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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent of: François Regnier

Patent No.: 4,661,491

Granted: April 28, 1987

Serial No. 06/867,031

Filing Date: May 27, 1986

For: ALFUZOSINE COMPOSITIONS AND USE

CERTIFICATE UNDER 37 C.F.R. 1.10(b)

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Date of Deposit 8/6/03

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8/6/03

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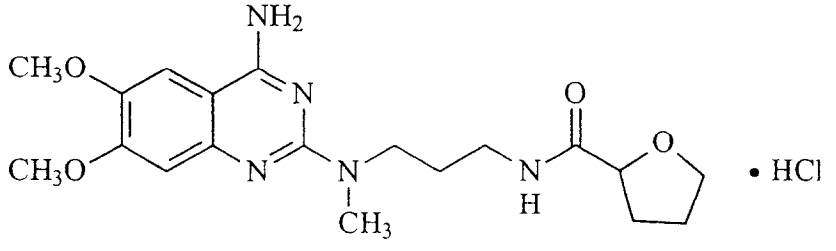
Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 AND 37 C.F.R. §1.740

Dear Sir:

Under the provisions of 35 U.S.C. §156 and in accordance with 37 C.F.R. §1.740, Sanofi-Synthelabo, the owner of United States Patent No. 4,661,491 hereby requests that the term of said patent, originally expiring on May 27, 2006, be extended 1,481 days to expire on June 16, 2010. The chain of title of United States Patent No. 4,661,491 from the inventor to Sanofi-Synthelabo is attached hereto as Exhibit 1.

(1) Alfuzosin hydrochloride is the generic name of the compound having the chemical name (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furan carboxamide hydrochloride and having the structural formula:



2004E-0393

APP 1

(2) Alfuzosin hydrochloride was subject to regulatory review by the Food and Drug Administration (FDA) under Section 505(i) and 505(b) of the Federal Food, Drug and Cosmetic Act.

(3) Alfuzosin hydrochloride was approved for commercial marketing or use by the Food and Drug Administration under Section 505(b) of the Federal Food, Drug and Cosmetic Act on June 12, 2003.

(4) The active ingredient in the approved product is alfuzosin hydrochloride. Alfuzosin hydrochloride has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

(5) This application is being submitted within the sixty-day period permitted for submission pursuant to 37 C.F.R. §1.720(f). The last day on which this application can be submitted is August 10, 2003.

(6) The patent for which an extension is being sought is United States Patent No. 4,661,491 issued April 28, 1987 in the name of François Regnier and having an expiration date of May 27, 2006.

(7) A complete copy of United States Patent No. 4,661,491, including the entire specification, claims, and drawings, is attached hereto as Exhibit 2.

(8) Copies of the Maintenance Fee Statements showing payment of the 4th, 8th and 12th year maintenance fees in United States Patent No. 4,661,491 are attached hereto as Exhibit 3.

(9) Claims 1-5 of United States Patent No. 4,661,491 claim a method of using alfuzosin hydrochloride. A demonstration of how claim 5 reads on a method of using alfuzosin hydrochloride is set forth below:

> Claim 5 reads on a method for treating dysuria in male patients having benign hypertrophy of the prostate using alfuzosin hydrochloride.

10.) Alfuzosin hydrochloride was subject to a regulatory review period consisting of (a) the period from August 31, 1996, the effective date of the Investigational New Drug (IND) Application No. 51,200 submitted August 1, 1996 under Section 505(i) of the Federal Food, Drug and Cosmetic Act to December 8, 2000, the initial submission date of the New Drug Application (NDA) No. 21-287 under Section 505(b) of the Federal Food, Drug and Cosmetic Act, (b) the period from December 8, 2000, the initial submission date of NDA No. 21-287 to October 5, 2001, the date an NDA approvable letter was received, (c) the period from October 5, 2001 to December 12, 2002, when a complete response to the October 5, 2001 approvable letter was filed, and (d) the period from December 12, 2002 to June 12, 2003, the date the NDA was approved.

(11) The significant activities undertaken by or on behalf of applicant and responses by the FDA during the applicable review period with respect to the alfuzosin hydrochloride are as follows:

SUMMARY OF ALFUZOSIN HYDROCHLORIDE IND ACTIVITIES

Date	Comm Type	Serial No.	Abstract
24-Apr-1996	LTF		Synthelabo submitted to Mr Stephen Trostle, CSO, Division of Metabolism and Endocrine Drug Products, information regarding the proposed IND submission for Alfuzosin HCL once-daily tablet
31-May-1996	LTF		FDA acknowleged receipt of Synthelabos's Drug Master File (DMF) submission of May 14, 1996. DMF Number assigned. DMF 11976 Title of Submission: Type II: Alfuzosin HCL Drug Substance Manufactured in Gargenville, France Holder of Submission: Synthelabo Recherche (LERS)
01-Aug-1996	SUB	000	Initial IND Application.
06-Aug-1996	LFF		The FDA acknowledged receipt of Synthelabo's IND and assigned IND Number 51,200.
14-Aug-1996	TEL		Ms. Christina Kish (FDA) called to arrange a teleconference on August 15, 1996. Ms. Kish indicated that there were clinical questions to be answered.
27-Aug-1996	FAC		Synthelabo provided the FDA with its version of the meeting minutes from the August 15, 1996 teleconference.
29-Aug-1996	SUB	001	As discussed during the teleconference on August 15, 1996, Synthelabo did the following · 1) Provided the Agency with the most recent alfuzosin safety data available from the ongoing European clinical trials, 2) Provided safety information from studies where higher doses (>10 mg/day, tid formulation) of alfuzosin were administered, 3) amend the protocol to include the following: exercise treadmill evaluations at screening, additional electrocardiograms, orthostatic hypotension definition, and evaluation of safety data before dose escalation
05-Sep-1996	TEL		Synthelabo contacted Ms. Christina Kish (FDA) Ms. Kish indicated that she has received the necessary information and Synthelabo may begin clinical trials.
10-Sep-1996	LFF		The FDA provided Synthelabo with the minutes from a teleconference held on August 15, 1996.
16-Sep-1996	SUB	002	Provided protocol PC ALF 96 US 1, A-C, which provides for the following· 1) exercise treadmill evaluations at screening, 2) additional electrocardiograms, 3) orthostatic hypotension definition, and 4) evaluation of safety data before dose escalation and agreement with FDA to proceed with the 22.5 and 30 mg doses, respectively. PC: Protocol PC ALF 96 US 1, A-B and A-A, which address changes to the range of clinical values which Synthelabo considers to be potentially clinically significant changes.
15-Nov-1996	SUB	004	Synthelabo provided the FDA with safety data from Study PC ALF 96 US 1 for review and the Quarterly Safety Report, as of September 30, 1996. That report provides safety data from ongoing studies using alfuzosin formulations administered orally, BID and OD (Geomatrix® formulation) and in patches.
15-Nov-1996	LFF		The FDA completed its review of the medical and chemistry portions of the IND and had comments and requests.
27-Nov-1996	TEL		Ms. Chirstina Kish, Project Manager, Division of Reproductive and Urologic Drug Products, telephoned Synthelabo to state that the Medical Reviewer (Dr Shames, Director Clinical Pharmacology) had some questions/concerns regarding Submission Number 004· Safety Data from Study PC ALF 96 US 1, and would like to discuss them with Synthelabo Research that day. Dr. Shames indicated: 1) that it was safe to proceed to the next dose level of 22.5 mg 2) wondered at what dose level effficacy was expected to be seen 3) wondered if dose titration was being condsidered with this drug as is done with other drugs 4) wondered what Synthelabo's plans were after the study
13-Dec-1996	FAC		Internal memo - Synthelabo Research ---Dr. Shames, Medical Reviewer for the alfuzosin IND, has completed his review of the safety data submitted for the 7.5 and 15 mg alfuzosin dose groups fo the PC ALF 96 US 1 (Submission 004). Synthelabo may proceed with the next dose level of 22.5 mg of alfuzosin. Those results must be submitted before proceeding with the 30 mg dose.

Date	Comm Type	Serial No.	Abstract
08-Jan-1997	SUB	006	Response to Information Request dated November 15, 1996 NP· Submitted Protocol No. 2360 95 BE.
14-Jan-1997	TEL		Bob Seevers, Reviewing Chemist, Division of Reproductive and Urologic Drug Products, telephoned with a question/comment regarding the response to the chemistry issue noted in the FDA Letter of November 15, 1996 (Synthelabo responded January 8, 1997 Submisson No 006) Seevers wanted to confirm that study ALFOD was not being in the US as the drug labeling in the protocol did not use the phrasing as specified in the CFR and noted in the FDA letter of November 15, 1996. Synthelabo confirmed that the study was not being conducted under the IND and that the protocol had since been appended
07-Feb-1997	SUB	008	Synthelabo provided the FDA with safety data from Study PC ALF 96 US 1 for review and the Quarterly Safety Report, as of December 31, 1996. That report provides safety data from ongoing studies using alfuzosin formulations administered orally, OD (Geomatrix® formulation), and in patches.
19-Feb-1997	TEL		Ms. Terri Rumble, CSO, Division of Reproductive and Urologic Drug Products, telephoned to inform Synthelabo that Dr. Shames, Medical Reviewer, Division of Reproductive and Urologic Drug Products, completed his review of Submission No. 008: Safety Data from Study PC ALF 96 US 1. Verbal permission was given allowing Synthelabo to continue to proceed to the next dosage level (30 mg alfuzosin or placebo). It was confirmed that Synthelabo could proceed with the study while waiting for the Agency's written approval.
21-Feb-1997	LFF		The FDA informed Synthelabo that it may proceed with the next higher dose of alfuzosin, 30 mg.
28-Apr-1997	TEL		Dr. Alexander Jordan, Pharm/Tox Reviewer, Division of Reproductive and Urologic Drug Products, telephoned and stated that additional information was needed for the FDA Carcinogenesis Assessment Committee presentation of the alfuzosin carcinogenicity study results. He requested the justification and rationale for the selection of doses used in the two Carcinogenicity Studies submitted to the IND. Specific concerns that should be addressed in the response were as follows: 1) Mouse.: the high rate of mortality in males. 2) Rat: 26 week tox.: the excessive mortality observed. For both species, the selection of strains for the preliminary and main studies should be justified in the context of the toxicity program.
06-Jun-1997	OTH		Submitted request for an End-of-Phase II Meeting. Synthelabo wants feedback from the Agency regarding the adequacy of the clinical studies to support an NDA for the alfuzosin hydrochloride once-daily formulation.
09-Jun-1997	LFF		The FDA sent a notice of meeting confirmation for the End-of-Phase II meeting for August 13, 1997
17-Jun-1997	LTF		Synthelabo submitted Original DMF Type II for Alfuzosin Hydrochloride (INN), SL77-04999-10, Drug Substance - Finorga, Chase sur Rhone, France.
24-Jun-1997	LFF		The FDA acknowledged receipt of Synthelabo's Drug Master File (DMF) submission and assigned DMF Number DMF 12546
30-Jun-1997	SUB	012	NP. Submitted Protocol 053 Info. Amend· CMC Synthelabo submitted a summary of the Clinical Information Amendment and the most recent Quarterly Safety Report, with safety data for ongoing studies, included as of March 31, 1997. Info. Amend: Clinical, includes eight reports.
15-Jul-1997	SUB	013	Synthelabo submitted the pre-meeting package for the August 13, 1997 End-of-Phase II Meeting.
29-Jul-1997	SUB	014	Synthelabo submitted supplementary information for the August 13, 1997 End-of-Phase II Meeting.
29-Jul-1997	TEL		Sam Haidir, Pharmacokinetics Reviewer, Division of Reproductive and Urologic Products, called to inquire about the status of the study entitled, "A study to evaluate the effect of food on the pharmacokinetics of alfuzosin in healthy, middle-aged male volunteers" (SKB food effect study, Submission No. 012, June 30, 1997). Synthelabo indicated that the study start date was Sept 2, 1997
06-Aug-1997	SUB	015	Synthelabo submitted a clarification to a previously submitted question for the August 13, 1997 End-of-Phase II Meeting.
13 Aug 1997			End of phase 2 meeting between FDA and Synthelabo
14-Aug-1997	TEL		Sam Haidar, Ph.D., Pharmacokinetics Reviewer, Division of Reproductive and Urologic Products, called with questions and comments regarding Study PC ALF 96 US 1 (food effect study). Sam asked for the composition of the meals given to the subjects in this study. He also stated that he spoke to a reviewer who had experience with food effect studies, and had several questions regarding the study.

Date	Comm Type	Serial No.	Abstract
14-Aug-1997	LTF		Synthelabo sent Sam H. Haidar, R Ph. Ph D , Pharmacokinetics Reviewer, Division of Reproductive and Urologic Drug Products, as requested, information concerning the meal composition given to subjects participating in Study 2439 96 US 1.
18-Aug-1997	SUB	016	Response to Information Request dated August 14, 1997. Info. Amend. CMC
21-Aug-1997	LFF		The FDA completed review of Synthelabo's June 30, 1997 submission which describes a protocol entitled, "A Study to Determine the Effect of Food on the Pharmacokinetics of Alfuzosin in Healthy Middle-aged Male Volunteers" and made the following comment and recommendation: Complete validation of the analytical method for the quantitation of alfuzosin, including the lower limit of quantitation/sensitivity, inter/intra assay precision, accuracy, specificity and linearity, should be included in the final report.
26-Aug-1997	SUB	017	Synthelabo submitted the Draft Meeting Minutes for the August 13, 1997 End-of-Phase II Meeting.
29-Aug-1997	SUB	018	Synthelabo submitted a response to the FDA's comment/recommendation letter dated August 21, 1997. Info Amend· Clinical, includes an upated Investigator's Brochure, Edition 2, dated July 1997.
05-Sep-1997	TEL		Ms Terri Rumble, CSO, Division of Reproductive and Urologic Products, called to ask if Synthelabo was aware that Dr. Roehrborn who functioned as an advisor to Synthelabo at the End-of-Phase II Meeting had written to the agency regarding his version of End-of-Phase II Meeting minutes. Ms Rumble wanted to know if Synthelabo wanted to: 1) Officially submit his documentation to the IND 2)Provide permission to the Agency to provide a general response to Dr Roehrborn 3)Have the agency not respond
08-Sep-1997	FAC		FDA provided Synthelabo with meeting minutes of the August 13, 1997 Alfuzosin End-of-Phase II Meeting held with the Div. of Reproductive and Urologic Drug Products
11-Sep-1997	TEL		Ms. Terri Rumble, CSO, Division of Reproductive and Urologic Products, called and stated the following regarding the submission of the End-of-Phase II Meeting minutes: There was no further feedback except to include justification for doses in the carcinogenicity study as "follow-up needed". There were no addtiional comments.
19-Sep-1997	SUB	019	Response to Information request dated August 13, 1997.
30-Oct-1997	SUB	024	Response to FDA Request for Information Submitted phase 3 clinical study protocols ALFUS (No 2560) and ALFOTAM (No. 2440 97 III UK). Info Amend Pharm/Tox, includes three pharmacology reports, one ADME report, one toxicology report, and two publications Synthelabo submitted the Quarterly Safety Report, with safety data for ongoing studies, included as of June 30, 1997. Info Amend· Clinical, includes two reports.
11-Nov-1997	SUB	025	Annual Report Info. Amend: Clinical [Rep. No 97-00852-EN-00 (IND ref no. C166)] Integrated Safety Summary, Phase I,III Clinical Studies as of June 30, 1997, and Quarterly Safety Report as of Sept 30 1997
12-Nov-1997	TEL		Ms Terri Rumble, CSO, Division of Reproductive and Urologic Products called and requested Synthelabo fax copies of the informed consent forms for the studies submitted as part of Submission 024. Dr. Shames the Medical Reviewer requested copies of the informed consent forms for the following studies: PC ALF 97 CA 1(renal Canadian), ALFUS, ALFOTAM. Also discussed: FDA did not plan to respond to Dr. Roehborn's submission.
12-Nov-1997	OTH		Synthelabo submitted to Ms Terri Rumble, CSO, Division of Reproductive and Urologic Drug Products, a copy of the draft informed consent for the PC ALF 97 CA 1Study.
09-Dec-1997	SUB	026	Info. Amend: CMC Response to FDA Request for Information
22-Dec-1997	SUB	027	Info. Amend: Clinical, includes revised Investigator's Brochure PC: For Protocol ALFUS (No. 2560), amendment-01.
08-Jan-1998	LFF		The Division of Reproductive and Urologic Drug Products completed review of the protocol amendments for protocols ALFUS-2560 and ALFOTAM-2440 (submitted Serial No. 024, 30 October 1997) that incorporated changes disscussed at the August 13, 1997, End-of-Phase II meeting. Comments and questions pertaining to the protocols were given. For Protocol ALFOTAM-2440 Clinically signifcant changes in the International Prostate Symptom Score (IPSS) and maximum urinary flow rates from baseline to last measurement should be defined prior to initiation of the study. The Informed Consent Document should be submitted for review as soon as it becomes available.
12-Jan-1998	TEL	V-CORRES	Synthelabo contacted the FDA to confirm the FDA request for Informed Consent Documents for both the ALFOTAM and ALFUS protocols, as specified in the January 8, 1998 letter.

Date	Comm Type	Serial No.	Abstract
05-Mar-1998	SUB	029	Response to FDA Request for Toxicology Information. Response to FDA Request for Clinical Information. Synthelabo submitted the Quarterly Safety Update as of December 31, 1997.
30-Mar-1998	SUB	031	Response to FDA Request for Information (Informed Consent Forms)
01-Apr-1998	LFF	V-163	The FDA completed review of Synthelabo's March 5, 1998 submission in which the company provided responses to questions by the FDA for toxicology information and Phase 3 study information. Additional pharmacology comments and questions were provided.
08-Apr-1998	TEL	V-163	Ms Terri Rumble, Project Manager, Division of Reproductive and Urologic Drug Products, called to relay a request from Dr. Shames, Medical Reviewer, Division of Reproductive and Urologic Drug Products for a teleconference to discuss Phase III issues which were submitted on March 5, 1998 (Submission 029)
10-Apr-1998	TEL		Mr. Olmstead, Project Manager, Division of Reproductive and Urologic Drug Products, called to follow-up on FDA's request for a teleconference to discuss Phase III study issues in Serial No. 029 (March 5, 1998) He indicated that Dr. Shames had only a few basic questions
14-Apr-1998	FAC		Synthelabo sent a fax to confirm the April 21, 1998 teleconference requested by Dr Shames, Medical Reviewer, Division of Reproductive and Urologic Products. Purpose of the teleconference: Discuss Synthelabo response to FDA (Submission 029, March 5, 1998) questions and comments regarding Phase III studies.
21-Apr-1998	TEL		Mr. Randy Olmstead, Project Manager for the Alfuzosin IND, Division of Reproductive and Urologic Drug Products, initiated the teleconference on 21 April 1998. Dr Shames requested this teleconference to discuss Synthelabo responses to the January 8, 1998 FDA letter with questions and comments regarding Phase III studies provided in Submission 029, dated March 5, 1998. Dr. Shames went through the 4 main issues of the response and the Agency's current questions/comments.
27-Apr-1998	FAC		Synthelabo faxed to FDA, Division of Reproductive and Urologic Drug Products, minutes from the April 21, 1998 teleconference. The teleconference was held as requested by Dr. Shames to discuss the Synthelabo responses to the January 8, 1998 FDA letter with questions/comments regarding Phase III studies provided in Submission 029, dated March 5, 1998.
01-Jul-1998	SUB	036	(Quarterly Safety Report)
10-Aug-1998	SUB	039	Quarterly Safety Update as of June 30, 1998
23-Nov-1998	SUB	055	Info Amend: Clinical. Includes. 1) Integrated Safety Summary, Phase I to II Clinical Studies, Status as of June 30th, 1998 (Report 98-00865-EN-00, IND Ref # C171) 2) Quaterly Safety Report as of September 30, 1998 which provides cumulative information on discontinuations due to adverse events and serious adverse events from ongoing studies or completed studies for which reports are not yet available.
22-Dec-1998	SUB	053	Response to FDA Request for Clinical Information Regarding Phase 3 Studies
13-Jan-1999	TEL		Randy Olmstead, Project Manager, Division of Reproductive and Urologic Products called to request a teleconference for 1 February 1999 to discuss Phase III issues which were submitted on December 2, 1998 (Submission No 053).
26-Jan-1999	TEL		Synthelabo called Dr. Alexander Jordan, Director, Pharmacology Division of Reproductive Health and Urologic Products, to obtain clarification on the Division's comment requesting results of the rodent carcinogenicity studies be submitted to the Division of Biometrics for review.
28-Jan-1999	SUB	058	Response to FDA Request for Information - Pharmacology/Toxicology
01-Feb-1999	TEL		Randy Olmstead, Project Manager, Division of Reproductive Health and Urologic Health Products, initiated the teleconference on February 1, 1999. The Division requested this teleconference to discusss Synthelabo's responses (Submission 053, dated 22 Decmber 1998) to the April 21, 1998 teleconference. The points highlighted: Efficacy Analysis
05-Feb-1999	FAC		FDA faxed Synthelabo a copy of their meeting minutes from the April 21, 1998 teleconference.
08-Feb-1999	TEL		FDA contacted Synthelabo via teleconference to discuss responses to the April 21, 1998 teleconference. During the aforementioned teleconference, Synthelabo responses to the FDA's Jan 8, 1998 letter with questions/comments regarding Phase III studies were discussed.
09-Feb-1999	FAC		Synthelabo faxed R. Olmstead, Project Manager, Division of Reproductive Health and Urologic Drug Products Synthelabo's minutes of the February 1, 1999 teleconference.
25-Feb-1999	SUB	060	Protocol Change (Modification No. 2 to ALFUS Study) Response to FDA Request for Information
23-Mar-1999	FAC		FDA provided Synthelabo, by fax, a copy of FDAs approved minutes for the February 1, 1999 teleconference.

Date	Comm Type	Serial No.	Abstract
23-Mar-1999	TEL		Synthelabo contacted R. Olmstead, Project Manager, Division of Reproductive Health and Urologic Health Products, on March 19, 1999, requesting the following information: 1) any comments on the Synthelabo minutes for the February 1, 1999 teleconference 2) when a copy of the FDA minutes for the same meeting would be available R. Olmstead returned the phone call on March 23, 1999 and indicated that there were no comments on the draft minutes provided by Synthelabo and that FDAs version of the meeting was now available.
26-Apr-1999	SUB	065	Response to FDA Request for Information Info. Amend: CMC
06-Jun-1999	LTF		Synthelabo would like to request a meeting for Alfuzosin. This is an End of Phase II meeting to obtain feedback from the Agency regarding the adequacy of the clinical studies to support an NDA for the alfuzosin hydrochloride once-daily formulation.
09-Jul-1999	SUB	077	Sanofi informed the FDA that it accepts sponsorship of IND 51,200 from Synthelabo Research, Inc.
02-Aug-1999	TEL		Evelyn Farinas, Project Manager Division of Reproductive and Urological Drug Product (FDA), returned Sanofi's call to initiate discussion of outstanding issues. 1) Dialogue to justify doses in rat and mouse carcinogenicity studies 2) Pre-NDA meeting procedure
05-Aug-1999	LFF		Ms. Terri Rumble, Chief Project Management Staff, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi regarding the July 9, 1999 submission to notify the change of sponsorship from Synthelabo Research, Inc. , effective on June 24, 1999. The submission contains all the information required to complete the change in sponsorship.
09-Aug-1999	FAC		Ms. Evelyn Farinas, FDA, sent a fax to Sanofi regarding pharmacology/toxicology comments and information requests for the IND. The review of the submission, dated January 28, 1999, was completed. A few requests were made in order to better prepare for the Executive Carcinogenicity Assessment Committee review: 1) resubmit the data on comparative drug metabolism in mice, rats, and humans, 2) resubmit the histopathology tables for neoplastic lesions from the rat and mouse carcinogenicity studies, and 3) submit steady state plasma drug AUC data from humans taking the 10 and 15 mg dose.
09-Aug-1999	LFF		Dr. Marianne Mann, Deputy Director, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi regarding the submission, dated January 28, 1999, is satisfactory, with the following comments: 1) resubmit the data on comparative drug metabolism in mice, rats, and humans, 2) resubmit the histopathology tables for neoplastic lesions from the rat and mouse carcinogenicity studies, and 3) submit steady state plasma drug AUC data from humans taking the 10 and 15 mg dose.
09-Aug-1999	TEL		Evelyn Farinas, Project Manager, Division of Reproductive and Urological Drug Products (FDA), called Sanofi to follow-up on adequacy of doses used in carcinogenicity studies.
25-Aug-1999	SUB	083	Sanofi requested a meeting with the Division to obtain agreement on clinical information to be presented in an NDA for Alfuzosin.
01-Sep-1999	SUB	084	Sanofi informed the FDA that it has changed its corporate name to Sanofi-Synthelabo effective 01 September 1999.
07-Sep-1999	TEL		Randy Olmstead (FDA) contacted Sanofi-Synthelabo with regard to our preNDA meeting. The meeting is scheduled for October 29, 1999 at 12:30 p.m.
08-Sep-1999	LFF		Dr. Marianne Mann, Deputy Director, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi-Synthelabo stating that the submission serial number 065 review was completed, with a list of seven statistical recommendations and comments.
10-Sep-1999	LFF		Ms. Terri Rumble, BSN, Chief, Project Management Staff, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi-Synthelabo to acknowledge the receipt of the August 25, 1999 correspondence requesting a Pre-NDA meeting to discuss drug development of Alfuzosin. The type B meeting will be held on October 29, 1999 at 12:30 pm.
17-Sep-1999	LFF		Ms. Terri Rumble, Chief, Project Management Staff, Division of Reproductive and Urologic Drug Products, sent a letter to acknowledge receipt of the September 1, 1999 correspondence notifying the FDA that the corporate name and address has been changed to Sanofi-Synthelabo.
20-Sep-1999	FAC		Sanofi-Synthelabo letter to Division of Reproductive & Urological Drug Products. Request for a teleconference with the statistician to address the statistical analysis plan in phase III studies of ALFUS and ALFOTAM.
21-Sep-1999	TEL		Evelyn Farinas, Project Manager Division of Reproductive and Urological Drug Product (FDA), called to confirm teleconference. The teleconference is scheduled for Wednesday, 29 September at 9:00a.m..

Date	Comm Type	Serial No.	Abstract
28-Sep-1999	SUB	088	Sanofi-Synthelabo provided the FDA with its proposal on the issues to be discussed during the 29 September 1999 teleconference with the FDA reviewing statistician to discuss proposed changes to the statistical analysis plan for the Phase 3 confirmatory clincial studies, ALFUS and ALFOTAM.
29-Sep-1999	SUB	089	Sanofi-Synthelabo submitted the Pre-Meeting Package for the pre-NDA meeting with the FDA scheduled for 29 October 1999.
29-Sep-1999	TEL		Sanofi-Synthelabo had a teleconference with Evelyn Farinas, Project Manager and Lisa Kammerman, Ph D., Statistician, Division of Reproductive and Urological Drug Products (FDA), on the revisions to the statistical analysis plans for ALFUS and ALFOTAM. Proposed changes: 1) Adjustment for multiple comparisons 2) Definition of intent-to-treat (ITT) population 3) Primary statistical analysis
30-Sep-1999	FAC		Sanofi-Synthelabo sent a fax to Ms. Evelyn Farinas, Project Manager, and Ms Lisa Kammerman, PhD, Statistician, Division of Reproductive and Urologic Drug Products, FDA, in reference to a teleconference on the revisions of the statistical analysis plan for ALFUS and ALFOTAM. A letter was provided to the FDA on September 28 (serial 28) stating Sanofi-Synthelabo's position on each of the proposed changes: 1) adjustment for multiple comparisons, 2) definition of intent-to-treat (ITT) population, and 3) primary statistical analysis.
15-Oct-1999	SUB	091	Response to FDA Request for Information dated 08 September primary analytic method.
16-Oct-1999	TEL		Evelyn Farinas, Project Manager Division of Reproductive & Urological Drug Products called to review the results of the Divison's internal meeting to review pre-NDA background package.
22-Oct-1999	FAC		Sanofi-Synthelabo received a fax from Ms. Evelyn R. Farinas, RPh, MGA, Regulatory Project Manager, in reference to the teleconference on September 29, 1999 regarding the IND 51,200. The objective of the meeting was to obtain advice regarding proposed changes to the statistical analysis plan for Phase 3 studies, ALFUS and ALFOTAM. It wassubmitted for review by the Division on September 28, 1999 (Serial No. 088).
10-Nov-1999	LFF		Dr. Lisa Rarick, Director, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi-Synthelabo stating that the Division has completed the review of the submission with the following recommendations: 1) the format that is proposed in the meeting package is acceptable, 2) case report forms for active control subjects should be included, 3) follow the electronic submission guidance if full electronic submission is planned, and 4) address the CMC and Pharmacology/Toxicology issues later in submission.
25-Feb-2000	SUB	106	Request for FDA Concurrence on Pre-NDA Proposal: Sanofi-Synthelabo requesting FDA's concurrence on a proposal not to provide narratives for Non-Serious Adverse Events resulting from study discontinuations in an NDA planned for later this year Study discontinuations, due to non-serious adverse events, will be provided in listings and case report forms Narratives for serious adverse events will be included in the NDA.
01-Mar-2000	TEL		Evelyn Farinas, Project Manager, Division of Reproductive and Urological Drug Products (FDA), returned the Sanofi-Synthelabo call of 29 February. Sanofi-Synthelabo explained that we wanted to request a meeting with the Division to review the efficacy results for alfuzosin on which the NDA would be based. Evelyn agreed to review this with the Medical Reviewer and her supervisor and agreed to get back to us in a day or two.
29-Mar-2000	SUB	108	Request for Type B Pre-NDA Meeting with the Division to obtain agreement on information to be presented in an NDA for Alfuzosin HCl in a once-daily 10 mg extended- release formulation. The NDA is planned to be submitted by the end of this year. In the proposed meeting, Sanofi-Synthelabo seeks to obtain agreement on issues regarding the clinical data (Item 8), human pharmacology and bioavailability (Item 6), and on electronic data presentation (Items11 and 12). The development plan for this extended-release formulation was reviewed with the Division in an End-of-Phase-II meeting on 13 August 1997.
11-Apr-2000	TEL		Sanofi-Synthelabo contacted Dr. Jeri El Hage, Toxicology reviewer, Division of Reproductive and Urological Drug Products, FDA, to check to see if she accepts carcinogenicity datasets done as per the FDA 1997 electronic guidelines. Dr El Hage had some questions, since she was newly assigned to the study, about the data, quantitative data, and history of the report. For the NDA she requires us to resubmit all data from the IND, with updates, as per the current FDA guidelines.

Date	Comm Type	Serial No.	Abstract
14-Apr-2000	SUB	110	Request for Confirmation of Type B Pre-NDA Meeting: Reference is made to the telephone conversation between Evelyn Farinas, Regulatory Project Manager, FDA, and Quyen Vinh, Director, Drug Regulatory Affairs, Sanofi-Synthelabo on 13 April 2000 regarding the scheduled dates for the Type B Pre-NDA meeting and for submission of the background package for this meeting. Sanofi-Synthelabo would like to confirm that the Type B Pre-NDA meeting will take place on 24 May 2000 at 3.00 PM at the Agency, and that the Agency agrees that the background package for this meeting will be sent via courier on 01 May 2000 to arrive at the FDA the following day, 02 May 2000.
21-Apr-2000	TEL		Sanofi-Synthelabo contacted Felicia Woodward-Farmer, Central Document Room, FDA to obtain a number for the NDA submission It was assigned No. 21-187.
25-Apr-2000	LFF		Ms. Terri Rumble, BSN, Chief, Project Management Staff, Division of Reproductive and Urologic Drug Products, sent a letter to Sanofi-Synthelabo to acknowledge receipt of the March 29, 2000 correspondence requesting a Pre-NDA meeting to discuss the drug development of alfuzosin. The type B meeting will be held on May 24, 2000 at 3:00 pm.
01-May-2000	SUB	112	Information Amendment: Clinical/ Response to FDA Request for Information Per telephone conversation, 03 March 2000, Ms. Evelyn Farinas, (FDA) Project Mgr.,requested a copy of the protocols for the four core studies to aid in the review of the Alfuzosin Pre-NDA Meeting Briefing Package. The protocols are: ALFORTI, ALFUS, ALFOTAM, and ALFOD sent in this submission, along with all amendments; Amendments, 1, 2, and 3.
01-May-2000	SUB	113	Pre-NDA Meeting Briefing Package: In response to Sanofi-Synthelabo's 29 March 2000 (Serial No. 108) request for a Pre-NDA Meeting date, the Division agreed to a Type B meeting in a facsimile letter dated 26 April 2000. The issues for agreement at this meeting focus on clinical data, human pharmacokinetics, and the electronic data presentations proposed for the upcoming NDA.
09-May-2000	SUB	114	Request for FDA Review and Concurrence. Sanofi-Synthelabo requests concurrence on the adequacy of Biopharmaceutics and CMC proposals for the alfuzosin hydrochloride NDA planned for submission by the end of this year. Attachment 1 presents information and proposals relating to the dissolution method, tablet marking, and stability that will support this marketing application
24 May 2000			PreNDA meeting with FDA
14-Jun-2000	FAC		Ms. Evelyn Farinas, RPh, MGA, Regulatory Project Manager, faxed Sanofi-Synthelabo on the meeting minutes of May 24, 2000 about the drug alfuzosin The objective of the meeting was to address and reach accordance on the Clinical, human Pharmacokinetics, and electronic submission questions posed by the sponsor in the May 1, 2000 meeting package, Serial No. 113.
21-Jun-2000	TEL		Sanofi-Synthelabo contacted Felicia Woodard-Farmer, Central Documant Room FDA to obtain number for the NDA. Felicia has assigned NUMBER 21-287 to the Alfuzosin NDA.
22-Jun-2000	TEL		Sanofi-Synthelabo contacted Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DNDC II, FDA for clarification of comments in FDA's 24 May pre-NDA meeting minutes. Specifically asked for clarification of the debossed tablet stability requirements at the time of filing, and at the seven month update. Dr. Rhee stated that the FDA prefers a minimum of 12 months room temperature stability and 6 months accelerated stability width the proposed commercial product at the time of filing. Dr. Rhee requested that Sanofi-Synthelabo provide as much data as possible at filing.
06-Jul-2000	TEL		Sanofi-Synthelabo contacted Ms. Evelyn Farinas, Regulatory Health Project Manager, CDER, Division of Reproductive. and Urologic. Drug Prod., to ask about the update for the request for review on a brand name by the Nomenclature Review Committee within OPDRA. Sanofi-Synthelabo would like a review of the brand name Xatral for alfuzosin hydrochloride.
11-Jul-2000	SUB	123	IND Annual Report Waiver Request: As discussed on 11 July 2000 with Ms. Evelyn Farinas, Project Manager, Sanofi-Synthelabo requests a waiver from the requirement to provide the current IND Annual Report which would cover the time period from 31 August 1999 to 31 August 2000 and be due at the Agency no later than 30 October 2000. Sanofi-Synthelabo's proposal is to submit the NDA, currently in preparation, to satisfy the IND annual reporting requirement. The NDA is targeted for submission during the same week that the IND Annual Report would be due. The NDA submission will contain all of the clinical information, including safety information, and nonclinical information required in an annual report. Additional information on the only ongoing IND clinical study, an open-label extension study, will be provided in the NDA and the 120-day safety update to the NDA. Sanofi-Synthelabo requests confirmation that this proposal is acceptable to the Agency.

Date	Comm Type	Serial No.	Abstract
13-Jul-2000	SUB	125	Request for Brand Name Review: Sanofi-Synthelabo is requesting a review of the acceptability of proposed brand name, Xatral.
24-Jul-2000	SUB	127	Response to information request dated 09-Aug-1999. Submitted histopathology tables for neoplastic and nonneoplastic lesions PDF files for the neoplastic lesion tables were also included. Submitted electronic data sets of the rodent carcinogenicity studies to the Division of Biometrics for review. A package justifying doses in the carcinogenicity studies, and supporting study reports.
03-Aug-2000	SUB	129	Request for Waiver of Pediatric Study Requirements:Sanofi-Synthelabo requests a full waiver of the obligation to provide data regarding the use of alfuzosin hydrochloride in pediatric patients.
17-Aug-2000	FAC		FDA contacted Sanofi-Synthelabo concerning user fees. The user fee ID# 4010.
29-Aug-2000	LFF		Susan Allen, M.D., M.P.H., Director, Division of Reproductive and Urologic Drug Products, FDA contacted Sanofi-Synthelabo referring to a waiver request dated August 3, 2000 for pediatric studies under 21 CFR 314.55. After review, a waiver is justified for alfuzosin hydrochloride for the treatment of the signs and symptoms of benign prostatic hypertrophy for the pediatric population.
01-Sep-2000	SUB	133	Information Amendment: CMC: Request for Review and Comments, Sanofi-Synthelabo requests confirmation that the stability data for commercial containers is acceptable for alfuzosin hydrochloride NDA and that the unmarked tablet stability data can be used to support the proposed expiry period: data of packaging components are included in Attachment 1; data of commercial package are included in Attachment 2.
19-Sep-2000	TEL		Sanofi-Synthelabo contacted Evelyn Farinas, Project Manager, DRUDP, CDER, FDA to discuss the stability plan faxed to the agency August 31 and submitted as an IND amendment, SUB No 133, for Dr. Moo-Jhong Rhee to review and comment.
02-Oct-2000	TEL		David Lin, Ph D., Chemistry Reviewer, DNDC II, Dornette Spell Lesane, CSO, FDA contacted Sanofi-Synthelabo concerning FDA agreement with the debossed tablet stability plan.
16-Oct-2000	LFF		Daniel Shames, M.D., Acting Deputy Director, Division of Repoductive and Urologic Drug Products, FDA contacted Sanofi-Synthelabo referring to amendment dated September 18, 2000, Serial No 136, containing the proposal on how to address the unavailable case report forms in the upcoming NDA submission for alfuzosin The FDA completed the Clinical review of the submission and found it acceptable.
22-Jan-2001	SUB	151	Revised Clinical Investigator's Brochure Sanofi-Synthelabo is providing a revised Clinical Investigator Brochure (CIB), Version E05 dated 12 January 2001 submitted with the most recent NDA submission with the significant addition of the clinical section; updated efficacy and safety information relevant to "once daily" (OD) formulation; and the updated post marketing experience.
24-Jan-2001	TEL		Evelyn Farinas of the FDA left a voice mail with regards IVIVC to support pivotal bioequivalence in NDA. At FDA's request, Sanofi-Synthelabo performed an IVIVC bioequivalence studies of experimental formulations done in fasting state based on the NDA done on the fed state.
08-Feb-2001	SUB	152	Information Amendment: Revised, Clinical Investigator's Brochure (CIB) This version revises the presentation of clinical efficacy information to be consistent with the presentation proposed in the package insert of pending NDA 21-287 for Alfuzosin HCl.
13-Jul-2001	TEL		Evelyn Farinas, Project Manager, Division of Reproductive & Urological Drug Products, FDA left a voice mail message with response to Sanofi-Synthelabo's proposal to shorten the established name provided in Amendment 10 dated 10 July 2001. The acceptable established Name is Alfuzosin HCL extended release tablets. The Division found replacing Hydrochloride with HCL acceptable.
24-Oct-2001	SUB	181	Revised Clinical Investigator's Brochure; Sanofi-Synthelabo is amending the subject IND to provide for Addendum 1, dated 06 September 2001 (Attachment 1) to the Clinical Investigator's Brochure, version E06, previously submitted 06 February 2001, Serial No. 152. The only change to the previous version is the inclusion of the results of two interaction studies performed with the extended release formulation of alfuzosin and two different drugs, digoxin and ketoconazole.

SUMMARY OF ALFUZOSIN HYDROCHLORIDE NDA ACTIVITIES

Date	Comm Type	File Location	Abstract
08-Dec-2000	SUB		SANOFI-SYNTHELABO submitted NDA 21-287 for Alfuzosin HCL once daily for the treatment of the signs and symptoms of benign prostatic hyperplasia.
11-Dec-2000	LFF		SANOFI-SYNTHELABO received the FDA receipt letter for NDA 21-287 Alfuzosin submitted 08 December 2000, received by FDA 11 December 2000.
17-Jan-2001	SUB	1	SANOFI-SYNTHELABO response to issues raised in the 27 November 2000 teleconference with Dr. Parekh and Ms Farina regarding the pivotal bioavailability study included in the 08 December 2000 original NDA The major points raised were captured in FDA's 09 January 2001 minutes of this teleconference.
20-Feb-2001	SUB	2	Amendment No. 2 - Audit Response Letter SANOFI-SYNTHELABO is providing information requested by the FDA Scientific Investigations Division, to aid with the audit of three sites in clinical study ALFUS. The three sites are; Site Principal Investigator; Bannow, Hollander and; Kletscher The request was initiated, via telephone, on 05 February 2001. In response to the request, SANOFI-SYNTHELABO Inc provided and sent the information to Dr. Susan Molchan, of the Scientific Investigations Division, on 19 February 2001 - under Letter To FDA, (LTF), letter date of 19 February 2001.
26-Mar-2001	TEL		26 March 2001: SANOFI-SYNTHELABO contacted Evelyn Farinas, Project Manager, FDA to request a teleconference with Dr. Suong Tran (Chemistry reviewer) and Dr. Moo-Jhong Rhee (Chemistry team leader) regarding potential issues related to a possible tablet marking change. 27 March 2001: Evelyn Farinas confirmed a teleconference for 1.00 pm April 4, with Drs. Tran and Rhee. The Drs. requested specific questions and proposals to resolve any problems in a fax by 30 March 2001
06-Apr-2001	SUB		Four-month (120 Day) Safety Update submitted.
10-Apr-2001	SUB	3	Information amendment: Chemistry, Manufacturing and Controls (CMC) Sanofi-Synthelabo provided documentation pertaining to the 04 April 2001 teleconference between the Sponsor and the Division. The objectives of the teleconference were to discuss the requirements for a potential change in the tablet marking and the basis for the drug product expiry date. Also, in addition, labeling and CMC issues were discussed.
20-Apr-2001	SUB	4	Request for Brand Name. SANOFI-SYNTHELABO requested concurrence on the brand name. UROXATRAL
24-Apr-2001	FAC		Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP faxed to SANOFI-SYNTHELABO the minutes of the teleconference held 04 April 2001. The objective of the meeting was to convey resonses to the sponsor's questions faxed to the Division on March 30, 2001
25-Apr-2001	SUB	5	Request for Concurrence on Final Safety Update· SANOFI-SYNTHELABO requested the Agency's concurrence on our proposal concerning the timing and content of the next NDA safety update.
08-May-2001	SUB	6	New Patent Information. SANOFI-SYNTHELABO provided updated Patent information and certification incorporating US patent no. 6,149,940
18-May-2001	SUB	7	Sanofi-Synthelabo provided additional information for selected potential brand name Uroxatral.
18-May-2001	TEL		Jeanine Best, FDA called Sanofi Synthelabo to request formatting of financial disclosure information into a table.
04-Jun-2001	LFF		FDA provided recommendations on next safety update in response to 25 April 2001 correspondence from Sanofi-Synthelabo.
27-Jun-2001	SUB	8	Sanofi-Synthelabo responded to the request of Ms. Jeanine Best on 18 May 2001 to provide a table of the results of the financial disclosure results in item 19 of the NDA.
29-Jun-2001	FAC		Evelyn Farinas, FDA faxed to Sanofi-Synthelabo a letter containing comments and information requests on the Chemistry section of the NDA.
02-Jul-2001	LFF		Moo-Jhong Rhee, Chemistry Team Leader, for the Division of Reproductive and Urologic Drug Products, contacted Sanofi-Synthelabo regarding comments on the Drug Master File for Alfuzosin drug substance , held by Sylachim.
06-Jul-2001	SUB	9	Second NDA safety update
10-Jul-2001	SUB	10	Sanofi-Synthelabo Inc requested a teleconference with the chemist to aid us in providing revised container labels and labeling, addressing the FDA's comments in a letter dated 29 June 2001.
19-Jul-2001	SUB	11	Sanofi-Synthelabo provided an update of stability data, comparative dissolution and statistical analysis of the stability data on unmarked and debossed tablets
25-Jul-2001	SUB	12	Response to FDA's June 29, 2001 Information Request Letter, providing 1. Revised Specification for Drug Product 2. Method Validation Package, 3 copies 3. Package Insert with Strikethrough 4. Package Insert 5. Authorization Letter for DMF 12546

Date	Comm Type	File Location	Abstract
25-Jul-2001	SUB	13	Response to Request; Sanofi-Synthelabo provided a WORD copy of the latest version, dated 23 July 2001, of the package insert.
30-Jul-2001	SUB	14	Sanofi-Synthelabo submitted a request of FDA's concurrence on the acceptability of the labels to be used on containers of UROXATRAL (alfuzosin HCl extended release tablets) The labels address the comments 15 and 17 in FDA's letter of 29 June 2001 from Dr. Moo-Jhong Rhee
07-Aug-2001	FAC		Evelyn Farinas, Division of Reproductive and Urologic Drug Products, faxed to Sanofi-Synthelabo request for additional Biopharmaceutics information.
13-Aug-2001	SUB	15	Sanofi-Synthelabo provided biopharmaceutics information requested in a 7 August 2001 Fax from the FDA. Included in this submission, are 1.) raw data used in developing and validating IVIVC under fasting conditions 2.) comparison of experimental and predicted plasma concentration profiles for formulations KYA01 and KYA02, and comparison of predicted concentration profiles for clinical (PDV03) and commercial (PDV08) formulations. 3.)raw data for showing condition independent dissolution of alfuzosin ER formulation
20-Aug-2001	FAC		Evelyn Farinas, FDA faxed to Sanofi-Synthelabo a request for Information concerning the Chemistry review.
21-Aug-2001	SUB	16	Response to 20 August 2001 Facsimile; Sanofi-Synthelabo submitted responses to the 20 August 2001 fax concerning comments on the chemistry, manufacturing and controls section of the NDA.
23-Aug-2001	FAC		Evelyn Farinas, Division of Reproductive and Urologic Drug Products FDA, faxed to Sanofi-Synthelabo memorandum of teleconference for 22 August 2001. Recommendations for proposed package insert.
28-Aug-2001	SUB	17	Sanofi-Synthelabo responded to a 22 August 2001 FAX from the Division providing revised package insert with a revision date of 24 August 2001.
29-Aug-2001	SUB	18	Sanofi-Synthelabo provided a full set of final container label artwork, requesting the FDA's concurrence on the acceptability of these labels. These labels were revised in response to comments in a 20 August 2001 Fax from the Division on container labels previously provided in Amendment 14, dated 30 July 2001.
31-Aug-2001	TEL		31 August 2001 teleconference: The Division called the teleconference to apprise Sanofi-Synthelabo of the status of the NDA review. The clinical review is completed. There is only one issue to resolve, which is cardiac repolarization.
05-Sep-2001	TEL		Evelyn Farinas, Project Manager, Division of Reproductive & Urological Drug Products informed Sanofi-Synthelabo that the review chemist found the the final container labels provided on 29 August 2001 (Amendment 18) to be "acceptable".
20-Sep-2001	SUB	19	Sanofi-Synthelabo responded to the FDA's 06 September facsimile concerning the Biopharmaceutics section of the NDA
21-Sep-2001	FAC		Evelyn Farinas, FDA faxed to Sanofi-Synthelabo the meeting minutes from the August 31, 2001 teleconference.
24-Sep-2001	SUB	20	This submission included a review of all relevant information concerning cardiovascular safety.
25-Sep-2001	SUB	21	Sanofi-Synthelabo responded to a 24 September 2001 telephone call from Dr. Randy Levin requesting a PDF electronic version of NDA Item 6 Human Pharmacology Summary, submitted 20 September 2001, Amendment 19 (Attachment 1), be sent to the Central Document Room for archiving.
05-Oct-2001	LFF		**Sanofi-Synthelabo received an NDA Approvable letter.** Before this application may be approved, however, it will be necessary for Sanofi-Synthelabo to address the safety concerned outlined.
08-Oct-2001	SUB	22	Sanofi-Synthelabo notified FDA of plans to amend the NDA to resolve the issues identified in FDA's 5 October 2001 approvable letter. Sanofi-Synthelabo will schedule a meeting with the Reproductive Drugs Division and the Cardiorenal Division to come to agreement on their resolution.
12-Oct-2001	FAC		Evelyn Farinas, Division of Reproductive and Urologic Drug Products, FDA faxed to Sanofi-Synthelabo the minutes of the October 5, 2001 teleconference. The meeting objective: to convey to the sponsor the Agency's decision regarding the approvability of NDA 21-287.
06-Nov-2001	SUB	23	Type A Meeting Request; Sanofi-Synthelabo requests an end of NDA meeting with FDA. The goal of the meeting is to gain concurrence on resolution of the issues identified in FDA "Approvable Letter" dated 05 October 2001.
19-Nov-2001	SUB	24	End of review meeting briefing document: An end of review meeting with the Division was requested on 6 November-2001 (Amendment 23) to resolve issues raised in FDA's 5 October 2001 approvable letter The attached information package contains our proposals to address the issues in the letter
26-Nov-2001	LFF		Evelyn R. Farinas, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products, contacted scheduled the meeting to discuss resolution of the issues identified in the FDA "Approvable Letter" of October 5, 2001 for 7 December 2001.
28-Nov-2001	SUB	25	Sanofi-Synthelabo requested a postponement of the NDA end-of-review meeting until early January 2002, since Sanofi-Synthelabo's cardiologist consultant is unavailable on 7 December 2001 and he is needed to address the central issue of the meeting

Date	Comm Type	File Location	Abstract
03-Dec-2001	LFF		Evelyn R. Farinas, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products, FDA rescheduled the meeting to resolve Approvable letter issues forJanuary 7, 2002
18-Jan-2002	SUB	26	Meeting Minutes, Sanofi-Synthelabo provided minutes of the 07 January 2002 NDA end-of-review meeting.
07-Feb-2002	SUB	27	Sanofi-Synthelabo requested a meeting or teleconference to obtain FDA concurrence on the proposal to resolve issues identified in the 5 October 2001 Approvable letter as clarified in our 7 January 2002 meeting. Sanofi-Synthelabo anticipates that an information package will be available by 22 February 2002 and will be available for discussions at the earliest convenience
13-Feb-2002	FAC		Evelyn Farinas, Division of Reproductive and Urologic Drug Products faxed to Sanofi-Synthelabo the meeting minutes from the January 7, 2002 meeting. The meeting objective was to discuss the issues raised in the October 5, 2001 FDA Approvable letter
14-Feb-2002	SUB	28	Meeting Information Package Response to 5 October 2001 approvable letter; The attachment to this document contains Sanofi-Synthelabo's proposal to respond to all issues raised in the 5 October 2001 FDA letter indicating that this NDA was approvable. It incorporates clarifications provided in the 7 January 2002 end-of-review meeting with the FDA
26-Feb-2002	LFF		Dr. Daniel Shames, Acting Director, Division of Reproductive and Urologic Drug Products, sent a letter acknowledging the February 11, 2002 request for a meeting to discuss NDA approvable letter issues.
19-Mar-2002	MOM	30	Meeting Minutes. Sanofi-Synthelabo provided FDA with the minutes of a teleconference that was held with FDA Reproductive and Cardiorenal Drug Division representatives to obtain FDA comments on a protocol for a clinical study to assess the cardiac repolarization potential of alfuzosin. Teleconference held 13 March 2002. Protocol had been provided in NDA Amendment 28 to address the principle FDA comment in the 05 Oct 2001 Approvable letter.
19-Mar-2002	SUB	31	Request for Special Protocol Assessment; As required by FDA guideline, Sanofi-Synthelabo is providing notice of intent to make a request for a Special Protocol Assessment. In a 13 March 2002 teleconference with Dr. Hirsch of FDA, and Sanofi-Synthelabo discussed a protocol for a clinical study (provided in Amendment 28 dated 14 February 2002) to assess the potential of alfuzosin to affect cardiac repolarization to resolve the principal issue in the 5 October 2001 NDA Approvable letter. Sanofi-Synthelabo agreed to provide a revised protocol to address FDA comments. In this teleconference Dr. Hirsch indicated that the revised protocol would qualify for 45-day review. The revised protocol will be provided to the FDA early during the week of 25 March 2002
29-Mar-2002	SUB	32	Request for Special Protocol Assessment Sanofi-Synthelabo requested a Special Protocol Assessment of the clinical protocol to assess the potential of alfuzosin to affect cardiac repolarization (protocol PDY5105). In a 13 March 2002 teleconference with Dr Hirsch of your Division we discussed a draft of this protocol (provided in Amendment 28 dated 14 February 2002) to resolve the principal issue in the 5 October 2001 NDA Approvable letter. In this teleconference Sanofi-Synthelabo agreed to provide a revised protocol to address FDA comments and Dr. Hirsch indicated that the revised protocol would qualify for 45-day review.
17-Apr-2002	FAC		Sanofi-Synthelabo was sent the meeting minutes for the teleconference held March 13, 2002 to provide feedback to Sanofi-Synthelabo on the proposed cardiac repolarization study
01-May-2002	LFF		Division of Reproductive and Urologic Drug Products FDA confirms receipt of submission dated February 14, 2002, with a proposal for a revised QTc study, as well as a proposal and preliminary results of a ketoconazole-alfuzosin drug interaction study. Stated that the drug interaction study with ketoconazole (at 400 mg daily for 8 days) is adequate to address the concern regarding the magnitude of the interaction with ketoconazole - final study results have to be reviewed.--
16-May-2002	LFF		Division of Reproductive and Urologic Drug Product FDA made comments on Protocol PDY5105 to address the cardiac repolarization issue. Design acceptable but FDA commented on the statistical tests.
01-Jul-2002	SUB	33	Response to information requested on 29 March 2002. Sanofi-Synthelabo responded to question for protocol PDY5105
01-Jul-2002	SUB	33	Response to 16 May 2002 FDA letter Sanofi-Synthelabo addressed statistical test question in 16 May 2002 letter from FDA.
10-Sep-2002	SUB	34	Sanofi-Synthelabo responded to one of the two issues identified in the 05 October 2001 NDA Approvable letter. Sanofi-Synthelabo provided a report of the results of study INT5056, addressing interaction with ketoconazole 400 mg
09-Oct-2002	SUB	35	Sanofi-Synthelabo provided corrected CMC information. The info pertaining to the specifications for wall thickness for the 30mL and 75mL container was provided in error in the NDA and is now being corrected.

Date	Comm Type	File Location	Abstract
16-Oct-2002	TEL		Sanofi-Synthelabo contacted Ms. Mercier to confirm the timing of the safety update, per the approvable letter. 1. A safety update must accompany the response to the approvable letter 2. A final update needs to go in three months later or mid review cycle
12-Dec-2002	SUB	36	**Complete Response to 5 October 2001 Approvable letter**
28-Jan-2003	LFF		FDA acknowleges receipt on 12 Dec 2002 of Sanofi-Synthelabo's resubmission to NDA for alfuzosin HCL. The resubmission contains additional clinical, labeling and SAE information -- FDA considers this a complete class 2 response to their action letter (dated 10/5/01). Therefore, the primary user fee goal date is 12 June 2003
31-Jan-2003	TEL		Jean King left voice mail(s) with Sanofi-Synthelabo to request the following: -An electronic file of the ECG and Holter pharmacodynamic data generated in study PDY5105. PK data not included -An explanation of why the numbers of patients in the table on page 7 of the synopsis and page 78 in Table (15 2 1) 1 differ in the report of study PDY5105.
05-Feb-2003	SUB	38	Response to FDA Request for Information 31 January 2003 from Jean King (FDA)
26-Feb-2003	LFF		FDA acknowledged receipt of 12 Dec 2002 submission providing a complete response to 05 Oct. 2001 NDA Approvable Letter. FDA has completed filing review and requests clarification In Study PDY 5105. FDA requests submission of electronic SAS transport files containing the raw QT data sets from Study PDY5105
03-Mar-2003	TEL		Ms. Jean King, PM, Div. Reproductive & Urological DP, Re: Status of NDA Review An FDA letter dated 26 Feb 2003 contains the preliminary (filing) review of Sanofi-Synthelabo's complete response to the NDA Approvable letter (12 Dec 2002). Ms King said the requests in this letter were the same to which Sanofi-Synthelabo had already responded Ms. King requested a WORD version of the pkg. insert. Ms. King confirmed on 04 March that a PPI would be requested.
12-Mar-2003	SUB	39	Final NDA Safety Update
26-Mar-2003	LFF		Jayne E. Peterson, Advisors and Consultants Staff, FDA faxed a letter notifying Sanofi-Synthelabo that alfuzosin will be on the agenda for upcoming FDA Cardiorenal Drugs Advisory Committee meeting on 29 May 2003. Letter requested a fully releasable background pkg. for this mtg. by 28 Apr 2003 and names and affiliations of Sanofi-Synthelabo speakers and titles of their presentations, and names of any and all consultants, former Advisory Committee members, and Special Government Employees who will be attending.
01-Apr-2003	FAC		Fax from Jean King, Div of Reproductive & Urologic Drug Products requesting electronic files containing QT data for study PDY5105
04-Apr-2003	SUB	40	Response to FDA Information Fax Request dated 01 April 2003 Sanofi-Synthelabo is submitting data files for clinical study PDY5105.
15-Apr-2003	SUB		Letter to Jayne Peterson, FDA. Ms. Peterson requested two items from NDA 21-287 (10 April 2003) Sanofi-Synthelabo sent: 1. List of Clinical Investigators in NDA, and 2. U.S Co-marketing Partners and Sub-contractors.
16-Apr-2003	SUB	41	Sanofi-Synthelabo provided a draft patient package insert requested by Ms Jean King
25-Apr-2003	EML		Jayne Peterson, Advisors and Consultants Staff, FDA notified Sanofi-Synthelabo that the Center has agreed to an extension of the due date of the background package for the 29 May 2003 Cardiovascular & Renal Drugs Advisory Committee meeting re: Alfuzosin. Package due 01 May rather than 28 April.
30-Apr-2003	SUB	42	Advisory Committee Meeting Package sent to FDA Cardiorenal Advisory Committee staff.
29-May-2003			Alfuzosin cardiac repolarization study presented to FDA Cardiorenal Advisory Committee
12-June-2003			NDA approved

(12) In the opinion of the Applicant, U.S. Patent No. 4,661,491 is eligible for an extension of 1,481 days. The length of said extension was calculated as follows:

1. The number of days for the testing phase 1992
as defined in 37 CFR 1.775 (c)(1)

2 The number of days for the approval phase 485
as defined in 37 CFR 1.775(c)(2)

3 Total of line 1 and 2 2477

4. The number of days of the period of line
2 which occurred prior to the issue date of the patent 0

5. The number of days of the period of line 2 during 0
which the Applicant failed to act with due diligence
as defined in 37 CFR 1.775(d)(1)(ii)

6. Total of line 4 and line 5 0

7. Total of line 3 less the amount of line 6 2477

8. The number of days of the period of line 1 0
which occurred prior to the issue date of the patent

9. The number of days of the period of line 1 during 0
which the Applicant failed to act with due diligence
as defined in 37 CFR 1.775(d)(1)(ii)

10. The total of line 8 and line 9 0

11. Total of line 7 less the amount of line 10 2477

12. The number of days from line 1 1992

13. The number of days from line 10 0

14. The total of line 12 less the amount of line 13 1992

15. One half of line 14 996

16. The total of line 11 less the amount of line 15 1481

17. The original expiration date of the patent ..... May 27, 2006

18. The expiration date of the patent if extended by the ..... June 16, 2010
number of days on line 16

19. Date of the FDA final approval ..... June 12, 2003

20. Limitation set forth in 37 CFR 1.775(d)(3) ..... 14 years

21. The number of years on line 20 added to the date on line 19 ..... June 12, 2017

22. Earlier of the dates of line 18 or line 21 ..... June 16, 2010

23. Original expiration date of patent ..... May 27, 2006

24. The limitation set forth in 37 C.f.R. 1.775(d)(5) ..... 5 years

25. The number of years on line 24 added to the date on line 23 ..... May 27, 2011

26 The earlier of the dates appearing on line 22 or line 25 ..... June 16, 2010

27. The original expiration date of the patent ..... May 27, 2006

28. The number of days by which line 26 and line 27 differ 1481

(13) Sanofi-Synthelabo acknowledges its duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information of which it is aware which is material to the determination of entitlement to the extension sought.

(14) The Commissioner is hereby authorized to charge to Deposit Account No. 19-0091 the prescribed fee of $1,120 under 37 C.F.R. §1.20(j), and to charge any additional fees which may be required, or credit any overpayment to said Deposit Account.

(15) Correspondence relating to this application should be directed to:

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Telephone or facsimile communications relating to this application can be directed to the undersigned at the numbers listed below.

Respectfully submitted,

Dated: August 6, 2003

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