CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Correspondence

10 June 2003

Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products, HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: **NDA 21-287; alfuzosin HCl**
Amendment No. 044
Revised Package Insert

Dear Dr. Shames:

We are providing a revised draft package insert in response to FDA comments on our 12 December 2002 draft labeling, provided to us in a 03 June 2003 FAX.

Sanofi-Synthelabo Inc. has retained the current proposed trade name in the draft package insert as a placeholder. We will respond to you separately regarding the trade name. We are also responding separately with comments on your proposal for the patient package insert received in a 05 June 2003 FAX.

We have incorporated all FDA comments from the 03 June 2003 FAX into the draft labeling and used this 03 June 2003 version as the basis for our response. Any changes we have made to this 03 June 2003 version are underlined and any deletions are crossed out. The proposed revision is attached. Several of our proposed changes are annotated, with the annotations at the end of the draft package insert.

We suggest a face-to-face meeting with you at your earliest convenience, if there are package insert issues that cannot be readily resolved by teleconference. Please consider the value of such meeting in your review of the attached package insert draft.

The 03 June 2003 FDA FAX also included proposed text to describe the results of our study to assess the effect of alfuzosin on cardiac repolarization. This text is proposed in the Drug Interactions subsection of Clinical Pharmacology and in Contraindications where ketoconazole interaction is identified.

The proposed FDA statement regarding effect on cardiac repolarization does not agree with the conclusion of the recent Cardio-Renal Advisory Committee held on 29 May 2003. FDA's statement says that the "clinical significance of the above reported results on QT interval is

not known" although the Cardio-Renal Advisory Committee, voted unanimously in response to FDA's specific question, that the effect of alfuzosin on cardiac repolarization demonstrated in the two studies, even at a supratherapeutic dose was not clinically relevant. Further, reference to cardiac repolarization in FDA's proposed Contraindication for concomitant use of ketoconazole provides the same implication, but the Committee concluded that the study data using exposures higher than those produced by ketoconazole interaction do not demonstrate a clinically relevant effect on cardiac repolarization.

Since the effect of alfuzosin on cardiac repolarization is not clinically relevant, inclusion of these data in the label will not provide useful information to the prescribing physician. Therefore, we have proposed deletion of this text in the attached draft.

Sanofi-Synthelabo understands that this NDA and all information contained therein, unless otherwise made public by Sanofi-Synthelabo Inc., are CONFIDENTIAL.

Please contact me by phone (610-889-6028) or facsimile (610-889-6993) if you have any questions or comments concerning this submission.

Sincerely,

Sanofi-Synthelabo Inc.

Jon E. Villaume, Ph.D.
Senior Director
Drug Regulatory Affairs

sew

COPY OF FDA

34 pages redacted from this section of the approval package consisted of draft labeling

04 March 2003

RECEI
MAR 0 5
FDR/CL

Ms. Jean King, Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857-1706

RECEIVED
MAR 0 5 2003
FDR/CDER

Subject: **NDA 21-287**
Alfuzosin HCl once daily for benign prostatic hyperplasia
Desk copy: Word version of package insert

Dear Ms. King:

As promised in our telephone conversation yesterday, Sanofi-Synthelabo is providing a CD-Rom containing the current version of the package insert for alfuzosin in Microsoft Word (MS Word 6.0/95) format. The latest version of the draft package insert was submitted in Amendment 36, dated 12 December 2002, which is the same version included in this letter.

The package insert file was verified to be virus free prior to being copied to CD using Norton AntiVirus Corporate Edition, Version 7.51.847, with a virus definition date of 04 December 2003.

Sanofi-Synthelabo understands that this NDA and all information contained therein, unless otherwise made public by Sanofi-Synthelabo Inc., are CONFIDENTIAL.

Please contact me by phone (610-889-6028), or facsimile (610-889-6993) if you have any questions or comments concerning this submission.

Sincerely,

Sanofi-Synthelabo Inc.

Jon E. Villaume, Ph.D.
Senior Director
Drug Regulatory Affairs

sew

12 December 2002

Daniel Shames, M.D., Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: NDA 21-287
Alfuzosin HCl once daily for benign prostatic hyperplasia
Complete Response to 5 October 2001 NDA Approvable letter
Amendment 36

Dear Dr. Shames,

In this correspondence all issues raised in the 5 October 2001 NDA Approvable letter are addressed. The Approvable letter stated that the application did not have sufficient information to determine the following:

- whether the product had an effect on cardiac repolarization (as measured by QT interval of the electrocardiogram), and
- the effect of maximum doses of inhibitor of the cytochrome P450 3A4 isoenzyme (i.e., ketoconazole)

The Approvable letter also requested that all safety information be updated in our response.

In a meeting held on 7 January 2002 to discuss the Approvable letter, the Division affirmed that the method in the NDA for determining effect on QT interval should be validated for its ability to detect drug effect. FDA also agreed that the validation of the method to measure effect on QT interval and effect of maximum doses of CYP3A4 inhibitor could be addressed in separate studies.

In a 14 February 2002 correspondence (NDA amendment 28) we provided protocol PDY5105 to address QT interval method validation. In a 13 March 2002 teleconference FDA stated that the design was adequate, but commented on the power of the study to detect a signal from the positive control (FDA FAX minutes dated 17 April 2002) . The final protocol provided to FDA on 29 March 2002 (amendment 32) addressed this comment. In a letter dated 16 May 2002, FDA concurred with the adequacy of the design of this study.

Sanofi-Synthelabo Research
A division of Sanofi-Synthelabo Inc.
9 Great Valley Parkway, Malvern, PA 19355 - Tel.: (610) 889-8600

The 14 February 2002 correspondence also provided protocol INT5056 to address the effects of maximum doses of the CYP3A4 inhibitor, ketoconazole. In a letter dated 6 May 2002, FDA concurred with the adequacy of the design of this study.

The report of study PDY 5105 provided in Item 6 of this response confirms that alfuzosin does not produce a meaningful effect on the QT interval of the ECG. However, the lack of meaningful effect of a drug on QT interval of the electrocardiogram is only one component of the overall cardiovascular safety profile. For alfuzosin a large body of information relevant to cardiovascular safety is available. Therefore, we have also provided in Item 3 summary a discussion of all components of the profile available to make a determination of the cardiovascular safety of alfuzosin.

The complete report of study INT5056 was provided to the NDA on 10 September 2002 (amendment 34). A full copy of NDA Amendment 34 is also provided in Item 6 of this response. This study confirmed our previous predictions in a 19 November 2001 background package (amendment 24) that exposure (AUC) is increased by a factor of only 3 in the presence of a maximum dose of ketoconazole.

The Safety update in Item 9 of this response provides no evidence that the safety profile of alfuzosin has changed. While the additional exposure to the drug in this update is small, the exposure reported previously in the NDA from many clinical studies and 14 years European marketed use is substantial. In all this experience, there has been no evidence that alfuzosin has any effect on cardiac repolarization.

Labeling

The labeling has also been revised. A draft package insert is provided in Item 2 (proposed.pdf) of this Complete Response and an annotated version is provided in Item 3 (summary.pdf).

A desk copy of this submission is being provided to Ms. Margaret Kober. Included in the desk copy is a paper copy of all documents in the complete response, minus appendices, as well as a CD labeled Review Aid, which contains a Microsoft Word (MS Word 6.0/95) copy of the proposed labeling document.

Electronic format

The archival copy of this submission to NDA 21-287 (Amendment 36) is provided entirely in electronic format, consistent with the January 1999 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs." The archival copy is a fully electronic dossier, with the exception of administrative documents requiring an original signature that are provided in paper (cover letter and Form 356h). Full navigation to all provided documents is available from the submission Table of Contents (amendtoc.pdf).

Electronic Archival specifications

All electronic files included as the archival copy of this submission are provided on a single CD-Rom. This electronic submission is approximately 450 MB in total size. All files were checked and verified to be free of viruses prior to being copied to CD using Norton AntiVirus Corporate Edition, Version 7.51.847 with a virus definition date of 04 December 2002.

Sanofi-Synthelabo understands that this and all information contained therein, unless otherwise made public by Sanofi-Synthelabo Inc., are CONFIDENTIAL.

Please contact me by phone (610-889-6028) or facsimile (610-889-6993) if you have any questions or comments concerning this submission.

Sincerely,

Sanofi-Synthelabo Inc.

Jon Villaume

Jon E. Villaume, Ph.D.
Senior Director
Drug Regulatory Affairs

sew

65 pages redacted from this section of the approval package consisted of draft labeling

16 April 2003

Ms. Jean King
Division of Reproductive and Urologic Drug Products, HFD-580
Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Division Document Room
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: **NDA 21-287; alfuzosin HCl**
Desk Copy

Dear Ms King:

Reference is made to NDA 21-287; alfuzosin HCl, Amendment No. 041 dated 15 April 2003 and the contact of 03 March 2003, during which you requested a draft PPI (patient package insert) for alfuzosin. As requested, a desk copy containing a WORD version of the document, file name "patient pi.doc", is enclosed.

All files were verified to be free of viruses prior to being copied to CDROM using Norton AntiVirus Corporate Edition, Version 7.51.847 with a virus definition date of 09 April 2003.

Sanofi-Synthelabo understands that this NDA and all information contained therein, unless otherwise made public by Sanofi-Synthelabo Inc., are CONFIDENTIAL.

Please contact me by phone (610-889-6028) or facsimile (610-889-6993) if you have any questions or comments concerning this submission.

Sincerely,

Sanofi-Synthelabo Inc.

Jon E. Villaume, Ph.D.
Senior Director
Drug Regulatory Affairs

dmr

Sanofi-Synthelabo Research
A division of Sanofi-Synthelabo Inc.
9 Great Valley Parkway, Malvern, PA 19355 - Tel.: (610) 889-8600

28 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING ISSUES IDENTIFIED

NDA 21-287

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

Dear Dr. Villaume:

Please refer to your December 8, 2000 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alfuzosin HCL.

Additionally, we acknowledge receipt of your December 12, 2002 submission providing a complete response to our October 5, 2001 NDA Approvable Letter. We have completed our filing review of your application and have identified the following issues:

Clinical

The following is an area of concern and we request additional clarifying information:

- Please refer to Study PDY 5105 entitled "Effect of supra-therapeutic doses of alfuzosin ER on QT interval, using a rate-independent method, compared to placebo and to moxifloxacin in healthy volunteers". In Table (15.2.1) on page 78 of 100 and a similar table on page 7 of 100, the "n" value representing the number of patients whose data are analyzed varies between groups. Please provide an explanation for this variation.

Clinical Pharmacology and Biopharmaceutics

No review issues noted at time of filing.

Chemistry

No review issues noted at time of filing.

Statistics

No review issues noted at time of filing. However, to facilitate our review, we request your submission of electronic SAS transport files containing the raw QT data sets from Study PDY 5105. Data records should include all relevant patient variables to enable computation of the

various methods of QTc interval corrections and their analysis. Appropriate supporting documentation and data dictionaries should accompany this submission.

Pharmacology/Toxicology

No review issues noted at time of filing.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

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

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
2/26/03 05:38:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-287

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

Dear Dr. Villaume:

We acknowledge receipt on December 12, 2002 of your December 12, 2002 resubmission to your new drug application for alfuzosin HCL.

This resubmission contains additional clinical information, labeling information, and safety update report in response to our October 5, 2001 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the primary user fee goal date is June 12, 2003.

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
1/28/03 06:43:43 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-287

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

Dear Dr. Villaume:

Please refer to your New Drug Application (NDA) submitted under section 505b(i) of the Federal Food, Drug, and Cosmetic Act for alfuzosin hydrochloride.

We have reviewed your correspondence of July 10, 2001, requesting a teleconference with the Chemistry reviewer to discuss and obtain concurrence for your proposals to minimize the amount of text in the container labels. Upon review of your proposals, the Division has decided that written responses could be provided to you in lieu of a teleconference, in a more timely fashion.

Our comments, which have been conveyed to you previously by Ms. Farinas, are listed below.

Proposal #1: Use of "alfuzosin HCl tablets" in place of "alfuzosin hydrochloride extended-release tablets" proposed by the Division in the June 29, 2001, correspondence.

This proposal is not acceptable. The established name must be "alfuzosin hydrochloride extended-release tablets." The established name without the term "extended release" is misleading and incorrect because the drug product is an extended-release dosage form.

Proposal #2: Shortening the established name from "alfuzosin hydrochloride" to "alfuzosin HCl."

This proposal is acceptable. The Division agrees with shortening the established name from "alfuzosin hydrochloride extended-release tablets" to "alfuzosin HCl extended-release tablets."

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Evelyn Farinas
7/19/01 09:15:44 AM
CSO

Moo-Jhong Rhee
7/20/01 09:48:02 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DMF [redacted]

[redacted]
c/o Sanofi-Synthelabo Inc.
Attention: [redacted]
Assistant Director
CMC Drug Regulatory Affairs
90 Park Avenue 6th floor
NY, NY 10016

Dear Mr. [redacted]

Your letter dated October 9, 2000, authorizes us to reference Drug Master File (DMF) [redacted] in support of Sanofi-Synthelabo Inc.'s drug product application for alfuzosin, NDA 21-287.

As stated to Mr. Charles Ireland from Sanofi-Synthelabo, Inc., in a July 18, 2001, telephone communication, the original DMF letter sent to [redacted] was returned to our Division unopened.

As a follow up for your records, the July 2, 2001, letter to [redacted] is attached. Please note that this letter is the same that was sent to you via facsimile on July 9, 2001.

If you have any questions, call me at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Evelyn R. Farinas, R.Ph., M.G.A.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment: DMF letter dated July 2, 2001

DMF

Attention:

Dear Mr.

Your letter dated October 9, 2000, authorizes us to reference Drug Master File (DMF) in support of Sanofi-Synthelabo's drug product application for alfuzosin, NDA 21-287.

Your communications dated June 18, 1997 and October 27, 2000 were reviewed in support of this NDA. Since approval of Sanofi-Synthelabo's NDA is contingent upon adequate information being provided in a supporting DMF, please submit the following information as soon as possible.

1. Please provide information on the commercial sources of
2. The in-process limit for Impurity is not acceptable because the qualified level is 0.1%, as stated on page 104 of the DMF Version 2 (October 2000). The limit for Impurity I should be NMT 0.1%.
3. Please clarify whether reference standards are used in the testing of Assay by # 3, Assay by # 4, and Assay by # 6.
4. Please provide the procedure for replacing a reference standard lot, including information on the characterization of the new standard.
5. As batch analysis results show, Water Content ranges from % . The proposed % limit is excessive. Water Content limit should be NMT 0.5% to reflect manufacturing capability.
6. Referencing the European Pharmacopoeia test methods is not adequate. All test methods should be described in detail or an appropriate reference to the U.S. Pharmacopoeia should be made.
7. Acceptance criteria for in the drug substance should be established because the drug product dosage form is an extended-release tablet.
8. Regarding the test method for the determination of impurities, sample calculations for the Reference Solution 1 concentration and for the impurity percentage in the drug substance should be provided.
9. Please provide UV spectra for alfuzosin HCl, Impurities
10. Please submit chromatograms of the impurities at concentrations equivalent to the limit of detection.
11. Regarding the test method for the determination of residual solvents, a sample calculation for percentage in the drug substance should be provided.

12. The acceptance criterion for Impurity —should be NMT 0.10%.
13. The acceptance criterion for Total Impurities should be NMT 0.2% to reflect manufacturing capability.
14. Per ICH Q6A guidance, supporting data should be provided to show that the drug substance is not capable of supporting microbial growth.
15. Information on the components of the container/closure system should be provided. Compliance of these components with applicable FDA regulations should be stated. Information should be provided on the validation testing of the ——— bags and should include IR testing and USP testing for plastics. In addition, it should be clarified as to how the desiccant is placed (——— between the ——— bags.
16. The retest period of the drug substance should be established.
17. It should be clarified whether the container/closure system used for the drug substance on stability is the same as the system used for routine storage of the drug substance.
18. Container labels for storage and shipping of the drug substance should be provided. The labeling should indicate the name and NDC number of the drug substance, batch number, weight, Caution statement per FDA regulations, and manufacturing date of the lot.

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852

Sanofi-Synthelabo will be notified that the information in your DMF is inadequate to support their NDA. When you amend your DMF [redacted] please notify Sanofi-Synthelabo in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that your DMF has been amended. Please do not provide a copy of the amendment to the review chemist.

Suong Tran, Ph.D.
Division of Reproductive and Urologic Drug Products
HFD-580
5600 Fishers Lane
Rockville, MD 20857

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/2/01 03:08:28 PM

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ON ORIGINAL

Cc: Rhee. Tran, Rumble

Drafted by: Farinas/July 18, 2001
Initialed by: Rumble
Final: Farinas
filename: C:\Data\My Documents\NDA 21287 alfuzosin DMF second ltr.doc

DMF INFORMATION REQUEST

APPEARS THIS WAY
ON ORIGINAL

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/s/

Evelyn Farinas
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-287

DISCIPLINE REVIEW LETTER

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

Dear Dr. Villaume:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alfuzosin, 10 mg tablets.

Our review of the Chemistry, Manufacturing and Controls section of your submission indicated deficiencies in the Drug Master File (DMF) for alfuzosin. The information in the DMF is inadequate to support NDA 21-287. ( )the DMF holder, has been informed of the deficiencies. In addition, the DMF holder has been asked to notify you when the amendment to the DMF addressing the deficiencies is sent to the Agency, in accordance with 21 CFR 314.420 (c).

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
HFD-580
DNDC II
Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
7/2/01 03:10:52 PM

NDA 21-287

INFORMATION REQUEST LETTER

Sanofi-Synthelabo, Inc.
Attention: Jon E. Villaume, Ph.D.
Senior Director
9 Great Valley Parkway
P.O. Box 3026
Malvaern, PA 19355

Dear Dr. Villaume:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alfuzosin hydrochloride (HCl).

We are reviewing the Chemistry section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Please provide the regulatory specification for the drug substance as stated in the DMF (alfuzosin HCl) in the NDA section 4.1 Drug Substance.
2. Acceptance criteria for the drug substance should be implemented by Sanofi-Synthelabo for each drug substance batch prior to use in the manufacture of the drug product. The criteria should be the same as those of the regulatory specification as stated in the DMF (alfuzosin HCl). The assay results as determined by Sanofi-Synthelabo should be used in calculating the amount of alfuzosin HCl in the drug product manufacture.
3. The manufacturing process of the second, active, inner layer should include an in-process control for determining the potency. The amount of the active to be weighed for tablet compression should be based on the result of this potency assay.
4. The sampling procedures (selection of samples) used for release testing of the drug product should be provided.
5. Please provide the results for Average Tablet Weight for the drug product batches listed on page 98 of Volume 3.
6. Acceptance criteria for water content in the drug product should be established for both release and stability testing.
7. The proposed acceptance criteria for degradants are not acceptable because they exceed the qualified levels for the drug substance. In addition, they do not reflect the available stability results for the drug product. Acceptance criteria for degradants should be established in accordance with ICH Q6A. Furthermore, acceptance criteria for impurities/degradants (e.g., degradation products of the drug substance, potential reaction products of the drug substance with an excipient and/or the container/closure) should be implemented prior to the release of each drug product lot. Because only one lot per year will be placed on stability study, no information on impurities would be available for the majority of market product lots. Without impurity data at release, it would be difficult to be alerted to any unexpected problem in the manufacturing process or to validate any post-approval change in the manufacturing process.

8. The ——— test method and the — test method for determining residual solvents should have system suitability testing including capacity factor, tailing factor, and injection precision —.

9. Please provide the following information: a) procedures for Appearance testing; b) ——— operating conditions for Identity testing by — and c) method of calculation for alfuzosin content in the Dissolution test method.

10. Please clarify when the last time point occurs in the measurement of the Dissolution test.

11. Per 21 CFR 314.50(e)(2)(i), please provide three copies of the method validation package.

12. The proposed expiration dating period of ——— is not acceptable. The expiration dating period will be determined based on stability data that will be submitted in an amendment during the NDA review cycle.

13. The stability commitment should include a statement that "An extension of the expiration dating period will be based on full long-term stability data from three production lots in accordance with the stability protocol approved in the NDA."

14. The stability commitment should clearly state that at least one product lot per year for each container/closure configuration will be placed on stability. In addition, stability testing of such a lot should follow the testing schedule described in the stability protocol of Table (4.2.8.8.2)1. The proposed annual testing schedule is not acceptable.

15. Based on the stress data, the container labels of the drug product should include a statement "Protect from light and moisture".

16. Regarding the Package Insert:

    a. The established name should be "alfuzosin hydrochloride extended-release tablets".

    b. The term "hydroxypropylmethylcellulose" should be two separate words "hydroxypropyl methylcellulose" per USP/NF monographs.

    c. All compendial inactive ingredients should have the compendial references.

    d. The HOW SUPPLIED section should begin "[Proprietary Name] (afuzosin hydrochloride extended-release tablets) 10 mg is available as ..."

    e. The storage statement in the package insert should state "Store at 25 °C (77 °F); excursions permitted to 15-30 °C (59-86 °F)" [see USP Controlled Room Temperature]. Protect from light and moisture."

17. Regarding the container labeling:

    a. The format for names on all container labels should be as follows:

       proprietary name
       (alfuzosin hydrochloride extended-release tablets)
       10 mg

    b. All labels should include "See package insert for dosage information", "Protect from light and moisture", and on the larger containers "Dispense in a tight-light-resistant container per USP".

    c. The statement "Each (container) ... contains (net quantity) tablets of 10 mg alfuzosin hydrochloride" should be replaced by "(net quantity) tablets" in prominent text.

    d. The net quantity and dosage strength should be stated on separate lines.

    e. The dosage strength should be stated in prominent text immediately after the established

name.

f. [redacted] should be deleted.

g. The logo should be deleted because it makes the letter "X" look like the letter "Y". The logo also obstructs the established name.

h. As stated in the April 4, 2001 teleconference, all container labels should be submitted at least two months before the action goal date.

If you have any questions, call Evelyn Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moc-Jhong Rhee
6/29/01 03:59:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-287

INFORMATION REQUEST LETTER

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

Dear Dr. Villaume:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for alfuzosin.

We also refer to your submission dated April 25, 2001.

We are reviewing the Clinical and Biopharmaceutical sections of your submission and have the following comments.

1. You should submit Case Report Forms (CRF) for all deaths, serious Adverse Events (AEs) and discontinuation secondary to AEs from all sources providing new exposures.

2. If the study is still blinded, as in ALFAUR, the CRFs may be omitted.

3. Submission of the digoxin drug interaction study results at Month 7 is acceptable.

If you have any questions, call Evelyn R. Farinas, Regulatory Project Manager, at 301-827-4260.

Sincerely,

/S/

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Terri F. Rumble
6/4/01 03:40:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-287

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

Dear Dr. Villaume:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	alfuzosin HCl 10 mg extended release tablets
Review Priority Classification:	Standard (S)
Date of Application:	December 08, 2000
Date of Receipt:	December 11, 2000
Our Reference Number:	NDA 21-287

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 25, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 11, 2001 and the secondary user fee goal date will be December 11, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Terri F. Rumble
12/12/00 03:22:37 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Fawinas

Food and Drug Administration
Rockville MD 20857

JUL 31 2001

John E. Bannow, M.D.
820 Lester Ave.
Cedarwood Medical Center
St. Joseph, Michigan 49085

Dear Dr. Bannow:

Between May 29 and June 5, 2001, Mr. William Tingley representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #2560 (ALFUS), under NDA 21-287) of the investigational drug, alfuzosin, performed for Sanofi-Synthelabo. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all U.S. Federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects. At the conclusion of the inspection, Mr. Tingley discussed his findings with your research coordinator,

We appreciate the cooperation shown Mr. Tingley during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

JRM.

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 125
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA 21-287
HFD-580/Farinas
HFD-580/Benson
HFD-580/Batra
HFD-580/Hirsch
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10402
HFD-46/Molchan
HFR-CE7565/Tingley
HFR-CE7555/French
HFR-CE750/Dempster

Field Classification: Referred to Center
Headquarters Classification: NAI

___x__1)NAI
_____2)VAI (no response required)
_____3)VAI-R (30 day response requested)
_____4)VAI-RR (adequate response received)
_____5)OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
____deviation from protocol
____inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

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r/d: drafted/sem/07.25.01
reviewed:jrm: 7/26/01
final type:jau: 7/27/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT - 2

Bruce A. Kletscher, M.D.
Urology Associates, Ltd.
202 East Earll Drive, Suite 360
Phoenix, Arizona 85012

Dear Dr. Kletscher:

Between June 27 and July 11, 2001, Mr. Randall N. Johnson representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #2560/ALFUS) of the investigational drug alfuzosin, performed for Sanofi-Synthelabo. This inspection was a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your undated written response to the observations listed by Mr. Johnson on Form FDA 483, it appears that you have adequately addressed all of the inspectional observations.

Your written response will be included as a permanent part of your file. If information is requested from your file in accordance with the Freedom of Information Act, our response will include all the related correspondence in your file; this will serve to give a more complete picture of the inspection report. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

cc:
HFA-224
HFD-580/Doc. Rm.: NDA #21-287
HFD-580/MO/Benson
HFD-580/PM/Farinas
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP file #10466
HFD-46/GCPI Br. Chief/Martin
HFD-46/GCP Reviewer/Lewin
HFR-PA250/DIB/Kozick
HFR-PA2565/BIMO/Koller
HFR-PA2530/Field investigator/Johnson

Field Classification: VAI
Headquarters Classification:

__X__1) NAI
_____2) VAI no response required)
_____3) VAI-R (30 day response requested)
_____4) VAI-RR (adequate response received)
_____5) OAI-WL

Deficiencies noted:

____inadequate consent form
____inadequate drug accountability
____deviation from protocol
__X__inadequate records
____failure to report ADRs
____failure to obtain IRB approval
____failure to personally conduct or supervise study
____other

O: CL:/Kletscher Sep01 VAI-RR.doc
r/d: drafted/cl/09-28-01
reviewed:jrm:10/01/01
final type:jau:10/01/01