

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-774

APPROVABLE LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-774

Sanofi-Synthelabo Inc.
9 Great Valley Parkway
PO Box 3026
Malvern, PA 19355

Attention: Debra Gayda, PhD
Senior Director, Regulatory Affairs

Dear Dr. Gayda:

Please refer to your new drug application (NDA) dated June 8, 2004, received June 8, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ambien CR (zolpidem tartrate extended-release tablets).

We acknowledge receipt of your submissions dated August 27, September 1, October 5 and 6, 2004, and February 10 and 22, March 18 and 24, and April 1, 2005.

We have completed our review of this application, as submitted, with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

Perform at least one adequate and well-controlled trial in adults that supports not only an early treatment effect over a reasonable period during the night, but a reasonable degree of durability of that effect as well. The data in this application are inadequate to establish the efficacy of Ambien CR for the treatment of sleep maintenance insomnia.

Additionally, we have the following comments.

1. Provide revised testing criteria for the testing and testing of the validation batches and the routine commercial batches in conformity with the recommendations in the
2. The following comments pertain to the labeling. Additional comments will be provided once the aforementioned deficiencies are addressed.
 - a. Package Insert
 - i. We strongly recommend that you separate the package inserts for Ambien and Ambien CR.

- ii. Include revisions to the package insert, as indicated in the attached, edited document. Note that these revisions are only preliminary draft comments.

b. Carton and Container Labels; Blister Front Panel:

Increase the prominence of the established name on the blister front panel.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical 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 this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We

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will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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 Lisa Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE