn, M.D. Office Director, ODE-3
THROUGH:	Dan Shames, M.D. Deputy Division Director, HFD-580
DATE:	September 26, 2001
REGARDING:	Recommendations for regulatory action - NDA 21-287
SPONSOR:	Sanofi-Synthelabo Research
DATE SUBMITTED:	December 8, 2000
CDER STAMP DATE:	December 8, 2000
DIV DOC ROOM DATE:	December 11, 2000
DRUG PRODUCT:	*Trade name*: Uroxatral™ *Established name*: alfuzosin hydrochloride
DOSAGE: ROUTE: DOSAGE REGIMEN:	10 mg oral tablet take one 10 mg tablet by mouth daily
DRUG CLASS: PROPOSED INDICATION:	alpha-adrenergic blocker "Treatment of the signs and symptoms of benign prostatic hyperplasia."
RELATED INDs:	IND # [redacted] (Sanofi-Synthelabo, BPH)

Table of Contents

1. Materials used in conducting the review:

In arriving at my decision, I conducted a supervisory medical review of the following items:

From the original NDA:

1. Integrated Summaries of Efficacy (Volume 1.305) and Safety (Volume 1.308)
2. Narrative portions of final study reports for Studies ALFORTI (Volume 1.139), ALFUS (Volume 1.162), and ALFOTAM (Volume 1.184).
3. Clinical data summary (Volumes 1.2 and 1.125)
4. Proposed annotated physician package insert
5. Minutes of all previous FDA/sponsor interactions
6. 4-Month Safety Update
7. ISS Update, Addendum 16.1 ("Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization". (Derived from the 4-Month Safety Update)
8. Sponsor's fax dated September 24, 2001, marked "Urgent; For Your Review" .

Draft review by the primary medical officer:

Dr. George Benson's primary medical review of Studies ALFORTI, ALFUS and ALFOTAM, their open-label extensions, the NDA Integrated Summary of Safety (ISS) and the specific studies and summaries of data relevant to cardiovascular safety.

Consultation reports:

1. Dr. David Diwa's (OPDRA) Proprietary Name Review – dated May 18, 2001
2. Dr. MaryAnn Gordon's (Division of Cardio-Renal Drug Products) Consultation – dated August 29, 2001
3. Dr. Constance Lewin's (DSI) Evaluation of the Clinical Site Inspections – dated August 30, 2001
4. Barbara Chong's (DDMAC) Draft Review of Proposed Label – received on August 31, 2001

2. Executive summary:

2.1. Recommendation:

The purpose of this memorandum is to provide the Division Director with the supervisory medical officer's recommendation regarding this request for marketing approval.

In my opinion, while alfuzosin should not be approved for marketing at this time, it should be considered *approvable* pending satisfactory resolution of one clinical issue (#3 below).

The application is considered approvable for the following reasons:

1. Clinical effectiveness, as defined by relief of symptoms and signs of BPH, was demonstrated in three placebo-controlled trials in an appropriate patient population.
2. The overall clinical safety database, as collected in adequate controlled and uncontrolled human trials, demonstrates an adverse event profile consistent with the drug's pharmacological effect (alpha-adrenergic antagonism) with no irregular or extraordinary signals noted.
3. The results of a focused clinical investigation undertaken to define the effect of alfuzosin on cardiac repolarization demonstrated evidence of QT interval prolongation, and thus, a potential for unacceptably severe clinical adverse events in some percentage of patients.

My reason for this decision is that currently, the electrocardiographic data from Study PKD4532 and from the manual re-read of Study PC ALF 96 US01 indicates an effect of alfuzosin on prolonging the QT interval when standard methods of correction for heart rate are used.

The results of Study PKD4532 reveal that the effect on prolonging QTcF is dose-related. The magnitude of the effect (over placebo) is estimated to be approximately 10 milliseconds. Currently, CDER's experts believe that the degree of QT prolongation noted with alfuzosin could be a meaningful signal for the potential occurrence of severe post-marketing adverse events, including ventricular arrythmia and sudden death.

In my opinion, in order to obtain approval for this product, the sponsor should provide additional evidence that alfuzosin does NOT prolong the QT interval in humans at relevant doses. This may be accomplished through new human clinical investigations and/or re-analysis of completed investigations. Additional information should be submitted to validate the method of "selective beat averaging" from Holter monitoring in order to correct the QT interval for changes in heart rate.

If prolongation of the QT interval cannot be disproved despite additional clinical efforts and/or re-analysis of old data, then I believe that marketing approval could still be considered if it were shown that alfuzosin was no worse than all other members of its drug class in this regard. In this circumstance, additional regulatory action may be necessary and cannot be predicted at this time.

2.2. Clinically relevant issues derived from other disciplines' reviews

2.2.1. Clinical pharmacology and biopharmaceutics

In his draft review, Dr. Jarugula found the material submitted by the sponsor "acceptable", but specifically noted the following items:

1. In those patients with moderate and severe hepatic impairment, the systemic exposure of alfuzosin is increased by 3 to 4-fold. Such an increase would be associated with an unacceptably high incidence of orthostatic-type adverse events. Therefore, Dr. Jarugula recommends "contraindication in liver insufficiency". I discussed this with Dr. Jarugula and

he believes that all degrees of hepatic insufficiency should be included in the contraindication since "mild" patients were not specifically studied in the hepatic insufficiency trial. The sponsor has proposed a contraindication for those patients with moderate and severe degrees of hepatic insufficiency only. For those patients with mild degree of hepatic insufficiency, the sponsor proposed a cautionary statement as follows: "The physician should consider the risks and benefits of administering Uroxatral in this population." *The review team changed the proposed contraindication to include all degrees of hepatic insufficiency and I agree with this change to the draft label.*

2. The exposure of alfuzosin is increased by "up to 50%" in mild, moderate, and severe renal impairment. Dr. Jarugula notes that since a dose-related increase in vasodilatory adverse events was noted at a dose 50% higher than the recommended dose (which is 10 mg qday) , then "the label should recommend a caution when the drug is administered in patients with renal impairment". *The review team made such a change to the draft label and I agree with it.*

3. Potent CYP 450 3A4 inhibitors, such as ketoconozole, increases the AUC of alfuzosin by 2.5-fold. Thus, Dr. Jarugula recommends a contraindication for "potent inhibitors of CYP 450" and that "caution should be exercised" when alfuzosin is coadministered with moderate inhibitors of CYP 450. Clinically, Dr. Benson advises a contraindication for ketoconozole, itself and a cautionary statement for "moderate inhibitors of CYP 3A4". This reviewer recommends a contraindication for ketoconozole and other potent inhibitors of CYP 450 3A4 and a precaution for moderate inhibitors of CYP 450 3A4. *These changes were made to the draft label by the review team and I agree with them.*

2.2.2. Non-clinical pharmacology/toxicology

In her final review, overall, the toxicology reviewer, Dr. McLeod found the NDA to be "**approvable**" and noted no clinically relevant deficiencies in the sponsor's submission. Pre-clinical toxicity was only seen at large multiples of the proposed human exposure and was predominantly related to the drug's pharmacological action.

Dr. McLeod does point out that while the 2-year carcinogencity study in rats or mice did not reveal any treatment-related tumors, "the doses tested in female mice may not have constituted a maximally tolerated dose". *Such a statement was added to the appropriate section of the draft label by the review team and I agree with this revision.*

2.2.3. Biometrics

Dr. Sobhan's review concludes that "the results from all three trials demonstrated significantly ($p<0.1$) higher improvement in prostate symptom score (IPSS) and peak flow rate (PFR) for Uroxatral 10 mg daily dose compared to placebo." Thus, "the application demonstrate(s) **evidence in support of Uroxatral** 10 mg OD in the treatment of the signs and symptoms of BPH". There were no other relevant issues.

2.2.4. Chemistry, manufacturing, and controls

The chemist's review stated that "NDA 21-287 is recommended for **APPROVAL** from the CMC perspective."

Of note, the reviewer believed that there was no difference between plain and debossed tablets under both room temperature and accelerated condition during the 6-month stability studies. Thus, the expiry date for the drug product (debossed tablets) in all container/closure systems was set at 24 months based on the available stability data for the plain tablets.

3. Summary comments pertaining to efficacy:

3.1. Primary efficacy analysis:

In my opinion, the results of three adequate and well-controlled Phase 3 clinical trials demonstrate that alfuzosin extended-release tablets 10 mg daily are effective in relieving symptoms associated with benign prostatic hypertrophy (BPH).

The primary medical officer's review presents the efficacy data in great detail. Herein, I will present a brief outline of the same data.

Phase 2/3 study **ALFOD** investigated the effect of alfuzosin 7.5 mg relative to placebo on improving the signs and symptoms of BPH. The design of the study was adequate to meet its objectives. No significant difference was noted between drug and placebo in terms of improvement in maximum urinary flow rate. Urinary symptoms, based on the IPSS, were improved by drug more than by placebo, however, the change-from-baseline difference between them was only 1 point and was not statistically significant ($p = 0.07$).

Three Phase 3 studies were undertaken to assess the effect of alfuzosin 10 mg relative to placebo on improving the signs and symptoms of BPH. These were entitled ALFORTI, ALFOTAM, and ALFUS. These were multicenter, randomized, placebo-controlled studies. Each was designed with a four-week placebo run-in period and a 12-week double-blind treatment period.

ALFORTI was conducted entirely in Europe. It compared the immediate-release (IR) formulation of alfuzosin (2.5 mg three times daily), and the 10 mg extended-release (ER) formulation to placebo. The primary endpoints were the change-from baseline in the IPSS and maximum flow rate (or Qmax). Of those 447 randomized patients, 154 received placebo, 143 received the ER formulation, and 150 received the IR formulation. Based on the ITT population of 436 patients, both formulations were clinically and statistically superior to placebo in both primary endpoints as follows:

Table 1. Mean IPSS total score – ITT population, ALFORTI

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
D0	17.7	17.3	16.8
D end	12.8	10.4	10.5
D end – D0	-4.9	-6.9	-6.4
P versus placebo		0.002	0.02

Table 2. Changes in mean Qmax (mL/sec)- ITT population, ALFORTI

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
D0 (mean)	9.2	9.4	8.7
D end	10.6	11.7	11.9
D end – D0	1.4	2.3	3.2
P versus placebo		0.03	<0.0001

ALFOTAM was conducted in 79 centers in 9 countries outside the U.S. It compared alfuzosin ER 10 mg, alfuzosin ER 15 mg, and tamsulosin 0.4 mg, to placebo. The primary endpoints were identical to ALFORTI and design was similar. In this study, placebo responders during the run-in

period were not excluded prior to randomization. Of those 625 patients who were randomized, 154 received placebo, 154 received alfuzosin 10 mg, 159 received alfuzosin 15 mg and 158 received tamsulosin 0. 4 mg. Based on the ITT population of 578 patients, both formulations were clinically and statistically superior to placebo in both primary endpoints, (except for the 10 mg dose compared to placebo for Qmax), as follows.

Table 3. Mean IPSS total score – ITT population, ALFOTAM

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
D0	17.7	18.0	17.4	17.4
Dend	13.1	11.5	11.3	10.9
Dend-D0 (mean)	-4.6	-6.5	-6.0	-6.5
P value versus placebo		0.007	0.05	Not reported

Table 4. Mean Qmax – ITT population, ALFOTAM

	Placebo	Alfuzosin 10 mg	Alfuzosin 15 mg	Tamsulosin
D0	9.3	9.5	9.3	9.3
Dend	10.2	10.9	10.9	11.7
Dend-D0	0.9	1.5	1.6	2.4
P value versus placebo		**0.22**	0.09	Not reported

ALFUS was conducted in 30 centers in the U.S. and two in Canada. It compared alfuzosin ER 10 mg and alfuzosin ER 15 mg to placebo. The primary endpoints were identical to ALFORTI and design was similar. In this study, placebo responders during the run-in period were not excluded prior to randomization. Of those 536 patients who were randomized, 178 received placebo, 177 received alfuzosin 10 mg, and 181 received alfuzosin 15 mg. Based on the ITT population of 502 patients, both formulations were clinically and statistically superior to placebo in both primary endpoints, (except for the 15 mg dose compared to placebo for Qmax), as follows.

Table 5. Mean IPSS total score – ITT population, ALFUS

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
D0	18.2	18.2	17.7
D end	16.6	14.6	14.3
D end – D0	-1.6	-3.6	-3.4
P versus placebo		0.001	0.004

Table 6. Changes in mean Qmax (mL/sec)- ITT population, ALFUS

	Placebo	Alfuzosin 10 mg OD	Alfuzosin 2.5 mg tid
D0 (mean)	10.2	9.9	10.0
D end	10.3	11.6	11.0
D end – D0	0.1	1.7	0.9
P versus placebo		0.0004	**0.12**

3.2. Benefit over available therapies (efficacy):

In my opinion, no evidence has been presented to substantiate a benefit of Uroxatral over the existing products in terms of efficacy.

Theoretically, one dosage strength (10 mg) might simplify office management by precluding the need to up-titrate. On the other hand, since 7.5 mg was not shown to be effective and 15 mg had no better efficacy then 10 mg (but an increased incidence of vasodilatory adverse events), the single dose may actually be a drawback, reflective of a narrow therapeutic index.

4. Summary comments pertaining to safety:
The NDA contained data on an adequate number of patients exposed for a sufficiently long time. Specifically, in the three randomized, 12-week, placebo-controlled pivotal studies, a total of 474 patients were randomized to alfuzosin 10 mg ER and 340 patients were randomized to alfuzosin 15 mg ER. As of the cut-off date of October 31, 1999, 282 patients had completed an additional 9 months of therapy with the 10 mg ER dose and 363 had completed an additional 9 months of therapy with the 15 mg ER dose.

In addition, the sponsor submitted information relevant to a vast European post-marketing experience with alfuzosin. This summary included experience with the IR formulation since 1987, the SR formulation since 1993 and the ER formulation from the year 2000. The total human exposure to alfuzosin was estimated by the sponsor to be

4.1. Overall adverse reactions
Overall, the adverse reactions noted in this application were consistent with alfuzosin's known and expected pharmacological action as an alpha-adrenergic blocking agent. This class of drugs is known to induce such reactions as dizziness, syncope, hypotension, headache, rhinitis, fatigue, and dyspepsia. The overall adverse reactions reported by greater than 1% of patients in any treatment group, as tabulated for the four, double-blind, placebo-controlled, 3-month treatment period, pivotal studies (ALFOD, AFORTI, ALFOTAM and ALFUS) is shown in Table 7.

Table 7 is notable for the fairly low incidences of all alpha-adrenergic type symptoms for the 10 mg dose during the 3-month trials. Incidence rates for the 15 mg dose appear somewhat higher than those for the 10 mg dose, but still within an clinically acceptable range. It is difficult to explain why the overall incidence rates for commonly reported adverse events were lower in these trials than in the reported literature and in package inserts for other products in the class. It is possible that these low incidences may reflect the exclusion of those patients that demonstrated a positive orthostatic test prior to their being randomized.

The clinical review of alfuzosin focused specifically on "vasodilatory" adverse events, including dizziness, hypotension and syncope. Table 8 shows the number and percentage of patients reporting "vasodilatory-type" AEs during the double-blind treatment periods of the pivotal trials. The majority of vasodilatory events were rated as "mild" or "moderate" in severity. Dizziness was reported as severe in one patient of each treatment group, including placebo. One report of hypotension was rated as severe.

In my opinion, none of the overall adverse events or "vasodilatory" adverse events would preclude approval if there was not an effect on the QT interval.

Table 7. Frequency of Adverse Events Reported by >1% of Patients in Double-Blind Portion of Pivotal Trials.

	Placebo (N=678)	Alfuzosin 7.5 mg (N=204)	Alfuzosin 10 mg (N=473)	Alfuzosin 15 mg (N=335)
Dizziness	19 (2.8%)	3 (1.5%)	25 (5.3%)	27 (8.1%)
Upper resp. infection	4 (0.6%)	1 (0.5%)	14 (3.0%)	9 (2.7%)
Headache	12 (1.8%)	5 (2.5%)	14 (3.0%)	8 (2.4%)
Flu-like Symptoms	14 (2.1%)	1 (0.5%)	9 (1.9%)	6 (1.8%)
Fatigue	7 (1.0%)	6 (2.9%)	8 (1.7%)	10 (3.0%)
Rhinitis	12 (1.8%)	2 (1.0%)	7 (1.5%)	6 (1.8%)
Impotence	4 (0.6%)	0	7 (1.5%)	4 (1.2%)
Bronchitis	5 (0.7%)	5 (2.5%)	7 (1.5%)	2 (0.6%)
Sinusitis	8 (1.2%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Pain	4 (0.6%)	0	7 (1.5%)	0
Abdominal pain	7 (1.0%)	1 (0.5%)	7 (1.5%)	2 (0.6%)
Dyspepsia	7 (1.0%)	3 (1.5%)	6 (1.3%)	1 (0.3%)
Back pain	8 (1.2%)	3 (1.5%)	6 (1.3%)	9 (2.7%)
Inflicted injury	2 (0.3%)	0	6 (1.3%)	3 (0.9%)
Asthenia	5 (0.7%)	0	5 (1.1%)	4 (1.2%)
Constipation	3 (0.4%)	3 (1.5%)	5 (1.1%)	3 (0.9%)
Pharyngitis	2 (0.3%)	2 (1.0%)	5 (1.1%)	3 (0.9%)
Nausea	4 (0.6%)	2 (1.0%)	5 (1.1%)	2 (0.6%)
Somnolence	5 (0.7%)	0	4 (0.8%)	4 (1.2%)
Arthralgia	6 (0.9%)	4 (2.0%)	4 (0.8%)	4 (1.2%)
Diarrhea	10 (1.5%)	2 (1.0%)	3 (0.6%)	3 (0.9%)
Perpheral edema	4 (0.6%)	1 (0.5%)	2 (0.4%)	4 (1.2%)
Hypertension	9 (1.3%)	2 (1.0%)	2 (0.4%)	3 (0.9%)
Urinary tract infection	9 (1.3%)	2 (1.0%)	2 (0.4%)	1 (0.3%)
Arthrosis	2 (0.3%)	3 (1.5%)	2 (0.4%)	0

Table 8. Vasodilatory Adverse Events in Double-Blind Phase of Pivotal Studies

	Placebo N=678	Alfuzosin 7.5 mg N=204	Alfuzosin 10 mg N=473	Alfuzosin 15 mg N=335
Dizziness	19 (2.8%)	3 (1.5%)	25 (5.3%)	27 (8.1%)
Hypotension	0	0	2 (0.4%)	2 (0.6%)
Malaise	0	1 (0.5%)	2 (0.4%)	3 (0.9%)
Syncope	0	1 (0.5%)	1 (0.2%)	2 (0.6%)
Postural hypotension	0	0	0	0

4.2. Deaths and other non-fatal serious adverse events

4.2.1 Deaths

There were four reported deaths in the pivotal trials and their extensions. One patient died of an infection after suffering head trauma. One patient died of pneumonia and two others died of cancer.

4.2.2. *Non-fatal serious adverse events (SAEs)*

Dr. Benson's review of the serious adverse events notes that in the double-blind treatment periods and open-label extension periods, there was a total of 130 serious adverse events reported in 1608 patients. In the majority of these events, both the investigator and the primary medical reviewer believed that there was no relationship to drug. Many events reported were those commonly reported events in a population of middle-aged males including: diverticulitis, arthroses, upper respiratory infection, renal stone, lung cancer, basal cell carcinoma, peripheral edema, etc.

In the double-blind period, syncope was reported as an SAE in one patient in the 10 mg group and 3 patients in the 15 mg group. Also, the following potentially relevant events were reported in one patient each in the 10 mg group: substernal chest pain, angina pectoris aggravated, and coronary artery disorder. In the 15 mg group, potentially relevant reports included myocardial infarction, and atrial fibrillation in one patient each.

In the open-label extensions, there were 13 reports of syncope (0.8%), 10 reports of angina pectoris (0.6%), 4 reports of myocardial infarction (0.2%), 3 reports of coronary artery disorder (0.2%), and one report of substernal chest pain (0.1%). Of the 13 syncopal events, nine were in those taking 15 mg (9/707, 1.3%), and 3 were in those taking the 20 mg dose (3/690, 0.4%).

Overall, I believe that syncope is not unexpected in this class of drugs and the rates reported were not worse than those reported for other agents in this class. I also believe that the rare reports of angina pectoris and myocardial infarction should not be unexpected in this population. Causal relationship to drug cannot be drawn. Neither the deaths nor SAEs would preclude approval if there were no effect on the QT interval.

4.3 Potential effect on cardiac repolarization

4.3.1. Data from the original NDA

The original NDA submission for alfuzosin contained the results from one Phase 1 study (PC **ALF 96 US1**) which investigated the effect of alfuzosin ER on EKG parameters and cardiovascular safety. This was a single-center, randomized, double-blind, placebo-controlled, parallel, sequentially-dosed escalation study using doses of 7.5 mg, 15 mg, 22.5 mg, and 30 mg. Four sequential groups of 12 healthy subjects (9 drug and 3 placebo), 50 to 70 years of age, participated in this study.

A single dose of alfuzosin or placebo was administered 5 minutes after the evening meal on Study Day 1. Starting on Day 4, alfuzosin or placebo was administered once daily 5 minutes after the evening meal for 5 consecutive days. Blood samples were collected at the end of each dosing and for 72 hours after the last dose on Day 8 for purposes of describing pK.

Electrocardiograms (12-lead) were recorded at screening, on Day 1, and on Days 2, 5, 6, 7, 8, 9 and upon exit on Day 11. These were performed at a single timepoint: 15 hours after drug administration (the anticipated Tmax). ECG parameters recorded included heart rate, PR interval, QRS interval, QT interval, QTc, and ST segment. ECG intervals were read by computer. QT

interval was corrected using Bazett's formula [QTc = QT/√(R-R), where R-R was the interval between two successive QRS complexes].

Results of vital sign measurements revealed a drug-related increase in mean maximal increase in supine heart rate after single dose administration. The mean maximal increase from baseline in the placebo, 7.5 mg, 15 mg, 22.5 mg and 30 mg groups after a single dose was 8 bpm, 10.9 bpm, 12.3 bpm, 7 bpm, and 12.4 bpm.

Using automated ECG readings, there was again, a statistically significant overall difference between groups for change from baseline in HR. Upon closer analysis, differences were noted specifically between the 7.5 mg and placebo groups and between the 30 mg and placebo groups.

In analyzing the QT interval, using the automated readings, the sponsor reported the following results after single (Table 9) and multiple dose administrations (Table 10):

Table 9. Mean QT interval (msec) after single administration

	Placebo (N=11)	7.5 mg (N=9)	15.0 mg (N=9)	22.5 mg	30.0 mg
Baseline	393	402	396	399	409
15 hrs post-dose	389	377	388	395	381

Table 10. Mean QT interval (msec) after repeated administration (measured 15 hrs post-dose)

	Placebo	7.5 mg	15.0 mg	22.5 mg	30.0 mg
Baseline	393	402	396	399	409
Day 4	384	374	381	388	391
Day 5	380	384	385	381	372
Day 6	381	383	381	380	383
Day 7	379	384	387	381	387
Day 8	386	387	386	376	388

In the sponsor's opinion, when these QT intervals were corrected for heart rate using Bazett's formula (QTcB), "there was no statistically significant effect after single dose or repeated administration". This reviewer believes that the data presented concerning change in QTcB in this study during single and repeat dose administration supports the sponsor's position. Specifically, I do not note any particularly worrisome individual absolute QTcB values (using Bazett's correction formula) nor any worrisome individual changes from baseline values in QTcB.

Major deficiencies of this trial were that the QT interval was corrected using Bazett's correction factor only and that automated measurements were used. The same data should have been analyzed using a correction factor more appropriate for situations where a drug tends to increase heart rate (e.g. Fredericia's formula) and the ECG intervals should have been measured by hand. The sponsor did, however, provide such analyses in the 4-month safety update (see below).

4.3.2. Data from the 4-month safety update

In the 4-month safety update the sponsor submitted the results of two additional pre-clinical studies and three additional clinical studies as follows:

Pre-clinical study reports

1. FIP0020: Effects on the action potential of piglet purkinje fibres. Report Number 00-00312-EN-00
2. PGD0097: Effects on the herg channel stably expressed in mammalian cell line. Comparison with tamsulosin, doxazosin, and terazosin. Report Number 00-00329-EN-00

Clinical study reports

1. INT 4285: Assessment of pharmacokinetic drug interactions between alfuzosin 10 mg OD formulation and ketoconozole in healthy male subjects. Report Number CSRCO-INT4285

2. PDY4509: Manual reading of QT intervals of electrocardiogram from the PCALF96US1 study entitled: Study of the safety and pharmacokinetics of alfuzosin following single and repeated administration of increasing doses of once-daily tablets in healthy male subjects (50-70 years old). Addendum to Report Number: 00-00358-EN-2.

3. PKD4532: Effects of supratherapeutic doses of alfuzosin 10 mg OD formulation on ECG parameters. Report Number CSRCO-PKD4532.

Pre-clinical studies

The pre-clinical studies were reviewed by Dr McLeod of our Division in her Pharmacology review of the NDA and by Dr. John Koerner, a toxicologist assigned to the division of Cardio-Renal Drug Products.

Dr. McLeod's review of the purkinge fiber study notes that the no-effect level was calculated to be 0.1 micromolar (42.6 ng/mL) or about 2.6 times the expected clinical blood level. The lowest dose at which an effect was seen was 1 micromolar or about 26 times the clinical blood level. In regard to the HERG channel study, Dr. McLeod notes that the alfuzosin IC_{50} for inhibiting the I_{kr} (potassium channel current) was 83.3 micromolar (35,500 ng/mL) or approximately 2000 times the expected clinical blood level.

Based on the same data, Dr. Koerner concluded that alfuzosin had "low risk for repolarization abnormalities." Dr. Koerner did comment that metabolites of alfuzosin were not studied in the HERG channel study and that alfuzosin's "potency was likely underestimated". I agree with Dr. Koerner's assessment of this data.

Ketoconozole interaction study (INT 4285)

Dr. Jarugula of OCBP reviewed the ketoconozole interaction study (INT 4285) and noted that ketoconozole led to a 2.11-fold increase in Cmax and 2.46-fold increase in AUC. He also noted that ECG recordings were not obtained during the period in which drug and ketoconozole were taken simultaneously. Thus, the study was not considered adequate to determine whether the interaction of alfuzosin 10 mg and ketoconozole, a potent inhibitor of CYP 450 3A4, could result in QT prolongation. In addition, Dr. Jarugula noted that the dose of ketoconozole administered was 200 mg per day, which is less than the maximum recommended dose of 400 mg per day. Thus, the pharmacokinetic interaction may have somewhat underestimated.

Manual reading of QT intervals of electrocardiogram from the PC ALF 96 US1 study (PDY 4509):

The sponsor submitted a "re-analysis" of the QT data from PC ALF 96 US 01. The report states that "the aim of the report was to present the results of the manual electrocardiograms (ECG) readings, according to the state of the art, and the Committee for Proprietary Medicinal Products guideline."

The sponsor claims that the analysis of the ECGs was carried out under blind conditions. The intervals that were measured were RR, PR, QRS and QT. The QTc interval was determined using both Bazett's and Fredericia's formula. Raw data and absolute changes from baseline were summarized by dose group using descriptive statistics (mean, SD, minimum, maximum, N). A separate listing was maintained for all individual data from subjects presenting with at least one of the following relevant abnormalities:

1. QTc >430 ms and ...450 ms
2. QTc >450 ms
3. Delta QTc — 30 ms and ... 60 ms
4. Delta QTc > 60 ms

In terms of mean changes after single doses and after multiple doses (listed as Day 8), the results are listed in Tables 11 and 12 below:

Table 11. Mean (95% CI) differences from placebo in ECG parameters at Day 1

ECG parameter	Treatment vs. Placebo	7.5 mg vs. PL	15 mg vs. PL	22.5 mg vs. PL	30 mg vs. PL
Mean HR	P=0.0035	9.8 (3.4, 16.1)	4.3 (-2.0, 10.7)	2.8 (-3.6, 9.1)	11.6 (5.2, 17.9)
Mean QT	NS	-4.5 (-20.7, 11.7)	14.9 (-1.3, 31.2)	3.1 (-13.2, 19.3)	-10.2 (-26.4, 6.1)
Mean QTcB	P=0.0052	24.9 (8.6, 41.2)	29.1 (12.9, 45.4)	12.0 (-4.3, 28.3)	22.2 (6.0, 38.5)
Mean QTcF	P=0.0189	14.9 (1.3, 28.4)	23.8 (10.2, 37.3)	9.1 (-4.4, 22.7)	11.1 (-2.4, 24.7)

Table 12. Mean (95% CI) differences from placebo in ECG parameters at Day 8

ECG parameter	Treatment vs. Placebo	7.5 mg vs. PL	15 mg vs. PL	22.5 mg vs. PL	30 mg vs. PL
Mean HR	NS	3.9 (-2.3, 10.1)	1.1 (-5.1, 7.3)	6.0 (-0.2, 12.2)	3.1 (-3.1, 9.3)
Mean QT	NS	-4.7 (-22.1, 12.7)	-0.2 (-17.6, 17.1)	-9.5 (-26.8, 7.9)	4.3 (-13.1, 21.7)
Mean QTcB	NS	7.6 (-6.2, 21.5)	0.5 (-13.3, 14.3)	9.2 (-4.7, 23.0)	13.5 (-0.3, 27.3)
Mean QTcF	NS	3.8 (-8.9, 16.5)	0.3 (-12.4, 12.9)	3.6 (-9.1, 16.3)	10.9 (-1.8, 23.6)

Dr. Jarugula of OCPB and Dr. MayAnn Gordon of the Division of Cardio-Renal Drug Products reviewed this same data.

Dr. Jarugula concludes "when QT intervals are corrected for heart rate, alfuzosin in general seems to have increased the QTc compared to placebo. The alfuzosin effect on QT prolongation on Day 1 seems to be higher than on Day 8 when compared to placebo. Delta QTcB was statistically significantly higher in alfuzosin 7.5 mg group (+25 msec), 15 mg group (+29 msec) and 30 mg group (+22 msec) at Day 1 than in the placebo group. Similar differences (although less in magnitude) were observed with QTcF values".

Dr. Gordon concludes (for Day 1), "The mean changes from baseline with Bazett's correction were always higher on drug but not necessarily in a dose-related manner. The maximum values were usually higher on drug than on placebo." And (for Day 1), "As with the Bazett's correction, the mean changes from baseline with the Fredericia's correction were always higher on drug but not necessarily in a dose-related manner. The maximum values were usually higher on drug than on placebo."

In terms of individual "outliers", Table 13 describes these results:

Table 13. Post-dose abnormalities on ECG.

	PL # subjects	7.5 mg # subjects	15 mg # subjects	22.5 mg # subjects	30 mg # subjects
Available	**12**	**9**	**9**	**9**	**9**
QTcB >430 ms & ...450 ms	5	5	7	8	5
QTcB >450 ms	3	1	5	5	2
⊗ QTcB —30 ms & ...60 ms	5	7	5	6	7
⊗ QTcB > 60 ms	-	1	1	-	1
QTcF >430 ms & ...450 ms	7	1	4	4	3
QTcF >450 ms	-	-	1	1	-
⊗ QTcF —30 ms & ...60 ms	2	3	5	2	4
⊗ QTcF >60 ms	-	-	1	-	-

From this data, Dr. Jarugula concludes "Three subjects in the placebo group, two in the 7.5 mg group, five each in the 15 mg and 22.5 mg dose groups, and two in the 30 mg group had QTcB values >450 msec, while one subject in the 15 mg and 22.5 mg dose groups had QTcF >450 msec." Also, "One subject in the 15 mg dose group had a prolonged QTcB with a maximal value of 515 msec observed at Day 1, while his heart rate remained unchanged. His QTcB returned to normal over time, event though he continued on alfuzosin"

Dr. Gordon's only comment about this particular data was "The largest increase was reported for one subject in the 15 mg dose group (78/71 msec for QTcB/QTcF, respectively). The subject's values declined despite continued treatment."

Overall, for this study, the sponsor concluded: "The modifications observed in QTcB indicate a possible over-correction when the Bazett's formula is applied in conjunction with a high HR

value. This is confirmed by the results observed on the QTcF....Consequently, no clinically relevant effect of alfuzosin extended release up to 30 mg on repolarization was observed in this study as observed in the original results using automatic ECG analysis."

Based on these data and these consultants' comments, I tend to agree with Dr. Jarugula that when QT intervals are corrected for heart rate, alfuzosin in general does seem to increase the QTc compared to placebo. Such increases are still present when using the Fredericia's formula rather than the Bazett's formula, but they are lessened in magnitude. The "outlier" data is not particularly worrisome, although the numbers of subjects is clearly small.

Effects of supratherapeutic doses of alfuzosin 10 mg OD formulation on ECG parameters (PKD4532):

According to the final study report, this trial was begun August 15, 2000 and was completed on November 14, 2000. It should be noted that the NDA for alfuzosin was submitted on December 8, 2000. This study report was completed on March 16, 2000 and was submitted with the 4-month safety update.

The introduction to the study report provides a rationale for the sponsor's conducting this particular study. It states "Despite an excellent safety profile and paucity of cardiac dysrhythmias being reported during the extensive post-marketing experience, *it was still considered important to eliminate any concerns over the potential for the drug to induce electrophysiological changes in man.*"

This was a single center, placebo-controlled, double-blind, single-dose, randomized crossover study in 24 healthy young male volunteers. Single doses of 10 mg. 20 mg, and 40 mg of alfuzosin ER formulation were studied. Twelve-lead ECG recordings were performed pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18 and 24 hours after drug administration. Blood samples for measurement of alfuzosin were collected at various time intervals after dosing.

While HR, and PR, QRS, and QT intervals were measured automically, a manual reading was also performed. The QTc interval was calculated using Bazett's and Fridericia's formulas.

Cardiac monitoring was also performed by means of a 24-hour Holter monitoring procedure. A recording performed at screening served as a baseline. Holter monitoring was begun 5 minutes prior to dosing and continued for 24 hours. For the Holter recordings, QT measurements were performed manually. The sponsor provided details of the procedures for analyzing the Holter monitor recordings using a method referred to as "selective beat averaging".

Of note, the pharmacokinetic sampling revealed dose-proportionality up to 40 mg.

Analysis of the mean changes from baseline in heart rate, uncorrected QT interval, QTcB and QTcF are shown in Table 14 below. Analysis of "outliers" with potentially clinically significant abnormalities is shown in Table 15 below.

Table 14. Analysis of absolute ECG changes from baseline.

Parameter	Pairwise comparison	P-value	Mean difference	95% CI (upper bound)
Delta HR (bpm)	10 mg vs. PL	0.1011	+0.6	+1.3
	20 mg vs. PL	0.0001	+4.6	+5.4
	40 mg vs. PL	0.0001	+5.8	+6.5
Delta QT (ms)	10 mg vs. PL	0.8971	-1.1	+0.3
	20 mg vs. PL	1.0000	-6.3	-4.9
	40 mg vs. PL	1.0000	-4.7	-3.3
Delta QTcB (ms)	10 mg vs. PL	0.1416	+1.2	+3.0
	20 mg vs. PL	0.0001	+8.5	+10.3
	40 mg vs. PL	0.0001	+13.2	+15.0
Delta QTcF (ms)	**10 mg vs. PL**	**0.2673**	**+0.5**	**+1.8**
	20 mg vs. PL	**0.0001**	**+3.4**	**+4.7**
	40 mg vs. PL	**0.0001**	**+7.1**	**+8.4**

Table 15. Post-dose abnormalities on ECG.

	PL # subjects	10 mg # subjects	20 mg # subjects	40 mg # subjects
Available	**24**	**24**	**24**	**24**
QTcB >430 ms & …450 ms	3	7	5	5
QTcB >450 ms	2	1	1	2
⊗ QTcB —30 ms & …60 ms	12	10	16	16
⊗ QTcB > 60 ms	2	3	4	4
QTcF >430 ms & …450 ms	2	3	1	3
QTcF >450 ms	-	-	-	1
⊗ QTcF —30 ms & …60 ms	8	5	7	9
⊗ QTcF >60 ms	-	-	-	-

From these data, Dr. Jarugula concluded: "The mean corrected QT values (both QTcB and QTcF) increased in dose-dependent manner from 10 mg to 40 mg dose. There was also dose dependent increase in heart rate with alfuzosin treatment."

Dr. Gordon concluded: "Heart rate, QTcB and QTcF are significantly increased from baseline for the 20 mg and 40 mg doses compared to placebo." In addition, she states: "Subjects who took the 40 mg dose had a greater likelihood of having an abnormal QTcB and/or QTcF compared to those who took a lower dose or placebo."

The sponsor concluded: "The main pharmacodynamic effect of alfuzosin on the ECG assessments was a dose-dependent increase in heart rate and associated increase in QTc interval as corrected by Bazett's and Fridericia's formulae. The increase in QTc could be attributed to the inability of the formulae to reliably correct for heart rate."

I agree with the sponsor's acknowledgement that there is a dose-dependent increase in heart rate and associated increase in QTc interval as corrected by Bazett's and Fridericia's formulae. My understanding from CDER's experts in this field is that while Bazett's may not be adequate when heart rate is increased, the results using Fridericia's correction should not be ignored. Thus, in this particular study there is evidence of a dose-related increase in Fridericia's corrected QT interval. Again, I do not believe that the "outlier" data was worrisome, although the numbers were small.

While the magnitude of this prolongation at the 10 mg dose does not appear to be large (upper bound of the 95% CI = +1.8 [versus placebo]), the differences from placebo at 20 mg and 40 mg are probably not trivial. Further, Dr. Gordon summates her entire consult by stating: "The drug appears to be increasing corrected QT by perhaps **10 msec.**" This conclusion,"**10 msec**", was clearly supported by the Deputy Director of the Division of Cardio-Renal Drug Products during a meeting held on September 25, 2001. And, I have been advised by CDER's experts in this field that a 10 msec prolongation is considered clinically meaningful.

Holter monitoring results:
As noted previously, the sponsor is of the belief that Bazett's and Fridericia's correction formulae can introduce substantial variance and potential bias. Thus, the sponsor proceeded with analyzing the results of "QT intervals obtained from Holter monitoring individually fitted to identical HR, specific for each subject."

The sponsor described this process on page 58/119 of the study report and herein I quote a part of this discussion:

> "Comparisons were made for the same subject and for each serial comparison within the same range of RR values (RR overlap). Differences in QT interval at RR overlap, maximum RR overlap (the RR template for which the cumulative number of complexes of the two periods under comparison was maximum) and fixed RR (if available) were analyzed. Assessments were conducted for two circadian conditions, Peak and Night. Peak was defined as the time interval of 4 hours around the time of Cmax and Night was defined as the time interval from Hour 16 to Hour 20."

When the data from the Holter monitoring is analyzed thusly, the sponsor believes that significant differences were noted between drug and placebo as follows:

> For Peak, at "RR overlap" for alfuzosin 10 mg, 20 mg and 40 mg, there were mean differences from placebo of +1.7 (UB +2.9), +2.1 (UB +3.3), and +1.8 msec (UB +3.3), respectively.
>
> This effect was also seen for the 10 mg and 20 mg doses at maximum RR overlap. The differences from placebo were +2.5 (UB +4.0) and +2.2 msec (UB +3.7), respectively.
>
> And, at fixed RR, a difference from placebo of +2.0 msec (UB +3.2) was noted for the 10 mg dose.

From this data, the sponsor concludes that the mean differences from placebo in correctly QT were approximately +2 msec, with all upper bounds of the 95% Cis never exceeding +4 msec, regardless of the RR interval assessed. In addition, the sponsor believes that no dose effect was seen.

Dr. Jarugula did not comment on the appropriateness of this methodology although he did acknowledge that this data was submitted. In her written consult, Dr. Gordon did not mention this data, these procedures, nor this analytic methodology at all.

An inter-Divisional meeting was held on September 25 between the Division and several of CDER's experts on the QT interval, including the Deputy Director of the Division of Cardio-Renal Drug Products. In general, the Division was advised that Holter monitoring is not a preferred modality for this type of study. In addition, the group voiced a lack of familiarity with the sponsor's analytic methodology for this part of the study. Finally, it was clearly expressed at this meeting that the sponsor's proposed methodology was not considered "validated" and should be viewed as circumspect or "exploratory" until evidence to support its "validation" had been submitted and reviewed.

Given all this, it is my opinion that the sponsor's methodology for "selective beat averaging" using Holter monitoring may actually correct the measured QT interval better than either of the standard correction factors, **but we have not been provided with sufficient evidence to draw this conclusion**. Without such evidence, it would seem unreasonable for the Division to ignore the dose-related increase in QTc using the standard and accepted formula (Fridericia's) and to ignore the best possible advice from CDER's experts in this field. Thus, I must conclude that this study demonstrates evidence of QT prolongation with alfuzosin at doses two and four-fold higher than the recommended clinical dose.

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

/s/

Mark S. Hirsch
10/4/01 03:27:20 PM
MEDICAL OFFICER

Daniel A. Shames
10/9/01 10:49:27 AM
MEDICAL OFFICER

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number, Requested Trade Name, Generic Name and Strengths (modify as needed for an efficacy supplement and include type):

Applicant: NDA 21-287, Tradename- pending; former tradename- Uroxatral; Generic: alfuzosin hydrochloride, 10 mg extended release tablets

Date of Application:	December 8, 2000
Date of Receipt:	December 11, 2000
Date of Approvable Letter:	October 5, 2001
Complete Response Resubmitted:	December 12, 2002
Date of Complete Response Filing Meeting:	January 31, 2003
Filing Date:	February 12, 2003
PDUFA Date:	June 12, 2003

Indication(s) requested: Treatment of the signs and symptoms of benign prostatic hyperplasia

Type of Application: Full NDA ___X___ Supplement _____
(b)(1) ___X___ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S___X___ P_____
Resubmission after a withdrawal or refuse to file ___N/A____
Chemical Classification: (1,2,3 etc.) 1S
Other (orphan, OTC, etc.) N/A

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

If the application is affected by the application integrity policy (AIP), explain.

User Fee Status: Paid ___X___ Waived (e.g., small business, public health) _____
Exempt (orphan, government) ____
Form 3397 (User Fee Cover Sheet) submitted: YES___X___ NO_____
User Fee ID# 4010
Clinical data? YES ___X___ NO _____ Referenced to NDA# N/A
Date clock started after UN _____N/A_____

User Fee Goal date: June 12, 2003

Action Goal Date (optional) June 12, 2003

- Does the submission contain an accurate comprehensive index? YES NO

- Form 356h included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES NO

  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? YES NO N/A

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES; If yes, 5 years NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES NO
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? YES NO N/A
  If no, for what ages and/or indications was a waiver and/or deferral requested:

  * A complete waiver will be granted in action letter as the treatment indicated disease/condition (benign prosatic hyperplasia) does not exist in children

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

List referenced IND numbers:

End-of-Phase 2 Meeting? Date 8/13/1997 NO

If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date 5/24/2000 NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES NO

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support?

YES NO

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support?
YES NO

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? YES NO N/A

*This is not an application for an OTC product.

Advisory Committee Meeting needed? YES, date if known 5/29/03 NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES NO
- If no, did sponsor submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) package submitted? YES NO

- Parenteral Applications Consulted to Sterile Products (HFD-805)? YES NO

If 505(b)(2), complete the following: This section is not applicable to NDA 21-287

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)

YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?

YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

****MEMO OF FILING MEETING (DATED 2/4/02) is attached as hard copy only to this administrative review. Electronic signed copy of filing meeting minutes is available as separate document in DFS.**

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

/s/

Jean R. King
6/12/03 06:27:58 PM
CSO

Jean R. King
6/12/03 06:35:17 PM
CSO

Screening of New NDA for Statistical Filing
Division of Biometrics II

NDA #: 21-287

Applicant: Sanofi-Synthelabo, Inc

Trade/Generic Name: Uroxatral (alfuzosin HCl extended-release tablets)

Indication: treatment of the signs and symptoms of benign prostatic hyperplasia

Date of Submission: Dec 12, 2002

User Fee Goal Date: Jun 12, 2003

Project Manager: Jean King (HFD-580)

Medical Reviewer: Marcea Whitaker

Statistical Reviewer: Mahboob Sobhan

Comments: This resubmission is a class 2 response to the action letter dated Oct. 5, 2002. It contains additional clinical information, labeling information, and a safety update report. This NDA can be filed. Statistical review will focus on Study 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." Electronic data sets for this study have been requested from the sponsor.

Checklist for Fileability	Remarks (NA if not applicable)
Index sufficient to locate study reports, analyses, protocols, ISE, ISS, etc.	OK
Original protocols & subsequent amendments submitted	OK
Study designs utilized appropriate for the indications requested	OK
Endpoints and methods of analysis spelled out in the protocols	OK
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Data and reports from primary studies submitted to EDR according to Guidances	data sets requested from sponsor
Safety and efficacy for gender, racial, geriatric, and/or other necessary subgroups investigated	OK

Filed by: M. Welch

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/s/

Mike Welch
2/12/03 08:21:14 AM
BIOMETRICS

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Micro Efficacy Review

Not applicable to this application cycle.

/S/

J. M.S., RD
5/15/03

NDA 21-287
Alfuzosin Hydrochloride

Microbiology (Efficacy) Review

Not applicable to this application.

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Clinical Inspection Review Summary

Not applicable to this application cycle. See Clinical Inspection Review Summary, dated August 30, 2001 attached.

/S/ M.S., R.D.
5/15/03

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pages of trade

secret and/or

confidential

commercial

information

NDA 21-287
Alfuzosin Hydrochloride

DSI Memo – GLP inspection

Not applicable for this NDA