- the sponsor also indicated that all available information regarding QT interval prolongation had been submitted to the NDA (i.e., Adverse Event Reports, Post-Marketing Experience, and holter monitor study results)

Decisions made:

- DCRDP consult results will be discussed internally at the Office level prior to contacting the sponsor again
- DRUDP will contact the sponsor in one week to discuss the impact of the repolarization abnormality findings

Action Items:

- DRUDP Project Manager will contact the sponsor to schedule a teleconference during the week of September 4, 2001 (*the sponsor was notified by Ms. Farinas on September 10, 2001, indicating that a teleconference at this time was premature, and that the QT data remains under review)*
- 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/ September 4, 2001
concurrence: Rumble 9.6.01/Benson 9.6.01/Hirsch 9.7.01/Shames 9.10.01
final: Farinas/9.10.01

MEETING MINUTES

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/s/

Evelyn Farinas
9/10/01 05:09:57 PM
CSO

please note addition to Action Items/ERF

Daniel A. Shames
9/21/01 02:10:11 PM
MEDICAL OFFICER

Status Meeting Minutes

Date: August 28, 2001 **Time:** 12:00 PM, EST **Location:** PKLN; 17B43

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

Sponsor: Sanofi-Synthelabo, Inc.

Type of Meeting: Status/Label discussion

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Suong Tran, Ph.D.- Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Maboob Sobhan, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Venkat Jarugula, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Laurie McLeod, Ph.D. – Toxicologist, DRUDP (HFD-580)
Barbara Chong, Pharm.D. – Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Terri Rumble, R.N. – 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 progress of the review for this application.

Background: Sanofi-Synthelabo submitted an application for alfuzosin hydrochloride on December 8, 2000. Previously agreed internal deadlines were: finalized reviews, week of September 5, 2001; action package to the Division Director, week of September 5th, 2001; and action package to ODE III for Dr. Raczkowski's review, week of September 15, 2001. Previous status meetings held July 9 and August 9, 2001.

Discussion:
Clinical:

- review: near completion (about 99% completed)
- issues:
  - QT interval prolongation: Cardio Renal Consult pending, but Cardio Renal medical officer indicates that final written consult should be available this week; concern about potential risk to patients; no other drugs in this class show increased QT interval, but adequate testing may not have been conducted; there is an abundance of safety data provided for review
  - DSI inspections: one site inspection has been completed, and is acceptable; inspection on the other two sites is still pending
- label: revisions required, such as:
  - results of the Phase 3 pivotal trial should be included (rather than just two)

- secondary endpoints should be eliminated
- exclusion from studies of patients with baseline hypotension should be mentioned

- assessment: approval, most likely pending resolution of the QT interval prolongation

Chemistry:

- review: draft completed; pending Biopharmaceutics review of dissolution specifications and container label review (Biopharmaceutics indicated that dissolution specifications appeared adequate, but that a final determination will be made after discussion with OCPB management)
- issues: none; previous CMC issues resolved satisfactorily
- label: container label review pending; OPDRA indicated that container label appeared adequate
- assessment: approval, most likely

Toxicology:

- review: completed and signed in DFS; Executive CAC review and Carcinogenicity Statistics review have been signed in DFS
- issues: doses tested in female mice may not have constituted a maximally tolerated dose
- label: in a facsimile dated August 22, 2001, it was requested that the sponsor include as a second sentence in the Carcinogenesis, Mutagenesis, and Impairment of Fertility subsection, the following statement: "The doses tested in female mice may not have constituted a maximally tolerated dose."
- assessment: approval, most likely

Biopharmaceutics:

- review: near completion; may have additional comments and revisions on dissolution and *IV/IVC* subsequent to the September 12, 2001, discussion with OCPB management
- issues:
  - increased exposure in renal and hepatic impaired patients
  - increased exposure in ketoconazole drug interaction studies
- label: changes to the Precautions and Contraindications sections will be recommended, such as:
  - Contraindication statement with ketoconazole and other potent CYP 3A4 inhibitors; decision has not been made if the contraindication statement should identify by name the other potent CYP 3A4 inhibitors
  - Precaution statement with the use of mild CYP3A4 inhibitors
  - may consider a Caution statement for mild and moderate hepatic impairment, and a contraindication for severe hepatic impairment
  - discrepancies with foreign labels were noted, such as listing a contraindication for severe renal impaired patients
- assessment: approval, most likely

DDMAC:

- review: written comments on the label will be provided within one week
- issues: sponsor's proposed label contains promotional language
- label: Flomax label will be used for comparison
- assessment: no comments

Statistics:

- review: near completion (90% completed)
- issues: none
- label: will use Flomax label for comparison; it was recommended that the graphics and tables for inclusion in the label should be those that support the NDA, such as IPSS graphs for all three pivotal studies
- assessment: approval, most likely

Additional discussion:

- all reviewers must include a final Memo in DFS indicating agreement with the last FDA proposed label, and that there are no outstanding issues with this application

- FDA's proposed label will most likely be sent to the sponsor, after Dr. Raczkowski has reviewed it (goal date is the week after Labor Day)

Decisions made:

- Reviewers will make every effort to complete reviews the week of September 5, 2001
- FDA revised label will be presented to Dr. Raczkowski for his review and comments prior to forwarding the label to the sponsor
- Biopharmaceutics reviewer will discuss pending issues with OCPB management

Action Items:

- Clinical Team will discuss with Dr. Shames if a reference to the exclusion of patients with hypotension at baseline should be included in the label
- Project Manager to verify if the Toxicology revisions have been incorporated to the label in the N drive (*revisions were added*)
- Project Manager to contact the sponsor and verify that the foreign label submitted are complete, and not a synopsis (*Dr. Villaume, from Sanofi-Synthelabo stated that the foreign labels supplied are complete labels*)
- Project Manager to contact the sponsor to verify receipt data of the draft container labels (*Dr. Villaume, from Sanofi-Synthelabo indicated that draft container labels were being submitted to DRUDP)*

ADDENDUM:

- in correspondence dated August 28, 2001, and received August 29, 2001, the sponsor proposed the addition of the word "highest" to the toxicology request of August 22, 2001
- the sponsor's proposed second sentence to the Carcinogenesis. Mutagenesis, and Impairment of Fertility subsection, reads as follows: "The highest doses tested in female mice may not have constituted a maximally tolerated dose."
- the sponsor's proposed sentence was found acceptable by the Toxicology reviewer (Dr. McLeod)

Drafted: Farinas/9.9.01
Concurrence: Tran 9.10.01/Benson 9.10.01/Hirsch 9.10.01/Rumble 9.12.01/Jarugula 9.18.01
Finalized: Farinas 9.26.01

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/s/

Mark S. Hirsch
9/28/01 05:59:59 PM

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
CSQ

Teleconference Minutes

Date: August 10, 2001 **Time:** 10:00-10:15 AM, EDT **Location:** Parklawn; 17B-43

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

Sponsor: Sanofi-Synthelabo

Type of Meeting: clarification

Meeting Chair: Maboob Sobhan, Ph.D., Statistician, Division of Biometrics II @ 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:
Maboob Sobhan, Ph.D. - Statistician, Division of Biometrics II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Jon Villaume, Ph.D. - Senior Director Regulatory Affairs
Jean-Luc Bessy, Ph.D. – Statistician, France
Marie Christine De Lauche – Project Management, France

Meeting Objective: To obtain clarification regarding the statistical analysis plan.

Background: NDA 21-287 was submitted December 8, 2000, for alfuzosin HCl, which is a new molecular entity (NME). To continue the review of this application, clarification was needed regarding this NDA's statistical analysis plan.

Discussion:
- the sponsor was asked to indicate if a primary analysis based on evaluable patients (i.e., completers) was conducted
- the sponsor indicated that analysis on completers was done, and the data can be found in Tables 60 and 66, for peak flow rate and international prostate symptom score (IPSS), respectively

Action Items:
- minutes will be sent to the sponsor in 30 days

/S/ /S/

Minutes Preparer **Concurrence, Chair**

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/8.13.01
concurrence: Rumble 8.13.01/Sobhan 9.5.01
final: erf/9.5.01

MEETING MINUTES

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/s/

Evelyn Farinas
9/5/01 01:21:39 PM
CSO

Mahboob Sobhan
9/5/01 02:19:06 PM
BIOMETRICS

Status Meeting Minutes

Date: August 9, 2001 **Time:** 9:00-9:45 AM, EST **Location:** PKLN; 17B43

NDA 21-287 **Drug:** alfuzosin **Indication:** BPH

Sponsor: Sanofi-Synthelabo

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Suong Tran, Ph.D.- Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Clinical Pharmacology and Biopharmaceutics, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Laurie McLeod, Ph.D. – Toxicologist, DRUDP (HFD-580)
Barbara Chong, Pharm.D. – Reviewer, Division of Drug Marketing, Advertising and Communications (DDMAC; HFD-42)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the progress of the review for this application.

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; the pre-NDA meeting took place on May 24, 2000, and the filing meeting on January 22, 2000. The 10-month PDUFA goal date is October 8, 2001. First status meeting was held July 9, 2001.

Discussion:
Clinical:

- review status: nearing completion
- issues:
  - QT prolongation: several QT studies have been submitted; the most recent one showed that a few patients had QT prolongation, using the Bazett correction method only; post marketing experience in Europe has not revealed QT prolongation effects with any of the three marketed dosage forms; a consult (including clinical QT information as well as toxicology studies data) was sent to the Cardio Renal Division for safety evaluation
  - DSI: final memo pending; letter received from DSI indicating that one of the three investigators passed inspection
- label: all three pivotal studies should be described in the label, instead of just two as the sponsor has proposed; data in the proposed label regarding Cmax and renally impaired patients need additional review
- action recommendation: approval most likely, pending QT consult recommendations

Clinical Pharmacology and Biopharmaceutics:

- review status: nearing completion
- issues:
  - renal study: exposure increases were observed in renally impaired patients (about a 50% increase), which the sponsor indicated did not require dose adjustment since the clinical trials showed safety up to 15 mg dose; this is a review issue, which may be addressed in the label (it is not an approvability issue) [*these statements reflect Dr. Jarugula's comments sent to the PM via e-mail*]
  - potential ketoconazole drug interactions: will likely recommend a Warning or Contraindication statement in the label regarding co-administration with ketoconazole
  - pending issues from last status meeting: digoxin drug interaction study received, and is under review; bioequivalence study review is on going
- label: review is pending
- action recommendation: approval, most likely

Chemistry:

- review status: nearing completion
- issues:
  - stability data and expiratory date request under review; sponsor is requesting [redacted] date, but the Division recommends only two years
  - pending issues from last status meeting: DMF reviews completed, and data is acceptable; longer term stability data was submitted, and is under review
- label: review completed; comments sent to the sponsor; response from sponsor received
- action recommendation: approval, most likely

Toxicology:

- review status: draft completed, and sent to Team Leader for sign off
- issues:
  - CAC did not accept one of four segments of the dose study, which was done at less than the maximally tolerated dose, but which did not show tumors of any significance; CAC recommends that the label includes these findings; this is not an approvability issue
  - Toxicology studies data included in the Cardio Renal consult has not been reviewed; an additional review may be required
- label: review pending; will make changes to the proposed label to reflect CAC comments
- action recommendation: approval, most likely

Division of Drug Marketing, Advertising and Communication:

- label review: pending
- issues: none identified yet; will alert the team if issues arise

Statistics:

- review status: on going; plan to meet the internal goal date *[comments provided to PM via e-mail]*
- issues: none identified *[comments provided to PM via e-mail]*
- label: review pending *[comments provided to PM via e-mail]*
- action recommendation: not stated

Decisions made:

- Label reviews should be completed by the first week in September, so that the Action Package can be forwarded to the Division Director by the end of the week

Action Items:

- Project Manager (PM) to call the Cardio Renal Division the week of August 13, 2001, to inquire about the status of the QT consult for alfuzosin
- PM to verify with Dr. Allen the timing of sending DRUDP's proposed label to the sponsor
- Reviewers to make changes to the label in the N drive; PM to provide assistance if needed
- Medical Officer (Dr. Benson) to furnish to Dr. McLeod, for her review, a copy of the toxicology studies sent to the Cardio Renal Division
- DDMAC reviewer to provide labeling comments to the PM via e-mail by the end of the month
- PM to contact Dr. Sobhan (statistician) and get his comments regarding status of review for this NDA
- PM to postpone the Sept 10th "Just-in-case" meeting to allow Dr. Allen more time for review of the Action Package (*Sept. 10th meeting cancelled; if continued Action Package discussion/review is needed, time will be carved out of the Pre Approval Safety Conference with OPDRA)*

/S/

Minutes Preparer

Drafted: Farinas/8.10.01
Concurrence: Rumble 8.10.01/Hirsch 8.14.01/Benson 8.14.01/Tran 8.14.01/McLeod/Chong/
Finalized: Farinas/9.12.01

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/s/

Mark S. Hirsch
9/12/01 04:46:35 PM

Status Meeting Minutes

Date: July 9, 2001 **Time:** 10:30-11:10 AM, EST **Location:** Parklawn; 7B43

NDA 21-287 **Drug:** alfuzosin hydrochloride extended-release tablets **Indication:** BPH

Sponsor: Sanofi-Syntelabo, Inc.

Type of Meeting: status meeting

Meeting Chair: Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

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

FDA Attendees: Drs. Hirsch, Benson, Jarugula, Parekh, McLeod, Tran, Sobhan, Chong, and Ms. Best and Farinas

Meeting Objective: To discuss review status of this application.

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; the pre-NDA meeting took place on May 24, 2000, and the filing meeting on January 22, 2000. The 10-month PDUFA goal date is October 8, 2001.

Discussion:

Regulatory issues:

- NME requires office sign-off
- internal goal dates:
  - reviews completed and Action Package signed by reviewers week of September 5th, 2001
  - submission of Action Package to Division Director week of September 5th, 2001
  - submission of Action Package to Office for sign-off week of September 17th, 2001

Clinical:

- three pivotal studies have been reviewed
- target submission of executive summary to Team Leader prior to Labor Day
- proposed tradename Uroxatral has been accepted by OPDRA and is acceptable to the Division

Financial Disclosure:

- no issues; 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

Statistics:

- no issues have been uncovered to date
- target date for completion of review and Team Leader sign-off is Labor Day
- Division requests for consults to the statistics team usually pertain to efficacy rather than safety
- it was clarified that the incidence of adverse events is the primary concern; rarer adverse events are looked at individually

Clinical Pharmacology and Biopharmaceutics:

- target date for completion of review is Labor Day; every effort will be made to include comments and recommendations from the OCPB leadership prior to Labor Day
- since there was a two fold increase in exposure with food, clinical studies were done with food; pivotal bioequivalence study was conducted under fed conditions, which is different from guidance recommendations; however, OCPB leadership already stated that "fed conditions" is not a filing issue
- it was noted that the digoxin drug interaction study has not been submitted

Toxicology:

- draft review of NDA has been completed
- no safety issues
- minor concern with carcinogenicity studies representation in the label; will not affect approvability

Chemistry:

- review has been completed
- letters sent to the drug substance DMF holder and to the sponsor to request further information
- review includes discussions on the following alfuzosin HCl materials: clinical material PDV03, commercial-scale material PDV08 (plain tablets), commercial-scale "X10" material (debossed tablets), and commercial product (debossed tablets). The clinical material PDV03 was manufactured at a pilot plant. PDV08 and "X10" materials were manufactured at the same plant (same scale and equipment) as the commercial product. The "X10" material was supposed to be the commercial product until OPDRA's rejection of the name "Xatral". The commercial product with the debossing code for the accepted name "Uroxatral" has not yet been manufactured.
- Biopharmaceutics review will evaluate the bioequivalence between the clinical material PDV03 and the commercial-scale material PDV08 (plain tablets). This review will also evaluate the comparability (dissolution data) between the commercial-scale material PDV08 (plain tablets) and the commercial-scale "X10" material (debossed tablets).
- there are no batch analysis and stability data on the commercial tablet because the commercial product with the debossing code for the accepted name "Uroxatral" has not yet been manufactured.
- there are no stability data for the commercial-scale "X10" material (debossed tablets). The only primary stability data submitted to the NDA to date are six-month stability data for the commercial-scale material PDV08 (plain tablets). It was noted that these data show quality deterioration over six months, such as increase in friability and decrease in potency. A t-con was held with the sponsor on April 4, 2001, to discuss the stability data (refer to the t-con minutes). It was agreed that the shelf life of the commercial product can be based on the stability data for the commercial-scale material PDV08 (plain tablets) provided that the 6-month accelerated stability data are comparable. The sponsor agreed to provide additional stability data on the commercial-scale material PDV08 (plain tablets) and the commercial-scale "X10" material (debossed tablets) during the review cycle.
- these chemistry issues are not approvability issues; the shelf life of the commercial product, if approved, will be based on available stability data. If no additional stability data are submitted, a very short expiration date will be granted

Action Items:

- schedule pre-approval safety conference (Project Manager)
  - Pre-approval safety conference may be scheduled as part of the last status meeting
  - Provide most recently proposed label to OPDRA
  - Provide clinical review (may be in draft form) to OPDRA prior to the pre-approval safety conference
- Invite either the Office Director or the Deputy to the remaining status meetings
- Send a copy of the most recently proposed label to Dr. Abbey Jacobs (Pharmacology and Toxicology) for review
- Toxicology reviewer to provide review to Dr. Jacobs (may be draft)

/S/

Minutes Preparer

/S/

Concurrence, Chair

Drafted: Farinas/7.17.01
Concurrence: Rumble/Hirsch 7.18/Benson 7.18/Jarugula 7.18/Parekh/ McLeod/Rhee 7.24.01/Tran 7.18/Welch/Sobhan/Chong/Best 7.18.01
Final: Farinas/8.8.01

Status meeting minutes

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/s/

Mark S. Hirsch
8/17/01 11:22:12 AM

Teleconference Minutes

Date: April 4, 2001 **Time:** 1:00 – 1:20 PM, EDT **Location:** Parklawn; 7B-43

NDA 21,287 **Drug:** alfuzosin **Indication:** BPH

Sponsor: Sanofi-Synthelabo

Type of Meeting: Clarification

Meeting Chair: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Charles Ireland, Assistant Director, Drug Regulatory Affairs

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

FDA Attendees:
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Suong Tran, Ph.D. – Chemist, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Jon Villaume, Senior Director, Drug Regulatory Affairs, Sanofi-Synthelabo
Charles Ireland – Assistant Director, CMC Drug Regulatory Affairs, Sanofi-Synthelabo
George McCauley – Assistant Director, CMC Drug Regulatory Affairs (Post Marketing), Sanofi-Synthelabo
Kevin Maloviwski - Sanofi-Synthelabo

Meeting Objective: To convey responses to the sponsor's questions faxed to the Division on March 30, 2001.

Background: As a result of OPDRA's recommendation against the sponsor's proposed tradename Xatral, the sponsor is reviewing other potential brand names. Potentially, the future tradename submissions would not start with the letter "X" necessitating changes to the code on the tablet. The sponsor is requesting guidance and comments from the Division as stated in the March 31 submission.

Discussion:
Responses to the sponsor's questions:
Question #1: Does the agency agree that a submission to change the first letter of the tablet marking would be considered a minor amendment and not extend the review?

- yes, the Division agrees that this would be considered a minor amendment

Question #2: Does the agency agree that if the marking change described above was completed post approval that the submission should be annual reportable?

- no, the Division does not agree with the sponsor's proposal
- the post-approval submission will be a CBE-0 supplement
- the sponsor must show equivalency between new tablets and unmarked tablets
- the sponsor should provide dissolution data and batch release testing linking all tablets (i.e., new marking tablets, X-marked tablets, unmarked tablets)

Question #3: Does the Agency agree that the stability data for the unmarked tablet can be used to establish the shelf life of the proposed commercial product marked with either "X" or the first letter of the final brand name, followed by 10?

- yes, the Division agrees, provided that 6-month accelerated stability data (for all attributes in the stability protocol) will be comparable between the unmarked tablets and debossed tablets
- statistical analyses would be helpful for ease of review
- in addition, comparative dissolution profiles with the similarity factor calculations should be provided; three lots of each tablet (unmarked, "X10" marked, commercial marked) are preferable

Additional Comments:

- Water Content should be added to the release and stability specifications
- labeling changes should be made as follows:
  - the established name should state "alfuzosin hydrochloride extended-release tablets"
  - the dosage strength should be prominently stated immediately after the established name
  - " " can be deleted
  - "Each bottle contains # tablets" can be replaced by "-- tablets" in prominent text
  - should include "See package insert for dosage information.", "Protect from light and moisture", and on larger containers "Dispense in a tight, light-resistant container as described in the USP".
- the sponsor should provide all container labels at least two months before action goal date

Decisions made:

- a submission to change the first letter of the tablet marking would be considered a minor amendment and not extend the review clock
- a post-approval submission regarding tablet markings change will be considered as a CBE-0 supplement
- stability data for the unmarked tablet may be used to establish the shelf life of the proposed commercial product provided that 6-month accelerated stability data (for all attributes in the stability protocol) will be comparable between the unmarked tablets and debossed tablets
- the sponsor will submit container labels two months before the action goal date if possible for early comments and review by the Division

Action Items:

- minutes of this teleconference will be sent to the sponsor within 30 days

/S/
Minutes Preparer

/S/
Concurrence, Chair

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.

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/s/

Evelyn Farinas
4/23/01 03:29:48 PM
CSO

Moo-Jhong Rhee
4/23/01 05:31:55 PM
CHEMIST

Filing Meeting Minutes

Date: January22, 2000 **Time:** 12:00-12:30 PM, EST **Location:** PKLN; 17B43

NDA 21-287 **Drug:** alfuzosin **Indication:** BPH

Sponsor: Sanofi-Synthelabo

Type of Meeting: Filing

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

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

FDA Attendees:
Daniel Shames, M.D. – Deputy Director, DRUDP (HFD-580)
Mark Hirsch, M.D. - Urology 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)
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Suong Tran, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Michael Welch, Ph.D. – Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Ele Ibarra-Pratt – Division Scientific Investigations
Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., MGA – Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To determine if NDA 21-287 is fileable.

Background: Alfuzosin was originally synthesized and developed by Synthelabo Laboratories in France for the treatment of benign prostatic hyperplasia (BPH), and is currently marketed in several foreign countries. Sanofi-Synthelabo is submitting to the FDA NDA 21-287 for a 10 mg extended release tablet, as a once a day regimen. Key dates for this product are: August 2, 1996, submission of IND [redacted] August 13, 1997, End-of-Phase 2 meeting; and May 24, 2000, pre-NDA meeting. At the pre-NDA meeting, the Division indicated that ALFORTI, ALFOTAM, and ALFUS would be the three primary trials for the NDA review.

Discussion:
- Regulatory background:
  - pediatric waiver granted August 20, 2000

- user fee paid in full
- financial disclosure information submitted; review pending
- 10-month goal date: October 8, 2001
- status meetings scheduled for: July 9, August 9, September 10, September 17, 2001

- Clinical: Fileable
  - background on pivotal studies was provided by the Medical Officer
  - DSI inspections desired from the two largest USA sites; these would be routine inspections
- Chemistry: Fileable
  - this is a New Molecular Entity; the release system is also new
  - stability data is very limited; expiration data needs review
  - may required statistical review of the stability data
- Pharmacology/Toxicology: Fileable
  - reviewer and Team Leader submitted the NDA checklist indicating this NDA is fileable
  - statistical review of the Carcinogenicity study needs to be coordinated
- Clinical Pharmacology and Biopharmaceutics: Fileable
  - reviewer will prioritize and identify the key studies for review
  - dissolution testing has been submitted
  - BE study under fed conditions and the justification provided by the sponsor (dated 1/17/01) are review issues
- Biometrics: Fileable

- Label:
  - tradename consult to OPDRA has been submitted

Decisions made:

- NDA 21-287 is fileable

Action Items:

- investigators list will be provided to E. Ibarra Pratt, from DSI, for inspection site selection (*list picked up by Ms. Ibarra-Pratt on January 25, 2001)*
- sponsor will be called to determine status of Ketoconazole Drug interaction study (*sponsor called January 24, 2001; ketoconazole study results will be submitted with the Safety Update*)
- sponsor will be asked to submit an electronic copy of the proposed label (*electronic label submitted on January 24, 2001)*
- desk copy of Sanofi-Synthelabo's response regarding the pivotal bioavaibility study to be given to Dr. Jarugula (*given to Dr. Jarugula on January 24, 2001*)

Minutes Preparer | **Concurrence, Chair**

cc:
IND Arch:
HFD-580/DivFile

/s/

Daniel A. Shames
2/5/01 05:20:57 PM

HFD-580/ Allen/Shames/ Hirsch/Benson/ Parekh/ Rumble/ Tran/ Welch / Jarugula / Batra / Mitra
DSI - Ibarra-Pratt
drafted: Farinas, 01.23.01
concurrence: Shames 01.26.01/ Hirsch 1.30.01/Benson 01.26.01/ Parekh 01.26.01/ Tran 01.26.01/ Welch 01.26.01 / Jarugula 01.26.01 / Batra / Mitra/Rumble 1.25
DSI – Ibarra-Pratt 01.26.01
final: Farinas, 01.30.01

MEETING MINUTES

MEMO – NDA 21-287, alfuzosin

45 Day Filing Meeting Checklist
Project Management

ITEM	YES	NO	COMMENT
1) Do any of the following apply to this application (i.e., if yes, the application **~~MUST~~ BE REFUSED TO FILE** under 314.100(e) and there is no filing over protest):			
a. Is the drug product already covered by an approved application?		x	
b. Does the submission purport to be an abbreviated application under 314.55; however, the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.559b)?		x	
c. Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?		x	
2) Do any of the following apply to this application (i.e., if NO, the application **MAY BE REFUSED TO FILE** under 314.100(d) and there is the potential for filing over protest):			
a. Does the application contain a completed application form as required under 314.50 or 314.55?	x		
b. On its face, does the application contain the sections of an application required by regulation and Center guidelines?	x		

ITEM	YES	NO	COMMENT
c. Has the applicant submitted a complete environmental assessment, which addresses each of the items, specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR?	x		
d. On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?	x		
e. Is the NDA indexed and paginated?	x		
f. On its face, is the NDA legible?	x		
g. Has the applicant submitted all required copies of the submission and various sections of the submission?	x		
h. Has the sponsor submitted all special Studies/data requested by the Division during presubmission Discussion with the sponsor?	x		
i. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?	x		

j. If required, has the applicant submitted carcinogenicity studies?	x		
ITEM	**YES**	**NO**	**COMMENT**
k. On its face, does the application contain at least two adequate and well-controlled clinical trials?	x		
l. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	x		
m. Have all articles/study reports been submitted either in English or translated into English?	x		
n. Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?	x		
3) From a project management perspective, is this NDA fileable? If "no", please state why it is not.	x		

/S/

Regulatory Project Manager

/S/

Chief, Project Management Staff

cc:
Original NDA
HFD-580/DivFile
HFD-580/PM/

/s/

Daniel A. Shames
2/5/01 05:20:57 PM

D/I

Meeting Minutes

Date: May 24, 2000 **Time:** 3:00-4:15 PM EST **Location:** Parklawn; Conf. Rm C

IND [redacted] **Drug:** alfuzosin **Indication:** benign prostatic hypertrophy

Sponsor: Sanofi Synthelabo

Type of Meeting: Pre-NDA

Meeting Chair: Marianne Mann, MD – Deputy Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A.– Regulatory Project Manager

FDA Attendees:
Marianne Mann, MD – Deputy Director, DRUDP (HFD-580)
Daniel Shames, MD – Medical Team Leader, DRUDP (HFD-580)
Mark Hirsch, MD – Medical Officer, DRUDP (HFD-580)
Venkateswar Jarugula, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Jeri El-Hage, Ph.D. – Pharmacologist, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. – Team Leader, Division of Biometrics II (DBII; HFD-715)
Randy Olmstead – Technical Information Specialist
Evelyn R. Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Amy Naadimuthu, M.D. – Clinical Research
Pierre Rosenzweigh, M.D. – Clinical Research
James Oppermann, Ph.D. – Clinical Pharmacokinetics and Metabolism
Clemence Rauch, Ph.D. - Clinical Pharmacokinetics and Metabolism
Jose Necciari, Ph.D. - Clinical Pharmacokinetics and Metabolism
Marie-Christine Delauche, M.D. – Project Direction
Loic Darchy, M.S. – Biostatistics
Bruce Berger, M.D. – Drug Safety
William Friggle, M.S. – Scientific Information Systems
Richard Gural, Ph.D. – Regulatory Affairs
Jon Villaume, Ph.D. - Regulatory Affairs
Quyen Vinh, M.S. - Regulatory Affairs

Meeting Objective: To address and reach agreement on the Clinical, human Pharmacokinetics and electronic submission questions posed by the sponsor in the May 1, 2000 meeting package (Serial No. 113).

Background: Alfuzosin is an alpha blocker, used in Europe for over 15 years, as an immediate release formulation for the treatment of the signs and symptoms of benign prostatic hypertrophy (BPH). The new controlled release formulation has been approved in 9 countries. An End of Phase 2 meeting was held with the sponsor in August 1997, to discuss the results from ALFORTI study and to provide guidance for future studies. The sponsor accepted DRUDP's recommendations to conduct two additional studies. The sponsor submitted for the pre-NDA meeting in support of an NDA the results of four trials, ALFORTI, ALFUS, ALFOTAM and ALFOD. The sponsor is seeking NDA approval for the 10 mg controlled release formulation. For the pre-NDA meeting, the sponsor submitted in the meeting package a list of questions for DRUDP's consideration. Previously, the sponsor submitted (Serial No. 114) Chemistry and Bioequivalence questions for the Division's comments.

Discussion:

Clinical:

1.1 Division agrees that the presentation in the Integrated Summary of Effectiveness is adequate

- Protocols ALFORTI, ALFOTAM and ALFUS will be the primary trials for review
- sponsor should submit individual study reports as well as summaries
- sponsor defined "malaise" as "feeling faint"; sponsor will not use this term in the proposed label
- sponsor clarified that the meeting package contained an error regarding the so-called Bonferroni-Holm adjusted p-values for ALFORTI; the NDA will contain the correct information

1.2 Division agrees that registration for the 10 mg dose only is adequate, and that the label should include only the results of the controlled studies done with placebo versus the 10 mg dose

- sponsor should not include in the label any information from efficacy trials using the 15 mg dose
- Division recommends that the sponsor provide a separate volume with a detailed index of the four Phase 3 studies submitted

1.3 Division agrees with the presentation of adverse experiences in the Adverse Reactions section of the label proposed by the sponsor

- sponsor stated label will include a tabular display of adverse events occurring greater than or equal to 2% for the 10 mg dose and greater than placebo, plus a list of less frequent adverse events by body system
- sponsor should include textual representation in the label of adverse events possibly related to drug administration, and occurring at <2%

Pediatric Rule:

- Pediatric Rule requires assessment in the pediatric population only for the claimed indication(s)
- Pediatric Rule requires study in each age group in which the drug will provide meaningful therapeutic benefit, or will be used in a substantial number of pediatric patients for the claimed indications
- sponsor should provide justification if requesting a waiver or deferral

Human Pharmacokinetics:

2.1 the adequacy of the development plan to determine the potential for drug interactions with alfuzosin is a review issue

2.1.1 *in vitro* approach is acceptable for inhibition and induction

2.1.2 the effects of alfuzosin on narrow therapeutic index drugs is a review issue

- sponsor should provide the justification for the extrapolation of the 2.5 mg twice a day data and 5 mg twice a day data from the two studies to the 10 mg once a day dosing

- Division recommends a study with digoxin at the 10 mg dose; sponsor can submit study results up to seven months after the NDA has been submitted
- warfarin and digoxin are acceptable as narrow therapeutic index drugs

2.1.3 Division recommends that sponsor conduct CYP 3A4 studies using a strong inhibitor (ex. ketonazole)

2.1.4 no issues with protein binding

2.2 the approach to document the pharmacokinetics of alfuzosin in elderly and renally-impaired patients is adequate

- pharcokinetic results in hepatically-impaired patients is a review and labeling issue
- sponsor should provide justification for the extrapolation of 2.5 mg twice a day dosing results to the 10 mg once a day dosing
- Division indicated that clinical claims are not included in the Pharmacology section of the label

2.3 Division agrees that monitoring the levels of the individual enantiomers in the pharmacokinetic studies is not a requirement

- Division recommends that the sponsor measure both isomers in at least one study

Toxicology:

- sponsor will submit in-diet toxicokinetics data for mice and rats and carcinogenicity study results for CAC review

Electronic Data:

3.1 electronic clinical study databases

- Division recommends that the sponsor provide the data sets used to perform the primary efficacy analysis as a separate data set for ease of review
- Division recommends that the sponsor provide Biopharmaceutics data (i.e., summary reports, synopsis of studies) in Word and PDF formats for ease of review
- sponsor will provide samples to the Division of electronic data prior to NDA submission in order to verify that the structure of the electronic database is acceptable
- submission of patient profiles is not necessary
- it is acceptable to divide datasets larger than 25 MB into smaller datasets

3.2 case report forms

- sponsor proposed a two-tier bookmarking scheme for safety

3.3 review aids

- review aids should be provided in both Word and PDF formats

Chemistry (May 9, 2000 submission, Serial No. 114):

1. the combination of color, shape, size and proposed marking for the drug product is adequate to comply with 21CFR206.10
2. Division recommends that sponsor conduct stability studies with the embossed product

- Division recommends that the sponsor submit 6-month stability data under 25°C/60% RH and 40°C/75% at time of NDA submission
- sponsor can submit stability data through the review period as a rolling submission
- sponsor will verify if degradation products are being monitored

Biopharmaceutics (May 9, 2000 submission, Serial No. 114):

1. Division recommends that sponsor submit dissolution data over a range of pH values, and provide a rationale for the dissolution method used

- sponsor will provide the tablet holder if the FDA laboratories needs it
- sponsor indicated that the only difference between the product used in clinical trials and the to-be-marketed formulation was the markings

Decisions reached:

- the presentation in the Integrated Summary of Effectiveness is adequate
- registration for the 10 mg dose only is adequate
- only the results of the controlled studies done with placebo versus the 10 mg dose will be included in the label, unless additional safety information warrants inclusion based on review
- the proposed presentation of adverse experiences in the Adverse Reactions section of the label is adequate
- *in vitro* Pharmacokinetic study is acceptable for inhibition and induction
- the protocol to document the pharmacokinetics of alfuzosin in elderly and renally-impaired patients is adequate
- monitoring the levels of the individual enantiomers in the pharmacokinetic studies is not required
- the proposed electronic datasets submission is adequate
- submission of patient profiles is not necessary
- review aids will be provided in both Word and PDF formats
- the combination of color, shape, size and proposed marking for the drug product is adequate to comply with 21CFR206.10

Action Items:

- minutes will be provided to sponsor within 30 days
- sponsor will submit in-diet toxicokinetics data for mice and rats and carcinogenicity study results for CAC review
- the sponsor will provide a separate volume with a detailed index of the four Phase 3 studies
- the sponsor will provide samples of electronic data prior to NDA submission to verify adequacy of the structure of the electronic database
- the sponsor will verify if degradation products are being monitored
- the sponsor will provide the tablet holder to the FDA laboratories if needed
- the sponsor will submit additional stability data through the review period as a rolling submission

/S/
Minutes Preparer

/S/
Concurrence, Chair

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:
IND Arch: [redacted]
HFD-580/DivFile

HFD-580/Allen/Mann/Shames/Hirsch/Lin/Rhee/Jordan/ElHage/Kammerman/Parekh/Jarugula/Rumble/Farinas

drafted: Farinas, 5.24.00
concurrence: Mann 6.2.00/Shames 6.13.00/Hirsch 6.13.00/Rhee 6.1.00/Lin 6.7.00/Jarugula 6.13.00/Kammerman 6.1.00/ElHage 6.1.00/Olmstead 6.5.00/Rumble 6.1.00
final: Farinas, 6.14.00

MEETING MINUTES

Sanofi-Synthelabo
9 Great Valley Parkway
Malvern, PA 19355

FDA.CDER

Fax

To: Quyen H. Vinh
Director Regulatory Affairs

From: Evelyn R. Farinas, RPh, MGA,
Regulatory Project Manager

Fax: Fax: 9-1-610-889-6993

Date: June 14, 2000

Phone: Phone: 9-1-610-889-8794

Pages:

Re:

CC:

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

Dear Quyen:

This FAX is in reference to the meeting minutes of May 25, 2000. Hope that all is well with you.

Sincerely,

Evelyn R. Farinas

Regulatory Project Manager

DF.

MEMORANDUM OF MEETING MINUTES

DATE: August 13, 1997 **TIME:** 1:30 -3:30 pm **LOCATION:** Parklawn, Conf Rm. A

IND [redacted] **Drug:** Alfuzosin **Indication:** Benign Prostatic Hyperplasia

Sponsor: Synthelabo Research

Type Of Meeting: EOP2 Meeting

Meeting Chair: Lisa Rarick, M.D., Director, Division of Urologic and Reproductive Drug Products, (DRUDP; HFD-580)

External Lead: Stephane E. Allard, M.D., President, Synthelabo Research

Meeting Recorder: Terri Rumble, Project Manager, DRUDP; HFD-580

FDA Attendees:
Lisa Rarick, M.D., Director, DRUDP (HFD-580)
Heidi Jolson, M.D., M.P.H., Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D., Medical Officer, DRUDP (HFD-580)
Mark Hirsch, M.D., Medical Officer, DRUDP (HFD-580)
Robert Seevers, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Angelica Dorantes, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sam Haidar, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D., Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Baldeo Taneja, Ph.D., Reviewing Statistician, DBII @ DRUDP (HFD-580)
John Markow, R.Ph., Consumer Safety Officer, DRUDP (HFD-580)
Terri Rumble; B.S.N., Project Manager, DRUDP (HFD-580)

External Participants:
Stephane Allard, President, Synthelabo Research, US
P. Grippon, Strategy and Medical Development, Synthelabo Research, US
Alan Kerr, Regulatory Affairs, Synthelabo Group, France
Christine Mc Carthy, Strategy and Medical Development, Synthelabo Group, France
Richard Miller, Director, Clinical Pharmacology, Synthelabo Research, US
Jean Paul Thenot, Pharmacokinetic Department, Synthelabo Group, France
David Tudor, Biostatistics Department, Synthelabo Group, France
Donna Ward, Manager, Regulatory Affairs, Synthelabo Research, US

Meeting Objectives: To discuss the sponsor's EOP2 results, questions, and Phase 3 development plan.

FDA Discussion Points:
Sponsor's Presentations (see handouts attached)

-
- asked whether DRUDP has plans to develop guidelines for BPH; guidelines are not currently being drafted, but the proposal will be considered

Preclinical
- no issues pending
- the sponsor should justify the proposed doses for the proposed carcinogenicity studies

Chemistry
- ICH conditions for stability studies should be used for this drug product
- new guidances for the extended release products (SUPAC-ER) and *in vitro/in vivo* correlations (IVIVC) will be available in the next two months; the draft version can be accessed on the CDER Web site

Clinical
- the 7.5 mg daily dose (OD) dose was dropped from development for lack of effectiveness (European study); but the sponsor plans to use the data to demonstrate safety (the ALPHA report)
- the ALFOTAM study uses 0.4 mg of tamsulosin because it is the only dose registered in Europe

Design comments:
- DRUDP recommends that the studies have two primary endpoints: IPSS and Peak Flow Rate
- regarding the primary endpoints, the sponsor's advisor feels that the flow rate changes vary significantly and the patient's judgement of the flow rate has no correlation with the objective measurements; he cited 1994 BPH guidelines that support using IPSS alone as a satisfactory measurement of obstructive changes and response
- other approved products used these endpoints; the sponsor can include this endpoint in the US study only; the European trial has started and does include the peak flow rate as a secondary endpoint; if a change in flow rate will be reported in the label, it is to the sponsors advantage to adequately power all their studies to show this difference from placebo for the label; other products have change in Peak Flow Rate in the label implying relevance
- all tools and scales used for the studies should be validated with documentation provided in advance; DDMAC will be consulted regarding the Quality of Life scales; validation of these tools will be documented and referenced by the sponsor
- the sponsor claims that the first-dose effect (defined by the sponsor as an immediate effect) is not observed at doses below 30 mg; however, some effects are seen at lower doses, they occur several hours after administration, when the drug is not at peak concentrations; the plasma concentration increases rapidly for the 30 mg dose and has a slower peak with the other lower doses
- orthostatic vital signs are not checked immediately during the study; a small subgroup of patients in several of the centers should have their orthostatic BP measured at peak drug level (the morning after administration of the dose (the sponsor clarified that the dose is administered five minutes after the evening meal)

- the placebo run-in period for the studies should be eliminated to avoid removal of the placebo responders from the study
- Dr. ——— advisor to the sponsor, refuted the recommendation to eliminate the placebo run-in phase 3 of the clinical trial stating that studies are not able to mimic real-life in the clinical setting and this was the design used by other sponsors with approved products; without the run-in, the study would not include a second score that reflects regression to the mean and also a placebo effect occurs; he feels that these phenomena are eliminated in the run-in period; DRUDP suggested that the patient be given no placebo, but followed by a physician for a month, assessed and reassessed if the patient has scores close to 13; the advisor feels that this is an untested hypothesis to do as suggested and that eliminating the placebo run-in is unfair to this sponsor; and feels that this hypothesis should be tested independently of the sponsor coming in with new studies for NDA review; DRDUP recommended that the sponsor propose their design for Phase 3 taking into account the advice provided in this meeting
- to obtain a better estimate of the regression to the mean, the study could be designed to use one value as a baseline and another value as a screen
- the sponsor should consider that the magnitude of the difference is not significantly different than the treatment effect; DRUDP is committed to providing a level playing field to all sponsors; current regulatory decisions must be based on the current scientific information available and should be consistently applied to standards across products in the Division; if placebo responders are eliminated, there are issues as to whether the product will demonstrate the same magnitude of effectiveness
- one purpose of the run-in is to eliminate non-compliers, as well; DRUDP suggested the sponsor can deal with non-compliers in the protocol design; since patient noncompliance is a reality, it would be important to include those patients in the study results;
- the sponsor should submit revised protocols with justifications for their proposed study design; it is acceptable that the protocols differ somewhat between the European and US trials

Dose issues:

- since the efficacy of the doses is unknown, the sponsor wants to study both doses; this is acceptable; the sponsor believes the 10 mg dose will be efficacious because the 2.5 mg t.i.d. doses showed bioequivalence to the 10 mg dose (based on PK data)
- if both doses are effective, the sponsor will most likely pursue a label that approves both doses; the 15 mg dose could be used in patients who failed to respond to the 10 mg dose, thus improving efficacy in some patients
- the 9-month extension study assures safety for the 15 mg and the 10 mg dose
- tamsulosin is used in the trials to demonstrate similarity rather than superiority; the study is not powered to show a statistical difference regarding equivalence or superiority
- the sponsor needs to consider the implication of whether the European and US formulations are the same; if the studies are not powered adequately to show equivalence for the US formulation, the data may not be allowed in the label; the promotional claims could be at issue, if the study is not designed to show the comparison of these products; this is a review issue for the sponsor to consider if the sponsor wishes to pursue
- the sponsor was advised that to receive adequate feedback on the proposed studies and the impact on future US marketing, all studies need to be submitted to the IND even those conducted in Europe; otherwise, the sponsor loses the ability to get feedback regarding power, sample size, etc., especially once the study is under way

Biopharm

- the release of the drug is not an absorption effect, but an effect of the release within the stomach because the capsule stays in the upper GI tract
- drug-drug interaction studies are not proposed
- no data on metabolites have been provided; the sponsor has completed analyses determining the metabolic pathways and will provide these data to the IND; no concern for interactions was seen
- if there are any changes in the controlled-release formulation a study will be conducted
- the sponsor should provide PK/PD analysis data for the controlled-release formulation (% change in peak flow and symptom score related to the dose), if available
- *in vitro* and *in vivo* correlation is useful to establish the relationship between dissolution and absorption; if changes in the formulation occur at a later time, bioequivalence studies are not needed
- food effect protocol using a 15 mg dose and a standard meal is under review; the definition of the standard meal should be clarified

Statistics

- the sexual function inventory is used because the sponsor proposes that BPH patients have a higher incidence of sexual dysfunction; the purpose of including this tool is to distinguish this drug from the competitors on market; this would be a review issue with information for the label; if not compared directly to competitors, then the information cannot be included
- primary endpoints are changes in baseline to 3 mo; dropouts will have final assessments completed on the last visit
- the multiple comparison plans need to be clarified; the statistical plan will be revised based on the recommendations of the meeting

Questions of sponsor: (See handouts)

1. Study design: comments as discussed above

2. Choice of doses: comments as discussed above

3. Duration of studies: acceptable

4. Patient long-term exposure: acceptable

Action Items:

- the sponsor will provide an IND amendment including revisions and information addressed in this meeting
- minutes will be exchanged between the sponsor and DRUDP within the month

/S/

Minutes Preparer

/S/ 9/2/97

Concurrence, Chair

Attachment: Sponsor's Handout

cc:
Original IND [redacted]
HFD-580/DivFile/Rarick/Jolson/Shames/Hirsch/Jordan/Seevers/Rhee/Rumble/Mercier
HFD-870/Dorantes/Haidar
HFD-715/Kammerman/Taneja/Nevius

drafted: Rumble/8.14.97/wpfiles/minutes/ind[redacted]ep2.spn
concurrences: Rarick,8.18.97/Jolson,9.2.97/Shames,8.19.97/Hirsch,8.18.97/Seevers,8.18.97
/Dorantes,8.18.97/Haidar,8.18.97/Kammerman,8.18.97/Pauls,8.15.97
no response: Taneja
final: Rumble,9.2.97

MEETING MINUTES

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

King, Jean

om: Tran, Suong T
ent: Friday, May 16, 2003 1:59 PM
To: King, Jean
Cc: Benson, George; Rhee, Moo Jhong
Subject: Declined: NDA 21-287: Alfuzoin label review meeting

Hi Jean-

Please convey to the review team that the physician's insert on the N drive is acceptable to us chemists. The physician's insert already got revised by us in the first review cycle; the current version incorporated our comments and is acceptable. We also finalized our review of the container labels in the first review cycle with the name Uroxatral and the company submitted acceptable container labels for Uroxatral toward the end of the first review cycle.

If there's a new name or if there's any change to the Uroxatral container labels, then we'll have to review the new mock-up container labels (with colors and graphics).

Thanks,
Su

NDA 21-287
Alfuzosin hydrochloride

Federal Register Notices

This application was not the subject of any Federal Register Notices.

MEMORANDUM

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

DATE: June 12, 2003

FROM: Julie Beitz, MD

SUBJECT: Deputy Office Director Memo

TO: NDA 21-287 Uroxatral (alfuzosin HCl extended-release tablets); Sanofi-Synthelabo

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's recommendation for approval of Uroxatral, indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Uroxatral is not indicated for the treatment of hypertension. Alfuzosin is an alpha$_1$-adrenergic receptor antagonist. It has been marketed in Europe as immediate release (2.5 mg tid), sustained release (5 mg bid) and extended release (10 mg qd) formulations. The studies submitted under NDA 21-287 support approval for an extended release formulation (10 mg qd).

Safety and Effectiveness

The original NDA was submitted December 8, 2000. The efficacy of alfuzosin 10 mg qd was demonstrated in three 12-week, randomized, placebo-controlled, double-blind, parallel-group studies. Although there were no cases of torsade de pointes or ventricular arrhythmia identified in the NDA database, an approvable action was taken on October 5, 2001, because there were residual concerns about the drug's effect on the QT interval, especially when co-administered with potent CYP450 3A4 inhibitors (e.g., ketoconazole). The sponsor was advised to conduct additional pharmacokinetic and pharmacodynamic studies to determine the effect of maximum doses of CYP450 3A4 inhibitors on the QTc interval in subjects taking alfuzosin.

A complete response to the approvable action was submitted on December 12, 2002. It contained the results of Study PDY 5105, a 4-way crossover, single dose, placebo- and active-controlled, double-blind study in healthy male volunteers. Alfuzosin 10 mg and 40 mg were evaluated. The 40 mg dose was chosen as this dose achieves C_{max} and AUC levels that exceed those observed with co-administration of alfuzosin and ketoconazole 400 mg. A variety of QT correction formulae were applied to the data. For alfuzosin 10 mg, the mean QTc change from baseline at T_{max} relative to placebo was 1.8 msec using either the population- or the individual-specific QT correction methods. The 95% CI around these estimates were (-1.4, 5.0) and (-1.3, 5.0), respectively. For alfuzosin 40 mg, mean QTc change from baseline at T_{max} was 4.2 and 4.3 msec, for the two correction methods respectively. The 95% CI around these estimates were (-0.6, 9.0) and (-0.5, 9.2).

On May 29, 2003, the Cardiovascular and Renal Drugs Advisory Committee was convened to discuss alfuzosin's effects on QT prolongation and in particular, the design and analysis of Study PDY 5105. For that meeting, DRUDP and Office of Drug Safety staff also reviewed the postmarketing adverse event experience for alfuzosin in Europe. The WHO database contained no spontaneously reported cases of QT prolongation or torsades despite an estimated exposure of ——— herapy days. In addition, reports of torsade de pointes, polymorphic ventricular tachycardia and QT prolongation entered into FDA's AERS database were reviewed for three alpha$_1$-adrenergic receptor antagonists marketed extensively in the US for the treatment of BPH. Since approval, only two, three, and one such report were identified in association with terazosin, doxazosin and tamsulosin use, respectively.

The Committee stated that Study PDY 5105 was adequately designed to assess the effects of alfuzosin on QT prolongation. After considering the results of this study and concluding that a clear safety signal in the postmarketing experience was absent for this and related drugs, the Committee voted unanimously that clinically relevant QT prolongation associated with use of alfuzosin had not been demonstrated. The

Committee did express concern that QT effects had not been formally studied in the full spectrum of patients who may receive this drug, particularly those with concurrent medical conditions that would place them at higher risk for QT prolongation (e.g., hypokalemia or congestive heart failure). The Committee acknowledged that such studies would be difficult to conduct. DRUDP and ODEIII concur with the Committee's interpretation of the available safety data for alfuzosin and residual concerns about at-risk patients.

Tradename Review

At the time of the original NDA submission, the sponsor proposed to use the name "Xatral" which is the proprietary name under which alfuzosin is marketed in Europe. In a memo dated February 23, 2001, the Division of Medication Errors and Technology Support (DMETS, Office of Drug Safety) did not find this name acceptable because of its similarity to several US marketed products including Zestril, Detrol, Xanax, Xalatan, and Sectral. Subsequently, the sponsor submitted the name "Uroxatral". This proposal was reviewed by DMETS and found to be acceptable in a memo dated May 18, 2001.

On December 16, 2002, the sponsor submitted two alternative names for consideration, [redacted] and [redacted] In a memo dated March 11, 2003, DMETS did not recommend the use of '[redacted]' since it looked similar to "Duracef" and to "Aricept" when scripted out. Furthermore, Aricept, which is approved for the treatment of Alzheimer's disease, would be used in a similar patient population as alfuzosin.

In March 2003, DMETS did not object to the proposed name [redacted] from a safety perspective, although this was a tentative decision since they had not received the container label, carton and insert labeling from the sponsor to review. In the same memo, DDMAC did not recommend the use of either name from a promotional perspective, stating that '[redacted]' was misleading and implied total relief of BPH symptoms, and '[redacted]' was not acceptable since it was too fanciful.

DRUDP and ODEIII concur with DMETS' and DDMAC's recommendations regarding the choice of tradename. "Uroxatral" is acceptable from our standpoint. The sponsor however, has stated its intention to submit additional data in support of the use of '[redacted]' in a labeling supplement post-approval.

Phase 4 Studies

The sponsor has agreed to conduct a study to evaluate the effect of co-administration of alfuzosin and a phosphodiesterase type 5 inhibitor (sildenafil or vardenafil) on QT interval at steady state drug concentrations. Timelines for submission of the protocol, completion of the study, and submission of the final study report were negotiated.

/S/

Julie Beitz, MD
Deputy Director,
Office of Drug Evaluation III
CDER, FDA

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Julie Beitz
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DIRECTOR

MEMORANDUM

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

DATE: October 5, 2001

FROM: Florence Houn MD MPH

SUBJECT: Office Director's Memo

TO: NDA 21-287 Alfuzosin hydrochloride (Sanofi-Synthelabo)

This memo documents my concurrence with the Division of Reproductive and Urologic Drug Product's recommendation to issue an approvable letter to Sanofi-Synthelabo with regard to their marketing application of alfuzosin, indicated for treatment of the signs and symptoms of benign prostatic hyperplasia. The efficacy of this drug's 10mg dose was demonstrated in three phase 3 double-blind, placebo controlled trials. There is, however, an outstanding safety question relating to the drug's effect on the QT interval and subsequent risk of torsades de pointes and ventricular arrhythmia. Data submitted by Sanofi-synthelabo is inadequate and incomplete to allow FDA to determine the safety of the drug.

The company states there is no clinically significant QT effect ("not more than 2 ms at doses up to four times the therapeutic dose") and there is no dose-dependent effect. They further state that "alfuzosin exposure was only increased by a factor of two in the presence of ketoconazole, the most potent inhibitor of this {CYP 3A4} enzyme." The Division of Cardiorenal Drug Products finds that the average lengthening of QT using Fridericia's correction (used because the drug increases heart rate and therefore Bazett's may be less appropriate) is about 10msec for 40mg of the drug. There may be a dose-dependent effect on QTc (see tables in clinical reviewer's memo). The 200mg ketoconzale interaction study did not include electrocardiographic monitoring nor was the maximum dose of ketoconazole (400mg) used. Nevertheless, this study did show a 2.5 fold increase in alfuzosin maximum concentration. The company will need to provide validation for their methodology for QT calculation (selective beat averaging using holter monitoring). If there is no agreement on validation, the company may need to provide data that demonstrates no drug effect on cardiac repolarization using agreed upon methods and QT calculation formula. The company will need to conduct the drug interaction study with the maximum dose of ketoconazole in pharmacodynamic studies on ECG effects as well.

This safety information is needed prior to approval because should significant QT effect be present and/or should significant drug-drug interaction be present to augment QT prolongation, this drug may not be suitable for approval. Because there are currently marketed and available alpha adrenergic blockers, there is no public health access question to address. As there are other alpha adrenergic blockers on the market whose QT effects were not worked up because they were approved prior to the science for QT screening being developed, we have asked OPDRA to obtain post-marketing events to look for a signal of QT cardiac events. Should these marketed drugs reveal a signal, the division will pursue the need for defining the QT effect with the identified drug's manufacturer. Finally, the division will not be sending proposed labeling along with the AE letter because labeling may need to be substantially revised once we have the clinical data, or the drug may not be approved obviating labeling. We would be sending mixed signals to the manufacturer by proposing contraindications for 3A4 inhibitors in labeling when really we need this drug interaction thoroughly evaluated.

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Florence Houn
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Deputy Division Director's Memorandum

From: Donna J. Griebel, M. D.
Deputy Director, DRUDP

To: Florence Houn, MD
Director, ODE III

Regarding: Rationale for Regulatory Action of NDA 21-287

Date Submitted:	December 12, 2003
Memorandum completed:	June 12, 2003
Sponsor:	Sanofi Synthelabo, Inc.
Drug:	Trade: Uroxatral Generic: alfuzosin hydrochloride extended release
Drug Class:	alpha-1 adrenergic receptor blocker
Route and Administration:	One table by mouth daily
Dosage Form:	Tablet
Strength:	10 mg
Proposed Indication:	Treatment of signs and symptoms of benign prostatic hyperplasia
Related INDs:	[redacted]

1.0 Background

NDA 21-287 was initially submitted on December 11, 2000. An approvable action was taken on October 5, 2001. The approvable letter stated that : "This application lacks adequate information, including clinical pharmacology data, to determine whether the product is safe for use because alfuzosin may increase the QTc interval. The QTc interval must be measured using an FDA agreed upon validated methodology, Additional pharmacokinetic and pharmacodynamic studies are necessary to determine the effect of maximum doses of inhibitor of the cytochrome P450 3A4 isoenzyme (e.g. ketoconazole) on QTc interval." A complete response to the approvable letter was received on December 12, 2002.

2.0 NDA Data and Analyses

2.1 QT Prolongation

During the initial NDA review cycle, the applicant submitted QT data that included a trial comparing 3 dose levels of alfuzosin (10mg, 20 mg, 40mg) to placebo. The Bazett and Fridericia corrected data suggested a dose response in QT prolongation (QTcF: 10mg = 0.5 ms, 20 mg = 3.4 ms, 40 mg = 7.1 msec; relative to placebo). A consultation to the Division of Cardiorenal Drug Products regarding all QT data submitted from multiple trials (which were of variable design adequacy) concluded that the "drug appears to be increasing the corrected QT by perhaps 10 msec." The sponsor had proposed that Holter monitor data from the 3 dose level study, which showed a diminished effect on QT, was the most appropriate because they believe the Holter monitor method is the most optimal methodology for evaluating QT effects associated with a drug that affects heart rate. The Division of Cardiorenal Drug Products did not concur with this assessment of the validity of the Holter monitor methodology for assessing QT effects. There

was additional preclinical data as well that showed that alfuzosin inhibits Ikr (at 83 micromolar concentration) and has an effect on purkinje fiber (at 1 micromolar).

In response to the approvable letter, the applicant worked with the FDA to design trials to address the approvability issues. Trial PDY 5105 was a single center, single dose, 4 way crossover, randomized, double-blinded, double-dummy, placebo controlled study that enrolled 48 healthy men between the ages of 18 and 50 years and was designed to examine QT effects. Alfuzosin doses studied were 10 mg (the proposed to be marketed dose) and a supratherapetuic dose, 40 mg, which was selected to cover plasma levels that might be achieved by either CYP 3A4 inhibition and continuous daily dosing. Besides placebo, the study incorporated an active control, moxifloxacin 400 mg. Assessments were performed with both standard 12-lead ECGs and Holter moniter. The sponsor made the latter methodology the primary endpoint of the study.

The study results with the various correction methodologies are summarized in the table below.

Table 1. Mean QTc change from baseline at Tmax (relative to placebo) in PDY5105

	QT	Bazett's (QTcB)	Fridericia (QTcF)	Population (QTcN)	Individual (QTcNi)	Holter Monitor (Largest sample RR bins)
Alfuzosin 10 mg	-5.8 (-10.2,-1.4)	10.2 (3.9,16.6)	4.9 (0.9,8.8)	1.8 (-1.4,5.0)	1.8 (-1.3,5.0)	0.4 (-1.8,2.6)
Alfuzosin 40 mg	-4.2 (-8.5,0.2)	13.9 (5.8,22.0)	7.7 (1.9,13.5)	4.2 (-0.6,9.0)	4.3 (-0.5,9.2)	2.5 (0.4,4.7)
Moxifloxacin 400 mg	6.9 (2.3,11.5)	15.7 (10.8,20.6)	12.7 (8.6,16.8)	11.0 (7.0,15.0)	11.1 (7.2,15.0)	6.9 (4.8,9.1)

The Fridericia correction results are similar to those reviewed from the study submitted during the initial NDA review cycle. Again, the applicant has argued in this submission that the Holter monitor methodology results are the truest reflection of alfuzosin's effect on QT interval. A dose related increase is observed with all methodologies, although the study was not designed to show statistically significant differences between dose levels, and the confidence intervals overlap. The active control moxifloxacin appears to consistently cause a greater effect on QT than both alfuzosin dose levels, but again the study was not designed for valid statistical comparisons, and the confidence intervals for alfuzosin at the highest dose overlap with moxifloxacin.

Because alfuzosin increases heart rate, and change in heart rate is known to affect QT interval, the validity of the various QT correction methodologies presented in the NDA (Bazett's, Fridericia, Population specific, and Subject-specific) were the focus of extensive FDA review. The correction methodology that yields the least correlation of QT with heart rate, i.e. lowest QT/RR slope, has been considered the best reflection of the "true" QT interval effect, as reflected in literature reviews on the subject and in FDA presentations on this subject. An FDA analysis of the methodologies presented in the NDA found that, though plots of each patient's subject-corrected QTc ($QTcNi=QT/RR^{Bi}$) as a population suggested that the Fridericia correction ($QTcF=QT/RR^{1/3}$) yielded the QT/RR slope closest to zero, when the various methodologies were compared by plotting each individual patient's QT/RR slope for each correction methodology, the subject-specific correction method yielded the most slopes closest to zero.

The QT prolongation issues raised by these data were discussed in a Cardiovascular and Renal Drug Products Advisory Committee on May 29, 2003. The majority of the committee voted that the study PDY 5105 was adequate to evaluate the drug's effect on QT (Yes=12; No=1;

Abstain=1). The committee unanimously voted that the effect of alfuzosin on QT for the population intended for actual treatment had not been adequately studied. (This vote was in reaction to the ages studied (mean age 27) and the fact that the population was healthy (normal electrolytes and normal baseline cardiac function). There was concern expressed about the need to understand the effect of the drug in patients at higher risk for QT prolongation, i.e. hypokalemic or patients which CHF, but individual committee members expressed their belief that studies designed to answer those questions would be difficult to pass IRB review because of the potential risk to the patients.

Without a vote taken, the committee indicated a consensus that no single correction methodology presented was more valid than the others. They indicated that the Holter monitor data was of distinct scientific interest, but that because it is a new methodology, there is not enough experience with this QT analysis methodology to know if the results predict the lack of, or probability of, a clinical event of arrhythmia associated with the resulting QT observations. The committee indicated that since it is unknown whether one correction methodology is more valid than the others, sponsors should include a "menu" of correction methodologies in their studies of QT effects.

There was a unanimous committee vote of "no" to the question – "Do these data demonstrate a clinically relevant QT prolongation associated with alfuzosin?" There was discussion by members with their votes that indicated that they wanted to factor the drug's "benefit" into their decision, suggesting that they believed they were voting for "approval/nonapproval". In addition some members stated that the lack of Torsade de Pointes post-marketing safety reports from Europe, where alfuzosin has been marketed since 1987, was factored into their decisions.

2.2 Metabolic Inhibition

A drug interaction study with alfuzosin 10 mg and ketoconazole 200 mg per day was submitted with the original NDA and the approvable letter stated that additional pharmacokinetic and pharmacodynamic studies were necessary to determine the effect of maximum doses of inhibitor of the cytochrome P450 3A4 isoenzyme (e.g. ketoconazole) on QTc interval. In response, the applicant has submitted another drug interaction study (INT5056), which examined the interaction of alfuzosin with a higher dose of ketoconazole – 400 mg in a single center, open label, nonrandomized, two period crossover study in 12 healthy subjects aged 19-39. The study showed that repeated administration of ketoconazole 400 mg daily for 8 days increased the Cmax of alfuzosin 2.3 fold and the AUC by 3.0 fold.

3.0 Risk/Benefit Evaluation

The efficacy and clinical trial safety data were thoroughly reviewed during the initial NDA review and the clinical trial data supported the claim of improvement in the International Prostate Symptom Score and urine flow rate. The adverse events observed in the studies were those expected with an alpha-1 adrenergic antagonist, and only a low incidence of adverse events related to orthostatic changes of blood pressure, approximately 6%, was reported. The additional information available in this review cycle to factor into the risk/benefit assessment are the drug interaction data for combining alfuzosin with a maximal dose of the potent CYP 3A4 inhibitor ketoconazole, and the data from the active and placebo controlled trial to evaluate QT. That trial examined the impact of an alfuzosin dose that results in plasma levels that exceed the levels that would be expected with concomitant administration of ketoconazole 400mg. The DRUDP took the QT interval prolongation issue to advisory committee for input from clinicians with expertise

in cardiovascular disease and cardiac electrophysiology. Discussion at the meeting suggested that there is as yet no accepted QT correction methodology that is considered superior to other methods, and the committee did not consider the risk associated with the observed degree of prolongation alarming. Some concern was expressed about the unknown risks of combining the drug with other drugs that prolong QT, or administering the drug to populations who have risk factors for Torsades de Pointes. The committee was clearly reassured by the lack of post-marketing signal of Torsades de Pointes in the extensive postmarketing safety data available from Europe, where the drug has been approved since 1987. The review team worked with the Office of Drug Safety during the review to examine the post-marketing safety data base in AERS for evidence of a signal of Torsades de Pointes events in other drugs of the alpha-1 adrenergic antagonist class, tamsulosin, terazosin and doxazosin, and found only 6 reported cases of Torsades/polymorphic ventricular tachycardia/QT prolongation for all three drugs, which have a prolonged history of marketing. These cases had medical conditions or medications present as confounders.

Based on the discussion at the advisory committee meeting, and the review team's own conclusion that the QT interval prolongation was of a magnitude that is of unclear clinical significance, the reviewers concurred that alfuzosin should be approved. The review team agreed with concerns raised by advisory committee members regarding the unknown risk of adding alfuzosin as a concomitant medication to other medications known to prolong QT, or in patients with congenital prolongation of QT. The review team believed that the potential risk involved in those circumstances could be addressed with labeling. During the discussion at the advisory committee meeting regarding concomitant medications the point was made that little is known about the actual risks of combining two drugs that prolong QT.

With regard to the potential for significantly increasing drug levels with concomitant administration of potent CYP 3A4 inhibitors, the review team concurred that this did not preclude drug approval, and the levels achieved in such circumstances had been investigated within the context of the QT study that was submitted.

4.0 Risk Management

The product label that the applicant ultimately agreed to includes, in the Clinical Pharmacology section in a section labeled "Electrophysiology", a description of the QT study PDY5105 and the mean change in QT interval from baseline relative to placebo for both doses of alfuzosin and the active control moxifloxacin. The data from all correction methodologies, except Bazett's and the Holter monitor data, were included in tabular format. There is a summary statement of the findings, with language to explain that the study was not designed to make valid statistical comparisons between dose levels or drugs. A brief statement regarding the lack of Torsades de Pointes in the post-marketing data from outside the U.S. is included. Under Precautions, a subsection called "Patients with Congenital or Acquired QT Prolongation" was included that refers the reader back to the Clinical Pharmacology Electrophysiology section, and states that the QT data should be considered when making a clinical decision to start alfuzosin in a patient with a known history of prolonged QT or in a patient taking other medications known to prolong QT. The patient package insert instructs patients to inform their physician if they or their family has a history of congenital prolongation of QT. The patient package insert also instructs patients to inform their physician of all the medications they are taking.

Contraindications incorporated in the label included contraindications for co-administration of potent CYP3A4 inhibitors (including a list of examples) and administration of alfuzosin in patients with moderate or severe (Child-Pugh B and C) hepatic dysfunction. A warning regarding

potential postural hypotension and syncope was accepted for inclusion in the label by the applicant, and this warning included wording to use caution in patients taking other medications that cause a hypotensive response.

Because the sponsor presented data from the three phase 3 clinical trials that had supported the efficacy of alfuzosin to show that patients enrolled in these trials who had mild or moderate renal insufficiency did not have a higher incidence of adverse events than those who had normal renal function, the review team agreed to not make a global statement in the precaution section regarding administering alfuzosin to patients with renal insufficiency. (The pharmacokinetic data reviewed in the original NDA submission had shown that patients with mild, moderate and severe renal insufficiency have a 50% higher exposure to alfuzosin.) This information was provided in the Precautions section with the phase 3 clinical trial exploratory renal insufficiency safety analysis. Because there were no patients with severe renal insufficiency in those studies, the Precaution states that caution should be used when administering alfuzosin to patients with severe renal insufficiency.

The applicant agreed to a phase 4 commitment to study the QT effects of alfuzosin combined with phosphodiesterase type 5 inhibitors, two of which have shown QT effects. These drugs are very likely to be combined in the clinical setting and members of the advisory committee expressed that it would be of public health interest to know the effects of, and if there are risks associated with, combining the two classes.

The trade name Uroxatral was reviewed and approved by DMETS and DDMAC.

5.0 Conclusion and Regulatory Recommendation

I recommend that alfuzosin is approved for the proposed indication, "for the treatment of the signs and symptoms of benign prostatic hyperplasia", with labeling as described in Section 4.0 of this review to address the risk management issues that were identified in the original NDA review cycle and during the review of the data submitted in response to the October 5, 2001 approvable letter.

Donna Griebel, MD
Deputy Director, DRUDP, CDER

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/s/

Donna Griebel
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MEDICAL OFFICER

Deputy Division Director's Memorandum

FROM:	Daniel A. Shames, MD Deputy Director, DRUDP
TO:	Flo Houn, MD Director, ODE III
REGARDING:	Opinion and Rationale for Regulatory Action of **NDA 21-287**

Date submitted: December 8, 2000
Date received: December 8, 2000
Draft review completed: August 29, 2001
Memorandum completed: September 26, 2001

Sponsor:	Sanofi-Synthelabo Research 9 Great Valley Parkway Malvern, PA 19355
Drug:	Trade: **Uroxatral** Generic: **alfuzosin hydrochloride**
Drug Class	α_1 adrenergic receptor blocking agent
Route and Administration:	One tablet by mouth daily
Dosage form:	Tablet
Strength:	10 mg
Proposed indication:	Treatment of the signs and symptoms of benign prostatic hyperplasia
Related IND's:	[redacted]

1.0 BACKGROUND

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

Differing approaches to drug development have led to approvals in 2 classes of drugs for treating the symptoms of BPH. The first drugs to be approved for this indication were the alpha$_1$-adrenergic receptor blocking agents. These drugs are thought to improve symptoms of BPH by blocking alpha$_1$-adrenergic receptor mediated smooth muscle contraction in the prostatic stroma (and probably bladder neck) and thereby decreasing the magnitude of bladder outlet obstruction.

Currently approved alpha$_1$ adrenergic receptor blocking agents for the treatment of symptoms of BPH are terazosin (Hytrin), doxazosin (Cardura), and tamsulosin (Flomax). Alfuzosin (under the trade name Xatral) was initially approved for foreign marketing as an immediate release (IR) for the treatment of BPH in 1988. Between 1988 and May, 2000, a total of ——— alfuzosin 2.5 mg IR tablets, ——— 5 mg SR tablets, and ——— 10 mg ER tablets have been sold. The primary safety concern with alpha$_1$-adrenergic blocking agents is hypotension and related symptoms (dizziness, hypotension and syncope). Alfuzosin has never been withdrawn from the market in any country.

The second major class of drug therapy for BPH is 5 alpha-reductase inhibitors. Dihydrotestosterone (DHT) is thought to be the primary androgen responsible for facilitating hyperplastic growth of the prostate. DHT is produced from testosterone by the action of the enzyme 5 alpha-reductase. Treatment with a 5 alpha-reductase inhibitor is thought to decrease the size of the prostate (acting primarily on prostatic epithelium) and thereby decrease the degree of prostatic obstruction. Finasteride (Proscar) is the only currently approved 5 alpha-reductase for use in treating the symptoms of BPH.

2.0 NDA: DATA AND ANALYSES

2.1 Conduct of Trials: The sponsor submitted four Phase 3 studies in support of the NDA. They were ALFOD, ALFUS, ALFORTI, and ALFOTAM. ALFOD studied only the 7.5-mg ER (Extended Release) dose versus placebo. The other three Phase 3 studies evaluated the 10-mg alfuzosin ER dose and 2 of the 3 also evaluated the 15-mg alfuzosin ER dose. Each of the four Phase 3 trials consisted of a 12- week double-blind phase and a 9-month extension phase.

The four Phase 3 alfuzosin ER formulation trials all had a double-blind, multicenter, randomized, parallel-group design. Three of the studies were done in Europe (ALFOD, ALFORTI, and ALFOTAM) and one in the United States (ALFUS). The doses of alfuzosin ER studies were 7.5, 10, and 15 mg. Each study had a 4-week, single-blind placebo run-in period after which patients were randomized to a 12-week double-blind treatment period.

In all three phase 3 studies utilizing the 10 mg alfuzosin ER dose, the study population consisted of men >50 years of age who had experienced lower urinary tract symptoms for at least 6 months.

2.2 Pharmacokinetic Issues: Cmax and AUC values were 2.5 times and 2.1 times higher, respectively, in the fed condition than in the fasted condition. In the clinical trials, patients were instructed to take the medication with meals.

A plateau of plasma concentration was observed between 3 and 16 hours after dosing. Steady-state plasma concentration was reached after two, once-daily administrations. Dose proportionality was demonstrated at single and repeated doses (from 7.5 mg up to 30 mg). Alfuzosin is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2. Ketoconazole increases the alfuzosin C_{max} 2-fold and the AUC 2.5-fold. The C_{max} of alfuzosin is increased 1.5-fold in patients with mild, moderate, and severe renal insufficiency.

2.3 Efficacy: The primary efficacy endpoints in the trials were changes from baseline in the International Prostate Symptom Score (IPSS) and the peak urinary flow rate (Q_{max}) (In ALFORTI Q_{max} was a secondary endpoint.). The IPSS is a validated symptom-scoring instrument and is identical to the American Urologic Association Symptom Index (AUASI). In ALFOD, which only studied 7.5 mg and placebo, the change from baseline in IPSS was 1.0 (p-value = 0.03) and the change from baseline in Qmax (0.4 cc/sec) was not statistically significant (p-value = 0.31). The sponsor therefore proposed 10 mg as the to- be-marketed dose, and only trials incorporating efficacy data for the 10 mg dose were fully reviewed.

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

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

2.4 Safety: 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 with a variety of doses and dosage forms. The primary safety data for the alfuzosin 10-mg ER formulation is derived from the pivotal 12-week double-blind trials and their open-label extension phases.

During the 12-week double blind portion of the trials, 429 patients completed the 10mg arms and 291 the 15-mg arms. 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.

The primary safety concern with alpha$_1$-adrenergic blocking agents is hypotension and related symptoms (dizziness and syncope). Although data concerning direct comparisons with other alpha$_1$ blockers is limited, the incidence of "vasodilatory" adverse events observed with alfuzosin appears to be similar to other agents in this drug class. 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 necessary.

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. A discussion of the sponsor's and CDER's analysis of this data is found below.

3.0 ISSUE OF PRIMARY CONCERN

3.1 QT Interval Prolongation: The Division reviewed the five studies included in the safety update as well as the "Assessment of the Potential Effect of Alfuzosin on Cardiac Repolarization" which represented the sponsor's analysis of the data. In PKD4532 (which studied placebo and 10, 20, and 40 mg of alfuzosin), the QTcB (Bazett's correction) 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 (Fridericia's correction) prolongation of > 60 msec. 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 sponsor believes that the QTcB is "biased toward reporting normal QT as abnormally long when corrected." The sponsor also believes that the technique using Holter monitor recording and analysis of QT/RR pairs is more accurate than traditional QTc analyses in the case of alfuzosin. The sponsor maintains that the Holter-QT/RR technique showed no clinically significant difference between alfuzosin and placebo.

The sponsor's conclusions are as follows: