CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-287

Approval Letter(s)

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) dated December 8, 2000, received December 8, 2000, submitted under section 505(b) pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Uroxatral (alfuzosin hydrochloride) extended release tablets, 10 mg per day.

We acknowledge receipt of your submissions dated February 25, March 19, September 10, October 14, December 12, and December 16, 2002, as well as February 5, March 12, April 4, April 16, May 22, and June 10, 2003. The December 12, 2002 submission constituted a complete response to our October 5, 2001 action letter.

This amended new drug application provides for the use of Uroxatral (alfuzosin hydrochloride) extended release tablets, 10 mg daily for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the attached labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling [the package insert (PI) and patient package insert (PPI) received electronically on June 12, 2003, and the immediate container and carton labels previously submitted August 30, 2001]. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-287". Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitment in your submission dated June 12, 2003. This commitment is listed below.

Commitment # 1

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

The timeline is as follows:

- Draft protocol submission — within six months of the date of this letter
- Study initiation — within 12 months of the date of this letter
- Submission of Final Study Report — within 20 months of the date of this letter

Submit clinical protocol(s) to your IND for this product and the study final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of this commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and number of patients entered into the study. All submissions, including supplements, relating to this postmarketing study commitment must be prominently labeled "**Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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}

Florence Houn, M.D., M.P.H.
Office Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Julie Beitz
6/12/03 08:29:36 PM
Signing for Florence Houn, MD

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21-287

Approvable Letter (S)

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, Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malverne, PA 19355

Dear Dr. Villaume:

Please refer to your new drug application (NDA) dated December 8, 2000, received December 11, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uroxatral (alfuzosin hydrochloride) 10 mg extended release tablets.

We acknowledge receipt of your submissions dated January 17 and 23, February 20, March 31, April 6, 10, 20 and 25, May 8 and 18, June 27, July 6, 10, 19, 25 and 30, August 13, 21, 28, and 29, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the safety concern outlined below:

This application lacks adequate information, including clinical pharmacology data, to determine whether the product is safe for use because alfuzosin may increase the QTc interval. The QTc interval must be measured using an FDA agreed upon validated methodology. Additional pharmacokinetic and pharmacodynamic studies are necessary to determine the effect of maximum doses of inhibitor of the cytochrome P450 3A4 isozyme (e.g. ketoconazole) on QTc interval. We request that prior to initiation of these studies you obtain consultation and agreement on protocols from the Division of Reproductive and Urologic Drug Products. It will be necessary for you to submit draft labeling revised to reflect new data collected in additional studies performed.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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}

Florence Houn, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Florence Houn
10/5/01 12:44:04 PM

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

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