A search of the World Health Organization's Adverse Event database provided the following data for all salts and esters of alfuzosin.

**Table Two**
**Alfuzosin Adverse Event Terms**
**Reported by the WHO[1]**

| Adverse Event | # | Adverse Event | # | Adverse Event | # |
|---|---|---|---|---|---|
| Angina Pectoris Aggravated | 5 | ECG Abnormal Specific | 1 | Myocardial Infarction | 14 |
| Angina Pectoris | 14 | Extrasystoles | 2 | Myocardial Ischemia | 1 |
| Arrhythmia | 7 | Fibrillation Atrial | 13 | Palpitation | 28 |
| Arrhythmia Atrial | 1 | Fibrillation Ventricular | 2 | Sudden Death | 3 |
| Blood Pressure Fluctuation | 1 | Heart Murmur | 1 | Syncope | 53 |
| Bradycardia | 8 | Hypertension | 4 | Tachycardia | 13 |
| Cardiac Arrest | 1 | Hypertension Aggravated | 1 | Tachycardia Supraventricular | 2 |
| Cardiac Failure | 2 | Hypertension Intracranial | 1 | Thrombosis Coronary | 1 |
| Cardiac Failure Left | 2 | Hypotension | 57 | Vasodilation | 1 |
| Cardiac Failure Right | 1 | Hypotension Postural | 42 | | |

1. These numbers may include duplicates.

The WHO data provides a line listing of cardiovascular adverse events reported with alfuzosin. The most frequently reported events are hypotension, syncope, postural hypotension, palpitation, angina pectoris, myocardial infarction, tachycardia, and atrial fibrillation. The WHO data does not provide information on any Torsade de Pointes or QT prolongation cases. However, seven cases of arrhythmia and three cases of sudden death are listed.

## OPDRA CONCLUSION

This document provides an overview of the available postmarketing data on QT prolongation, Torsade de Pointes, and ventricular arrhythmias reported for tamsulosin, terazosin, and doxazosin. Additionally, it also provides foreign postmarketing data for alfuzosin.

The specific terms QT prolongation and Torsade de Pointes are not included in the WHO line listing. Reports of arrhythmias were noted; however, the WHO line listings do not provide sufficient data to determine if a signal exists between the postmarketing alfuzosin data and QT prolongation, Torsade de Pointes, and ventricular arrhythmias.

Specific cases of QT prolongation, Torsade de Pointes, and ventricular arrhythmias were identified in the overview of the postmarketing data for tamsulosin, terazosin, and doxazosin. However, these cases were not compelling and contained confounding factors which make causality assessment difficult.

Signed 1-29-2002
Denise P. Toyer, Pharm.D.
Safety Evaluator

**Concur:**

Signed 1-29-2002
Debra E. Boxwell, Pharm.D.
Team Leader

Signed 1-29-2002
Julie Beitz, M.D.
Division Director

D010494

**NDA # 21-287**
**HFD-580 (Division File)/Farinas/Benson/Hirsch**
**HFD-430 Boxwell/Toyer/Dempsey/Beitz/Johnston/Lu/Karwoski/Drug**

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Application Integrity Policy (AIP)

This application is not the subject of an AIP investigation.

1 1S1 Ms. RD
5/16/03

**NDA 21-287**
Alfuzosin Hydrochloride

Application Integrity Policy Information

This application is not the subject of an AIP investigation.

## King, Jean

| | |
|---|---|
| om: | Jon.Villaume@us.sanofi.com |
| Sent: | Thursday, June 12, 2003 6:16 PM |
| To: | kingje@cder.fda.gov |
| Cc: | GV-RDU@sanofi-synthelabo.com |
| Subject: | NDA 21-287 Phase 4 commitment |

mmsinfo.txt

Ms Jean King
FDA Reproductive Drugs Division

This will confirm that Sanofi-Synthelabo accepts the phase 4 commitment requested in your 12 June 2003 fax to conduct a study of the impact on QT
interval prolongation of combining a phosphodiesterase-5 inhibitor (sildenafil or vardenafil) with alfuzosin at steady state drug levels.

A draft protocol for this study will be provided within 6 months of NDA approval; study initiation will begin within 12 months of approval and a final report will be delivered within 20 months of approval.

Jon Villaume

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE: June 12, 2003**

**To:** Jon Villaume, Ph.D.

**Company:** Sanofi-Synthelabo, Inc.

**Fax number:** 610-889-6993

**Phone number:** 610-889-6028

**From:** Jean King

Division of Division of Reproductive and Urologic Drug Products

**Fax number:** 301-827-4267

**Phone number:** 301-827-4260

**Subject:** NDA 21-287: revised PI containing FDA comments and revised phase 4 commitment proposal for alfuzosin HCL

**Total no. of pages including cover:** 19

**Comments: Please see below.**

**Document to be mailed:** **YES** **NO**

Dear Dr. Villaume,

Please find attached the Division's revised PI for discussion on our continued teleconference this afternoon.

Additionally, our Phase 4 commitment proposal for NDA 21-287 (alfuzosin hydrochloride) has been revised as follows:

**Commitment # 1**

Sanofi-Synthelabo, Inc. will conduct a study to evaluate the impact on QT interval prolongation of combining a phosphodiesterase-5 inhibitor (sildenafil or vardenafil) with alfuzosin at steady state drug levels.

The timeline is as follows:

- Draft protocol submission — within six months of the date of this letter
- Study initiation — within 12 months of the date of this letter
- Submission of Clinical Study Report — within 18 months of the date of this letter

We will also discuss this on the conference call to be resumed this afternoon. A letter of acceptance that includes the agreed upon Phase 4 commitment must be sent via fax to us for incorporation into a final action letter.

Sincerely,

Jean King, M.S., R.D.
Regulatory Project Manager

Confirmation Report – Memory Send

Page : 001
Date & Time: Jun-10-03 04:00pm
Line 1 : 301-827-4267
Line 2 :
Machine ID : FDA/CDER/OND/ODE3/DRUDP

Job number : 177

Date : Jun-10 04:00pm

To : ☎916108896993

Number of pages : 002

Start time : Jun-10 04:00pm

End time : Jun-10 04:00pm

Pages sent : 002

Status : OK

Job number : 177 *** SEND SUCCESSFUL ***

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

**DATE: June 10, 2003**

**To:** Jon Villaume, Ph.D.
**Company:** Sanofi-Synthelabo, Inc.
**Fax number:** 610-889-6993
**Phone number:** 610-889-6028

**From:** Jean King
Division of Division of Reproductive and Urologic Drug Products
**Fax number:** 301-827-4267
**Phone number:** 301-827-4260

**Subject:** NDA 21-287: phase 4 commitment proposal for alfuzosin HCL

**Total no. of pages including cover:** 1

**Comments:** Please see below.

**Document to be mailed:** YES NO

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

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Dear Dr. Villaume,

Please find below a Phase 4 commitment proposal sent on behalf of the Division of Reproductive and Urologic Drug products for NDA 21-287 (alfuzosin hydrochloride):

- Conduct a study to evaluate the impact on QT interval prolongation of combining a phosphodiesterase-5 inhibitor (sildenafil or vardenafil) with alfuzosin at steady state drug levels.

A teleconference to discuss this proposal as well as labeling has been scheduled for tomorrow, June 11, 2003 from 11:00-1:00 PM Eastern.

Sincerely,

Jean King, M.S., R.D.
Regulatory Project Manager

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE: June 10, 2003**

**To:** Jon Villaume, Ph.D.

**Company:** Sanofi-Synthelabo, Inc.

**Fax number:** 610-889-6993

**Phone number:** 610-889-6028

**From:** Jean King

Division of Division of Reproductive and Urologic Drug Products

**Fax number:** 301-827-4267

**Phone number:** 301-827-4260

**Subject:** NDA 21-287: phase 4 commitment proposal for alfuzosin HCL

**Total no. of pages including cover:** 1

**Comments: Please see below.**

**Document to be mailed:** YES NO



Dear Dr. Villaume,

Please find below a Phase 4 commitment proposal sent on behalf of the Division of Reproductive and Urologic Drug products for NDA 21-287 (alfuzosin hydrochloride):

- Conduct a study to evaluate the impact on QT interval prolongation of combining a phosphodiesterase-5 inhibitor (sildenafil or vardenafil) with alfuzosin at steady state drug levels.

A teleconference to discuss this proposal as well as labeling has been scheduled for tomorrow, June 11, 2003 from 11:00-1:00 PM Eastern.

Sincerely,

Jean King, M.S., R.D.
Regulatory Project Manager

---

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/s/

---

Jean R. King
6/10/03 04:54:06 PM

NDA 21-287
Alfuzosin HCl
Sanofi-Synthelabo

Post Marketing Commitments

Not applicable for this application.

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Special Programs

Not applicable to this application.

/s/

F. M. S. RD

5/15/03

NDA 21-287
Alfuzosin Hydrochloride
10 mg extended release tablets

Public Communications

Not applicable for this application.

/S/ M.S., RD
5/16/03

NDA 21-287
Alfuzosin HCl
Sanofi-Synthelabo

Press Office Information

Not applicable for this application.

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 5, 2001

From: Jeanine Best, M.S.N., R.N.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-287

I have reviewed the financial disclosure information submitted by Sanofi-Syntholabo, Inc. in support of their NDA 21-287 for alfuzosin hydrochloride.

Three pivotal studies were conducted to assess the safety and efficacy of alfuzosin hydrochloride. This product is indicated for the once daily treatment of benign prostatic hyperplasia. The study numbers and the results of the review of financial disclosure documents are summarized below:

| Study Number/Title | Study Status | Financial Disclosure Review |
|---|---|---|
| Study ALFUS, 99-00591-EN-00 / "Efficacy and Safety of Alfuzosin Once-Daily Tablets at 2 Dosage Levels (10 mg and 15 mg) Versus Placebo in Patients with Benign Prostatic Hyperplasia: A Placebo-Controlled, Double-Blind Study, Conducted in 3 Parallel Groups for 3 Months Followed by two (a 9-Month and a 12-Month) Open-Label Extensions Of Alfuzosin OD (15 mg)" | Ongoing as of 2/2/99 | Appropriate documentation received, financial disclosure submitted. |
| Study ALFOTAM, 99-00925-EN-00 / "Efficacy and Safety of Two Dosages of Alfuzosin Geomatrix (10 mg and 15 mg) versus Tamsulosin (0.4 mg) and Placebo in Patients with Benign Prostatic Hyperplasia." | Ongoing as of 2/2/99 | Appropriate documentation received, financial disclosure submitted. |
| Study ALFORTI, 09-00741-EN-01/ "Efficacy and Safety of Alfuzosin Geomatrix 10 mg OD Versus Alfuzosin 2.5 mg TID and PLB in Patients with Symptomatic Benign Prostatic Hyperplasia." | Double-Blind, Efficacy phase completed 8/98: Open-Label, Follow-up Safety Phase completed 4/99 | Appropriate documentation received, no financial disclosure submitted. |

**Documents Reviewed:**

- financial certification and disclosure Information submitted December 8, 2000
- amendment to financial disclosure information submitted June 27, 2001; information submitted in response to Division request of May 18, 2001

**Study ALFUS**

There were 196 investigators (principal and subinvestigators) at 36 sites in this trial. Financial certification/disclosure information was received from all investigators except the following:

- Site 3830 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.1% of the patients in the study
- Site 3296 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.9% of the patients in the study
- Site 3309 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 3.2% of the patients in the study
- Site 3301 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 7.6% of the patients in the study
- Site 3305 had 3 subinvestigators for whom financial disclosure information was not received; this site enrolled 4.4% of the patients in the study
- Site 3298 had 2 subinvestigators for whom financial disclosure information was not received; this site enrolled 4.6% of the patients in the study
- Site 3314 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 4.6% of the patients in the study
- Site 3294 had 1 principal investigator and 9 subinvestigators for whom financial disclosure information was not received; this site enrolled 1.1% of the patients in the study; this site stopped participation in the study in September 1998, and all investigators at this site have refused to sign any financial certification documentation

One principal investigator in this study had disclosable information:

- Site 3311, Dr. Claus Roehrborn, principal investigator of this site also served as the principal investigator for the ALFUS study; Site 3311 enrolled 2.1% of the patients in the study

**Study ALFOTAM**

There were 156 principal and subinvestigators (investigators) at 82 sites in this trial. Financial certification/disclosure information was received for all principal investigators. The following sites had subinvestigators for whom financial certification/disclosure information was not received:

- Site 1157 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 1.5% of the patients in the study
- Site 2668 had 1 subinvestigator for whom financial disclosure information was not received; this site enrolled 2.8% of the patients in the study

Two principal investigators in this study had disclosable information:

- Site 3353, Dr. Jorgen Nordling, principal investigator of this site also served as the principal investigator for the ALFUS study, Site 3353 enrolled 3.8% of the patients in the study
- Site 104, Dr. Alain Jardin, principal investigator for this site, has also had an on-going relationship with Sanofi-Synthelabo's French operating division Site 104 enrolled 1.0% of the patients in the study

**Study ALFORTI**

The double-blind, efficacy phase of Study ALFORTI was completed in August 1998, therefore, there is no requirement for collection of certifications from the individual investigators. The sponsor has submitted certification for the requirements under 21 CFR 54.2, that none of the investigators participating in Study ALFORTI had "compensation affected by the outcome of clinical studies", or "proprietary interests in the tested product". The open-label, safety phase of Study ALFORTI was completed in April 1999, but does not meet the definition of a "covered clinical study" for financial disclosure requirements because the study was conducted at multiple sites (49), with 444 patients, in which no single investigator made a significant contribution to the demonstration of safety.

The sponsor employed the following mechanisms in an attempt to obtain Financial Disclosure forms from investigators:

- a request was made during the course of the trial
- if not received, follow-up telephone calls and/or mail requests were made

The sponsor states that the principal reason financial disclosure information could not be obtained was that the requirement to obtain certification went into effect after the studies were underway and that some investigators had left their sites and could not be contacted.

**Conclusion:**

Adequate documentation was submitted to comply with 21 CFR 54. While the sponsor could have used other means to obtain documentation from non-compliant investigators, the rate of return is acceptable. The disclosure of financial interests from three investigators is unlikely to bias the outcome of the studies because none of these investigators enrolled a significant amount of the study patients at their sites.

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/s/
Jeanine Best
7/5/01 03:08:51 PM
CSO

Confirmation Report – Memory Send

Page : 001
Date & Time: May-20-03 12:28pm
Line 1 : 301-827-4267
Line 2 :
Machine ID : FDA/CDER/OND/ODE3/DRUDP

Job number : 992
Date : May-20 12:27pm
To : ☎916108896993
Number of pages : 005
Start time : May-20 12:27pm
End time : May-20 12:28pm
Pages sent : 005
Status : OK

Job number : 992 *** SEND SUCCESSFUL ***

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: May 20, 2003

To: Jon Villaume, Ph.D.
Company: Sanofi-Synthelabo, Inc.
Fax number: 610-889-6993
Phone number: 610-889-6028

From: Jean King
Division of Division of Reproductive and Urologic Drug Products
Fax number: 301-827-4267
Phone number: 301-827-4260

Subject: NDA 21-287: trade name review advice lotter

Total no. of pages including cover:

Comments: Please find below comments regarding this request.

Document to be mailed: YES NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE:** May 20, 2003

**To:** Jon Villaume, Ph.D.

**Company:** Sanofi-Synthelabo, Inc.

**Fax number:** 610-889-6993

**Phone number:** 610-889-6028

**From:** Jean King

Division of Division of Reproductive and Urologic Drug Products

**Fax number:** 301-827-4267

**Phone number:** 301-827-4260

**Subject:** NDA 21-287: trade name review advice letter

**Total no. of pages including cover:**

**Comments: Please find below comments regarding this request.**

**Document to be mailed:** YES NO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-287

Sanofi-Synthelabo Inc.
Attention: Jon Villaume, Ph.D.
Senior Director
9 Great Valley Parkway
Malvern, PA 19355

Dear Dr. Villaume:

We acknowledge receipt on December 12, 2002, of your December 12, 2002, complete response submission (Amendment 036) to your new drug application for alfuzosin hydrochloride.

We also acknowledge receipt of your December 16, 2002, submission (Amendment 037) requesting a brand name review for your preferred brand name [redacted] and preferred alternate brand name, [redacted]

The Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) and the Division of Drug Marketing, Advertising, and Communications (DDMAC) completed the reviews of your submission and have the following comments and recommendations, which were conveyed to you during our teleconference on May 16, 2003.

DMETS and DDMAC Comments to the Sponsor

DMETS does not recommend the use of the proprietary name [redacted] However, DMETS has no objections to the use of the proprietary name [redacted] from a safety perspective.

In reviewing the proprietary name [redacted] the primary concerns raised were related to two look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Duricef and Aricept.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between [redacted] and Duricef or Aricept. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name [redacted] However, a negative finding does not discount the potential for name confusion given the limited predicative value of these studies, primarily due to the sample size.

Duricef and the proposed name [redacted] look similar when scripted (see below). Duricef contains cefadroxil, a cephalosporin antibiotic indicated for the treatment of urinary tract infections, skin

and skin structure infections, pharyngitis, and tonsillitis. Depending on the condition being treated, the recommended dose of Duricef can range from 1 to 2 grams per day, given in divided doses. Both names contain seven letters and similar letter combinations at the beginning of each name ("Duri" vs. [redacted]. The capital letters "D" and [redacted] can also look similar when scripted. Additionally, the letter combinations at the end of each name ("cef" vs. [redacted]) look almost identical when written. Although Duricef has multiple strengths (500 mg, 1 gram, 125 mg/mL, 250 mg/mL, and 500 mg/mL), Duricef and [redacted] do share overlapping numerals in their strengths (1 g vs. 10 mg). Additionally, the products overlap in dosage form (tablets), route of administration (oral), and dosing regimen (once daily). These similarities in addition to the similarities of the look-alike characteristics increase the potential for confusion between Duricef and [redacted]. Should a patient receive Duricef instead of [redacted] they would lose the pharmacological effects of [redacted] and would also be at risk for experiencing side effects associated with Duricef. These include gastrointestinal upset, anaphylaxis, rash, and blood dyscrasias.

**Duricef** **Urilief**

Duricef | |

Aricept and the proposed name [redacted] look similar when scripted (see below). Aricept contains the active ingredient donepezil, and is indicated for the treatment of mild to moderate dementia associated with Alzheimer's Disease. The recommended dosage of Aricept is 5 mg or 10 mg daily. Both Aricept and [redacted] contain seven letters and three syllables. Additionally the beginning of each name can look similar when scripted ("Ari" vs. [redacted]). The endings of the names are more distinguishable due to the presence of the letter "p" in Aricept. However, the ending letter combinations of each name share some look-alike characteristics ("cept" vs. [redacted]) due to the similarities in the scripted letter combinations "ce" and [redacted], and "t" and [redacted] In addition to the look alike characteristics of the drug products, Aricept and [redacted] also share overlapping strengths (10 mg), dosage form (tablet), route of administration (oral), and dosing regimen (once daily). If an inpatient or outpatient prescription order were written for either drug product for example "Aricept 10 mg qd" or [redacted] 10 mg qd", the similarities in the look-alike characteristics as well as the strength and dosing regimen of the products, would increase the likelihood of drug name confusion. Lastly, Aricept and [redacted] are likely to be used in ~~similar~~ patient populations. Therefore, if a prescription for either medication is written poorly, and misread, the error could remain undetected as either medication would be appropriate for use in the same patient population. Should a patient receive Aricept instead of [redacted] he would be at risk for experiencing side effects associated with Aricept, such as nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.

**Aricept** [redacted]

Aricept 10mg | Aricept 10mg

DMETS and DDMAC Recommendations to the Sponsor

1. DMETS does not recommend the use of the proprietary name [redacted]. However, DMETS has no objections to the use of the proprietary name [redacted] from a safety perspective. DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DMETS requests submission of the container label, carton and insert labeling when available.

3. DDMAC does not recommend the use of the names [redacted] and [redacted] from a promotional perspective for the following reasons: The name [redacted] is misleading and implies total relief of benign prostatic hyperplasia (BPH) symptoms, and the name [redacted] is not acceptable because it is overly fanciful.

If you have additional information that you would like DMETS to consider, please forward this to the Division of Reproductive and Urologic Drug Products.

If you have any questions, call Jean King, M.S., R.D., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

---

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/s/

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Donna Griebel
5/19/03 06:02:41 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

# FACSIMILE TRANSMITTAL SHEET

**DATE: April 1, 2003**

**To:** Jon Villaume, Ph.D.

**Company:** Sanofi-Synthelabo, Inc.

**Fax number:** 610-889-6993

**Phone number:** 610-889-6028

**From:** Jean King

Division of Division of Reproductive and Urologic Drug Products

**Fax number:** 301-827-4267

**Phone number:** 301-827-4260

**Subject:** NDA 21-287: Request for electronic files containing alfuzosin HCL QT data

**Total no. of pages including cover:**

**Comments: Please find below comments regarding this request.**

**Document to be mailed:** YES NO

Dear Dr. Villaume,

The Division is planning to complete an analysis of QT data for alfuzosin. We need the following electronic data files in SAS/ASCII format for study PDY5105:

- Data file that includes subject ID, dosing details, demographics, HR, RR intervals, QT and QTc measurements, plasma concentrations and Cmax and AUC of alfuzosin in one file (all tagged by subject ID) and the same for moxifloxacin in another file.

- All the control and data files (electronic) that were utilized in the QT analysis of the study PDY5105.

Sincerely,

Jean King, M.S., R.D.
Regulatory Project Manager

---

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/s/

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Jean R. King
4/1/03 02:51:49 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

# FACSIMILE TRANSMITTAL SHEET

**DATE: September 6, 2001**

| | |
|---|---|
| **To:** Kevin Malovisky | **From:** Evelyn R. Farinas |
| **Company:** Sanofi-Synthelabo, Inc. | Division of Division of Reproductive and Urologic Drug Products |
| **Fax number:** 9-1-610-889-6993 | **Fax number:** 301-827-4272 |
| **Phone number:** 9-1-610-889-6028 | **Phone number:** 301-827-4260 |

**Subject:** NDA 21-287 alfuzosin, request for editorial clarification of tables in Biopharmaceutics section

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO

Attachment:

Dear Kevin:

As Dr. Jarugula mentioned in today's telephone conversation, please correct the errors noted in the following tables:

| | |
|---|---|
| Table (1.4.2) | Page 26 |
| Table (1.4.3) | Page 28 |
| Table (1.4.~~4~~)1 | Page 32 |
| Table (1.4.5.3)3 | Page 41 |
| Table (1.5.2)2 | Page 44 |
| Table (1.5.5)1 | Page 49 |
| Table (1.6.2.2.2)1 | Page 54 |
| Table (2.5.4.1)1 | Page 74 |
| Table (3.2.2)1 | Page 79 |
| Table (3.3.2.2)1 | Page 86 |

Please also address Dr. Jarugula's question regarding whether there is a f ood effect with the immediate release 2.5 mg formulation.

Thanks for your looking into these requests.

Evelyn

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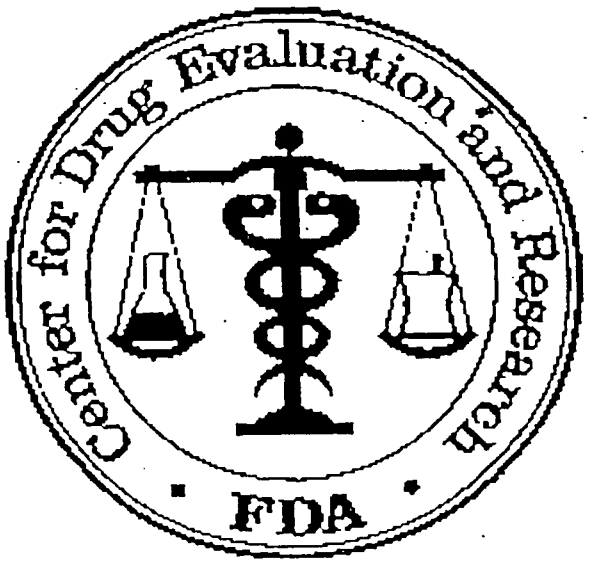
/s/

Evelyn Farinas
9/6/01 03:57:29 PM
CSO

FOOD AND DRUG ADMINISTRATION
DIVISION OF REPRODUCTIVE AND
UROLOGIC DRUG PRODUCTS, HFD-580
DOCUMENT CONTROL ROOM 17B-20
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

DATE: August 23/2001




TO: Sanofi - Synthelabo
Name: Dr. Jon Villaume
Fax No: 610 - 889 - 6993
Phone No:
Location:

FROM: DRUDP
Name: Evelyn Fariñas
Fax No: (301) 827-4267
Phone No: (301) 827-4260
Location: FDA, Division of Reproductive and Urologic Drug Products



Comments:

concurrence:

# MEMORANDUM OF TELECON

DATE: August 22, 2001

APPLICATION NUMBER: NDA 21-287, alfuzosin hydrochloride

BETWEEN:

Name: Jon Villaume, Senior Regulatory
Phone: 610-889-6028
Representing: Sanofi-Synthelabo

AND

Name: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: recommendations for proposed label

The Toxicology reviewer recommends that you incorporate the following, as a second sentence, in the first paragraph of the **"Carcinogenesis, Mutagenesis, and Impairment of Fertility"** subsection of the **PRECAUTIONS** section:

"The doses tested in female mice may not have constituted a maximally tolerated dose."

/S/

Evelyn R. Farinas
Regulatory Project Manager

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/s/

Evelyn Farinas
8/23/01 03:02:57 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

# FACSIMILE TRANSMITTAL SHEET

**DATE: August 20, 2001**

| | |
|---|---|
| **To:** Jon Villaume | **From:** Evelyn R. Farinas |
| **Company:** Sanofi-Synthelabo | Division of Reproductive and Urologic Drug Products |
| **Fax number:** 610-889-6993 | **Fax number:** 301-827-4267 |
| **Phone number:** | **Phone number:** (301) 827-4260 |

**Subject:** CMC information request

NDA 21-287

**Total no. of pages including cover:** 3

**Comments:** Please see attachments.

**Document to be mailed:** ☐ YES ☑ NO

Attachment:

Dear Jon:

The Chemistry reviewer will like your reply as soon as possible, and to accomplish that, she suggested a facsimile followed by a hard copy to the submission.

Please let me know if you have questions or need clarification.

Take care,

Evelyn

- In the drug product specification, if Average Tablet Weight is used instead of Water Content, acceptance criteria for Average Tablet Weight should be implemented for stability testing as well as release testing.

- Please confirm that the three lots 20017, 20020, and 20021 are production lots that are the same as to-be-marketed lots regarding manufacture and packaging.

- Based on the available stability data, the expiry for the drug product in all container/closure systems should be 24 months at room temperature.

- Please add the statement "An extension of the expiration dating period will be based on full long-term stability data from three production lots in accordance with the stability protocol approved in the NDA" to the post-approval stability commitment.

- The statement "Protect from light and moisture" should remain on the container labels and in the package insert because the drug substance is hygroscopic, and one of the major degradation products results from light exposure.

- Please remove the word "NEW" from all container labels.

- The size of the font used for the established name in the container labels is not acceptable:
  - The height of "alfuzosin HCl" should be more than 50% of the height of the capital letters in "Uroxatral"
  - The width of the letters in "alfuzosin HCl" is too narrow, rendering "alfuzosin HCl" almost illegible.

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/s/
---
Evelyn Farinas
9/12/01 08:17:15 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Researc
Office of Drug Evaluation III

# FACSIMILE TRANSMITTAL SHEET

**DATE: August 7, 2001**

| | |
|---|---|
| **To:** Jon Villaume | **From:** Evelyn R. Farinas |
| **Company:** Sanofi-Synthelabo | Division of Division of Reproductive and Urologic Drug Products |
| **Fax number:** 610-889-6993 | **Fax number:** 301-827-4267 |
| **Phone number:** 610-889-6028 | **Phone number:** 301-827-4260 |

**Subject:** Request for additional Biopharmaceutics information.

**Total no. of pages including cover:** 2

**Comments:**

**Document to be mailed:** ☐ YES ☑ NO



Attachment

August 7, 2001

Dear Jon:

Could you provide the following information to facilitate the biopharmaceutics review process:

1. Please provide all the raw data used in developing and validating IVIVC under fasting conditions (electronic version will be appreciated).

2. In order to better support the external predictability, please provide the comparison of experimental and predicted plasma concentration profiles for formulations KYA01 and KYA02, and comparison of predicted concentration profiles for clinical (PDV03) and commercial (PDV08) formulations.

3. Please provide raw data used for showing condition independent dissolution of alfuzocin ER formulation.

Thank you,,

Evelyn

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/s/

Evelyn Farinas
8/9/01 10:52:55 AM
CSO

# Meeting Minutes

**Date**: January 7, 2002 **Time**: 3:30-5:00 PM, EDT **Location**: PKLN; CR "C"

**NDA 21-287** **Drug:** alfuzosin hydrochloride

**Indication:** Benign Prostatic Hypertrophy (BPH)

**Sponsor**: Sanofi-Synthelabo, Inc.

**Type of Meeting**: Guidance (End of NDA Review)

**Meeting Chair**: Daniel Shames, M.D.

**Meeting Recorder**: Dornette Spell-LeSane, NP-C, MHA

**FDA Attendees**:
Daniel Shames, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Florence Houn, M.D., M.P.H., Office Director, ODE III (HFD-103)
Douglas C. Throckmorton, M.D., Deputy Division Director, Division of Cardio-Renal Drug Products (DCRDP; HFD-110)
Mark Hirsch, M.D., Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D., Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D., Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Sam Haidar, R.Ph., Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Judy Racoosin, M.D., M.P.H., Safety Team Leader, Division of Neuropharmacological Drug Products (HFD-120)
Harry Handelsman, M.D., Medical Officer DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

**External Attendees:**
Jon Villaume, Regulatory Affairs, Sanofi-Synthelabo

Alex Boddy, Biostatistics, Sanofi-Synthelabo
Jean-Lai Pinqurer, MD, Clinical Pharmacology, Sanofi-Synthelabo
Jim Opperman, Clinical Pharmacology, Sanofi-Synthelabo

Marie Delarnche, Project Director, Sanofi-Synthelabo
Richard Gural, Regulatory Affairs, Sanofi-Synthelabo
Neciar Joseph, Clinical Pharmacology, Sanofi-Synthelabo

**Meeting Objective**:
To discuss the issues raised in the October 5, 2001, FDA Approvable letter.

**Background**:
NDA 21-287 was submitted December 8, 2000, for alfuzosin HCl, which is a new molecular entity (NME). The End of Phase 2 meeting was held August 13, 1997, and the pre-NDA meeting took place on May 24, 2000. The 10-month PDUFA goal date was October 8, 2001. In the October 5, 2002, Approvable letter issued by the Agency, the sponsor was notified that the application lacked adequate information to determine whether the drug is safe for use because alfuzosin may increase the QTc interval. The Approvable letter stated that the QTc interval should be measured using a FDA agreed upon validated methodology. The Approvable letter also stated that additional pharmacokinetic and pharmacodynamic studies are necessary to determine the effect that maximum doses of an inhibitor of the cytochrome P450 3A4 isoenzyme (e.g., ketoconazole) has on the QTc interval. The sponsor requested an "end of review" meeting on November 6, 2001, and submitted a meeting package on November 19, 2001. The sponsor indicated that the meeting package contains their proposals to address the issues stated in the Approvable letter.

**Discussion:**

- Dr. Throckmorton stated that the question at the beginning of FDA's review was "Does this drug (alfuzosin hydrochloride) effect cardiac repolarization in humans?" The answer to this question remains unclear for this drug product; the methods used by Dr. Malik and the Holter recording models are not validated using appropriate concurrent controls in the materials submitted by the sponsor; in the absence of such controls the FDA cannot agree that alfuzosin has no effect on repolarization
- an additional study is necessary to address the repolarization issues; the Agency recommends that the sponsor propose a study using both standard correction methods and the Holter-based method they have proposed, incorporating controls to describe the sensitivity and specificity of those correction factors in the patient studies
- the sponsor presented the following slides: QT correction for changes in heart rate, QT correction for drug-induced change in HR and differences between Fridericia and Bazett methods, and assumptions used in the Malik method
- the Agency responded that the Malik method must be validated such that its ability to detect drug effect and not detect effect are demonstrated
- the sponsor presented slides regarding their heart rate independent method; and concluded that the Heart Rate Independent approach has been used in other clinical settings; validation procedures include lab validation using synthesized ECG files
- the agency stated that the data presented may not be sufficient to address validation needs and safety concerns
- the agency stated that *in vitro* data will not be helpful
- the Agency questioned machine read versus manual reading of ECG ; it was recommended that prior to initiating a new study on QT, the sponsor obtain comments from FDA on the protocol
- in summary, the Agency reiterated the need for an additional clinical trial with a positive and negative control to test the hypothesis that the drug does not affect repolarization; Postmarketing data will not be adequate to address this safety concern
- as was suggested by Dr. Racoosin at the meeting, one approach would be for the QT interval (and serum drug level) to be assessed in subjects at steady state on alfuzosin or the other selected controls; subsequently, an appropriate metabolic inhibitor would be added (400 mg of ketoconazole for alfuzosin), and the QT interval (and serum drug level) reassessed once

the subject had reached steady state again on their assigned drug; this approach would obviate the need for a separate clinical pharmacology study to assess the effect of full inhibition of CYP 3A4 on alfuzosin levels; note that this approach was used to assess the effect of ziprasidone on the QT interval; for details see the transcript for the ziprasidone advisory committee meeting, July 19, 2000 (http://www.fda.gov/ohrms/dockets/ac/cder00.htm#Psychopharmacolgic Drugs)

Clinical Pharmacology and Biopharmaceutic comments:

- based on the literature, there appears to be dose related-effect for ketoconazole interaction (4 to 16 fold change in midazolam, 9 to 22 fold change in triazolam; 2 to 4 fold change in alprazolam depending on the dose of ketoconazole).
- at 200 mg dose, although the mean change with alfuzosin was 2.5 fold; there were 3 out 12 subjects with more than 4fold increases in AUC.
- theoretically, in vivo prediction based on models using in vitro Ki might be true qualitatively; however models have not been consistent in predicting in vivo interactions quantitatively.
- interaction with alfuzosin at 400 mg dose of Ketoconazole could be potentially higher than 200 mg dose.
- drug interaction and QT effects of alfuzosin with 400 mg ketoconazole dose need to be further studied (if feasible ketoconazole part can be included in the clinical QT study). The fact that ketoconazole itself might have some QT effects should be considered in designing the drug interaction study.

**Decisions Reached:**

- there is insufficient evidence to resolve the safety issue; the sponsor must characterize drug effect on QT and validate the methods used; to address this issue, FDA stated that a study to show that alfuzosin does not have a QTc interval effect (or if it does, the study must quantify the effect) is needed; the study should be an adequately powered study with positive and negative controls that demonstrate small QT effects are captured by the assay; the sponsor is advised to provide to the FDA the protocol for comments prior to initiation of the study to ensure methods and analysis are acceptable
- the sponsor understands that FDA is asking for additional clinical and pharmacological studies
- the studies should be conducted using doses including therapeutic and supra-therapeutic doses (at least 3x)
- the Agency does not oppose the sponsor separating the two studies, the clinical from the pharmacokinetic studies

**Action Items:**

- the sponsor may review FDA recommendations and submit a proposal to the Agency as a "Complete Response"
- Biopharmaceutics review team will provide literature references for ketoconazole drug interaction studies (see below)
- the sponsor may request further discussion from the Clinical Pharmacology and Biopharmaceutics reviewers as needed
- meeting minutes will be conveyed to the sponsor within 30 days

Literature references for ketoconazole drug interaction studies:

1. Pharmacogenetics 1999: 9(6): 725-34
2. Clin Pharmacol Ther 1998:64:237-247
3. J Pharmacol Exper Ther 1996:276:370-379
4. Clin Pharmacol Ther 1998:64:237-247
5. Clin Pharmacol Ther 1994:56:601-607
6. J Clin Pharmacol 1999 Dec:39(12):1212-20
7. Clin Pharmacol Ther 1999 Nov:66(5):461-71
8. Clin Pharmacol Ther 1994 May:55(5):481-5

**Note to Sponsor**: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

NDA 21-287
Drafted: Spell-LeSane/1.23.02
Concurrence: Moore 1.23.02/Throckmorton 1.23.02/Houn 1.23.02/Batra 1.23.02 Hirsch 1.28.02/Racoosin 1.28.02; Jarugula 1.28.02/
Finalized: Farinas/2.13.02

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/s/

Daniel A. Shames
2/13/02 03:00:40 PM

# Meeting Minutes

**Date:** September 25, 2001 **Time:** 4:30-5:30 PM, EST **Location:** PKLN; 17B45

**NDA 21-287** **Drug:** alfuzosin hydrochloride

**Indication:** benign prostatic hyperplasia (BPH)

**Sponsor:** Sanofi-Synthelabo, Inc.

**Type of Meeting:** Multidivisional Advisory Meeting

**Meeting Chair:** Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD 180)

**Meeting Recorder:** Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**FDA Attendees:**
Florence Houn, M.D. - Director, Office of Drug Evaluation III (ODE III; HFD 103
Susan Allen, M.D., M.P.H. - Director, DRUDP (HFD 180)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Douglas Throckmorton, M.D. – Deputy Director, Division of CardioRenal Drug Products (DCRDP; HFD 110)
Mark Hirsch, M.D. – Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Venkat Jarugula, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Judy Racoosin, M.D., M.P.H.– Safety Team Leader, Division of Neuropharmacological Drug Products (DNDP; HFD-120)
Leonard Sacks, M.D. – Medical Officer, DSPIDP (HFD 590)
Joette Meyer, Pharm.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DSPIDP (HFD 880)
Phil Colangelo, Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DSPIDP (HFD 880)
Melodi McNeil – Acting ADRA, ODE III (HFD-103)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

**Meeting Objective:** To discuss the impact of QT interval prolongation findings on any future action for this NDA.

**Background:**
The sponsor submitted this application for alfuzosin hydrochloride on December 8, 2000, for the treatment of BPH. Alfuzosin hydrochloride is an alpha blocker, similar to Hytrin, Cardura and Flomax. A Phase 1 study showed that one patient experienced a prolonged QT interval of 71 milliseconds. A retest of this patient showed a normal QT interval. The 120-day safety review, submitted in April 2001, included results of four additional studies addressing QT interval. Of

these, Study 4532 showed dose-related increases in the mean QT interval with the 20-mg and with the 40-mg dose. The sponsor stated that alpha blockers increase the heart rate, and thus, the Bazett's and the Fridericia's corrections of QT interval in Study 4532 were performed. The sponsor argues that Bazett's and Fridericia's corrections over-estimate the QT interval and that QT measurement using Holter monitoring is more accurate. The sponsor calculated QT intervals using Holter monitor readings, which indicated a mean increase in the QT interval of only two milliseconds. The CardioRenal Division was asked to review the results of the studies addressing the prolongation of the QT interval provided by the sponsor in the 120-day safety update. The CardioRenal Division concluded that alfuzosin prolongs the QT interval by approximately 10 milliseconds.

**Discussion:**

- Regarding alfuzosin, it was stated that:
  - alfuzosin has been approved in foreign markets, in several dosage forms
  - efficacy appears to be similar to that of other alpha blockers indicated for BPH; administration of 15 mg of alfuzosin led to increased incidence of adverse events compared to 10 mg
  - Study 4532, in this NDA, raised concerns about the potential for QT interval prolongation with the use of alfuzosin
- Regarding the use of Holter Monitor, it was stated that:
  - there are concerns about the validity of using HM to assess QT interval
  - Fridericia's correction is considered a more accurate alternative method for correcting QT measurements for heart rate where increasing heart rate is an issue; however, the Fridericia correction may still cause a slight underestimation of the corrected QT duration
  - as an alternate method to correct QT interval for heart rate, some Divisions have asked sponsors to generate their own correction factors using baseline ECGs or baseline ECGs from the placebo group
  - to strengthen the findings of HM method used, the sponsor should validate it using another drug known to cause QT interval prolongation and one that is not known to prolong QT (a negative control)
- Regarding the significance of the magnitude of increases in the QT interval, it was stated that:
  - the ketoconazole alfuzosin drug interaction study in this NDA was conducted with a low ketoconazole dose (i.e., 200 mg) and the QT interval was not recorded at an appropriate time; the alfuzosin levels increased two and a half times (2.5) with the concomitant use of 200 mg of ketoconazole; potentially, a higher ketoconazole dose would yield greater levels of alfuzosin
  - in situations where there are existing therapies, the tolerance for risk is lower in "me-too" drugs
- Regarding the sponsor's contention that their long marketing history in Europe without evidence of Torsades de Pointes cases indicates a lack of evidence of effect on the QT interval:
  - cases of Torsades de Pointes are difficult to document even with drugs known to substantially prolong the QT interval
  - sudden deaths occurring in the population of patients likely to use alfuzosin (i.e., elderly men) are not uncommon and would not likely be attributed to the drug; therefore, lack of reported cases does not ensure a lack of effect on the QT
- Regarding a dose response QT interval effect, it was stated that:
  - seeing a dose response QT interval increase provides greater confidence that there may be a real effect on the QT interval

- data obtained from the use of Fridericia's correction should not be discounted because if anything, it will slightly underestimate the QT interval duration in a drug that causes tachycardia

- Regarding the availability of QT interval history with alpha blockers, it was stated that:
  - the incidence of QT interval prolongation with other alpha blockers indicated to treat BPH is not known
  - an OPDRA consult regarding data on incidence of QT interval prolongation for older alpha blockers was not issued; however
- Regarding possible sponsor's approaches to address the alfuzosin QT interval prolongation, it was stated that DRUDP could request:
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**Decisions:**

- the data submitted by the sponsor appears to indicate that there is a real QT interval prolongation effect
- DRUDP will recommend an approvable action, and recommend study(ies) for the sponsor to address the QT interval prolongation
- members of the QT working group, and experts participating in this meeting, will provide advise to assess the validity of the protocols requested from the sponsor when these arrive at DRUDP

**Action Items:**

- DRUDP will recommend an approvable action for this application
- QT working group and experts will be asked to provide advice when the requested studies to assess QT interval increase are submitted

ADDENDUM:
The Office of Postmarketing Drug Risk Assessment (OPDRA) was asked to review the available databases for reports indicating that alfuzosin prolongs the QT interval. In addition, OPDRA was asked to research the available databases for reports indicating that Hytrin, Cardura or Flomax prolong the QT interval.

Drafted: Farinas 9.26.01
Concurrence: Shames 9.26.01/Rumble/Benson 9.26.01/Batra 9.26.01/Jarugula 9.26.01 /Hirsch 9.26.01/Allen /McNeil 9.27.01/Sacks 10.2.01/Throckmorton 10.1.01/Racoosin 9.28.01/Meyer 10.01.01
Finalized: Farinas/10.3.01

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/s/

Daniel A. Shames
10/3/01 11:23:14 AM

Teleconference Minutes

**Date:** September 6, 2001 **Time:** 2:40-2:50 PM, EDT **Location:** PKLN; 17b45

NDA 21-287 **Drug:** alfuzosin hydrochloride **Indication:** benign prostatic hyperplasia

**Sponsor:** Sanofi-Synthelabo, Inc.

**Type of Meeting:** Guidance

**Meeting Chair:** Venkat Jarugula, Ph.D. - Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

**External Lead:** Kevin Malovisky, Regulatory Affairs

**Meeting Recorder:** Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

**FDA Attendees:**
Venkat Jarugula, Ph.D. - Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

**External Attendees:**
Kevin Malovisky – Regulatory Affairs

**Meeting Objective:** To notify the sponsor of editorial errors discovered in tables in the Biopharmaceutics section of this application.

**Background:** NDA 21-287 was submitted December 8, 2000, for alfuzosin HCl, which is a new molecular entity (NME). Editorial errors were discovered in the Biopharmaceutics section of this application during its ongoing review.

**Discussion:**

- the sponsor was asked to review and correct editorial errors found in the following tables in the Biopharmaceutics section:

| | |
|---|---|
| Table (1.4.2) | Page 26 |
| Table (1.4.3) | Page 28 |
| Table (1.4.4)1 | Page 32 |
| Table (1.4.5.3)3 | Page 41 |
| Table (1.5.2)2 | Page 44 |
| Table (1.5.5)1 | Page 49 |
| Table (1.6.2.2.2)1 | Page 54 |
| Table (2.5.4.1)1 | Page 74 |
| Table (3.2.2)1 | Page 79 |
| Table (3.3.2.2)1 | Page 86 |

- it was noted that in some of the tables listed, doses and values were listed incorrectly; an example of the errors noted is the replacement of "2.5 mg" by "22.5 mg"
- it was noted that the tables in the individual studies appear to be free of errors

- the sponsor was asked to provide information addressing whether there is a food effect with the 2.5 mg immediate release formulation

**Decisions made**:

- the sponsor will review and revise the accuracy of all the tables in the Biopharmaceutics section of the application
- the sponsor will address Dr. Jarugula's question regarding availability of food effect data, with the 2.5 mg immediate release formulation

**Action Items**:

- the sponsor will resubmit the tables in the Biopharmaceutics section, with corrections as needed, as soon as errors are rectified
- minutes will be sent to the sponsor in 30 days

**Note to sponsor**: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original IND
HFD-580/DivFile
HFD-580/Allen/Shames/

drafted: Farinas/9.6.01/
concurrence: Rumble 9.7.01/Jarugula
final: Farinas/9.26.01

MEETING MINUTES

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/s/

Evelyn Farinas
9/26/01 01:37:52 PM
CSO

Venkateswar Jarugula
9/28/01 04:25:24 PM
BIOPHARMACEUTICS

# Status Meeting Minutes

**Date:** September 7, 2001 **Time:** 12:0-1:00 PM, EST **Location:** PKLN; 13B45

**NDA 21-287** **Drug:** alfuzosin hydrochloride **Indication:** benign prostatic hyperplasia (BPH)

**Sponsor:** Sanofi-Synthelabo, Inc.

**Type of Meeting:** Status

**Meeting Chair:** Victor Raczkowski, M.D., Deputy Director, Office of Drug Evaluation III (ODE III), Center for Drug Evaluation and Research (CDER)

**Meeting Recorder:** Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**FDA Attendees:**
Victor Raczkowski, M.D. - Deputy Director, ODE III, CDER (HFD-103)
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Venkat Jarugula, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

**Meeting Objective:** To discuss impact of CardioRenal Consult regarding QT interval prolongation on future regulatory action for this pending NDA application.

**Background:**
The sponsor submitted this application for alfuzosin hydrochloride on December 8, 2000, for the treatment of BPH. Alfuzosin hydrochloride is an alpha blocker, similar to Hytrin, Cardura and Flomax. A Phase 1 study showed that one patient experienced a prolonged QT interval of 71 milliseconds. A retest of this patient showed a normal QT interval. The 120-day safety review, submitted in April 2001, included results of four additional studies addressing QT interval. Of these, Study 4532 showed dose-related increases in the mean QT interval with the 20-mg and with the 40-mg dose. The sponsor stated that alpha blockers increase the heart rate, and thus, the Bazett's and the Fridericia's corrections of QT interval in Study 4532 were performed. The sponsor argues that Bazett's and Fridericia's corrections over-estimate the QT interval and that QT measurement using Holter monitoring is more accurate. The sponsor calculated QT intervals using Holter monitor readings, which indicated a mean increase in the QT interval of only two milliseconds. The CardioRenal Division was asked to review the results of the studies addressing the prolongation of the QT interval provided by the sponsor in the 120-day safety update. The CardioRenal Division concluded that alfuzosin prolongs the QT interval by approximately 10 Milliseconds, and that there was a risk of sudden death which was difficult to quantify.

**Discussion:**

- regarding alfuzosin hydrochloride:
  - the safety record for alfuzosin hydrochloride, both in postmarketing experience and clinical studies, has not shown Torsade de Pointes; however, some patients (four) experienced syncope in clinical trials
  - Pharmacokinetics of alfuzosin hydrochloride indicate that this drug is extensively metabolized to inactive metabolites, predominantly by CYP 450 3A4; at this time, it appears that the metabolites do not have a role in the QT interval prolongation
- regarding increases in the QT interval:
  - a dose-related increase in the QT interval is seen and is concerning
  - further discussion with others in CDER who have expertise in QT interval issues may be valuable
- regarding impact of QT interval prolongation on the drug approval process:
  - the risk/benefit ratio of a drug plays a big role in the approval of drugs with demonstrable QT interval prolongation
  - it appears that this drug does not offer any therapeutic advantage over approved products for the same indication, but may potentially pose an increased safety risk because of the dose-related increase in QT interval
- regarding additional data required from the sponsor:
  - additional data must show that the signal of QT interval prolongation is not real, that the QT prolongation does not translate into Torsades de Pointes at anticipated clinical doses, or that this signal is not worse than the effect of other alpha blockers (i.e, a class effect)
  - to accomplish this, the sponsor could do the following:
    -
    -
    -
    -
    -
    -

**Decisions made:**

- the sponsor will be notified that the data submitted is being reviewed and evaluated, and that at this time, a teleconference is premature; the sponsor will be informed that the Agency continues to have safety concerns (*sponsor notified on September 10, 2001, by Ms. Farinas)*
- consideration is being given to an approvable or not approvable action
- a multi-divisional meeting of CDER experts regarding QT interval prolongation assessment will be convened to further discuss the QT interval prolongation findings from alfuzosin

**Action Items:**

- DRUDP will call the sponsor to cancel the teleconference scheduled for the week of September 10, 2001 (*Project Manager notified Dr. Villaume on September 10, 2001, that review of the application continued, and that meeting was premature at this time.)*
- DRUDP to provide a copy of the sponsor's arguments regarding QT issues to Dr. Raczkowski (*provided by Dr. Benson on September 6, 2001*)
- DRUDP to convene a multi-divisional meeting with experts in CDER to further discuss QT interval findings with alfuzosin hydrochloride

Drafted: September 9, 2001
Concurrence: Benson 9.12.01/Hirsch 9.26.01/Rumble 9.11.01/Shames 9.11.01/Raczkowski 9.25.01
Finalized: September 26, 2001

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/s/

Victor Raczkowski
10/3/01 09:03:23 AM

# Teleconference Minutes

**Date:** August 31, 2001 **Time:** 11:30-11:55 AM, EST **Location:** PKLN; 17B45

**NDA** 21-287 **Drug:** alfuzosin hydrochloride **Indication:** benign prostatic hyperplasia

**Sponsor:** Sanofi-Synthelabo, Inc.

**Type of Meeting:** Information

**Meeting Chair:** Daniel Shames, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**External Lead:** Jon Villaume, Ph.D., Senior Director Regulatory Affairs

**Meeting Recorder:** Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

**FDA Attendees:**
Daniel Shames, M.D. - Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. - Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. - Medical Officer, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

**External Attendees:**
Jon Villaume, Ph.D. - Senior Director Regulatory Affairs
Bruce Berger, M.D. – US Safety Officer, Pharmacovigilance
Amy Naadimuthu, M.D. – Clinician US
Phillipe D'Anjou, M.D. – Clinical Pharmacology Unit, France
Jean Lois Pinquair, M.D. – Clinical Pharmacology Unit, France
Mary Christine Delouche – Project Management Group, France

**Meeting Objective:** To discuss potential QT prolongation impact on any future FDA decisions.

**Discussion:**

- the sponsor was informed that the purpose of this teleconference was to alert the sponsor to the findings of a DCRDP consult regarding potential QT interval prolongation; the DCRDP review indicated that there are repolarization abnormalities due to alfuzosin therapy
- this issue may affect the approvability of alfuzosin
- in response to the sponsor's question, DRUDP stated that the review had originated at the Cardio Renal reviewer's level and had supervisory signature
- DRUDP indicated that the sponsor will be contacted again, possibly within one week, to discuss this issue in greater depth; further internal discussions at the Office level and with DCRDP will take place before DRUDP can revisit this issue with the sponsor
- DRUDP indicated that review of the NDA was almost complete, and that comments regarding other issues including revised labeling would be conveyed in the near future
- the sponsor indicated that it was understood that DRUDP will be contacting Sanofi-Synthelabo within one week of this teleconference, subsequent to discussions at a higher management level