DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-908 S-020, S-024, S-025

Sanofi- Synthelabo Research
Attention: Daryl DeKarske, MPH
9 Great Valley Parkway
Malvern, PA 19355

Dear Mr. DeKarske:

Please refer to the supplemental new drug applications noted below submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ambien (zolpidem tartrate) Tablets.

Application	Submitted on:	Received on:	Provides for:
S-024	March 27, 2007	March 28, 2007	"Changes Being Effected" Supplement; revisions to Overdose section.
S-025	August 14, 2007	August 15, 2007	"Prior Approval" Supplement: Medication Guide.

We note that Supplemental Application **S-025** was submitted in response to an Agency request included in a December 4, 2006 letter.

We have completed our review of supplemental application **(S-025)** and it is approved, effective on the date of this letter.

Additionally, we have completed our review of Supplemental Application **(S-024)** and have determined that it is approvable. However, after review of your proposed Package Insert included with this supplement, we have determined that additional modifications are needed. Before supplement **S-024** may be approved, you must address the deficiencies described below.

Additional Labeling Changes

- In section 4.1, (b) (4) section 5.2 Severe anaphylactic and anaphylactoid reactions).

- Your proposal to add the following sentence, "Ambien should be used with caution in patients with sleep apnea syndrome and myasthenia gravis" is acceptable.

- In section 5.3, please remove the brackets around the last two sentences in the first paragraph, i.e. the sentences describing the incidence of hallucinations seen in the clinical trials. Additionally there should be a cross reference to section 8.4 where the pediatric trial is described in detail. In the second paragraph of this section, the first sentence should read as follows:

Complex behaviors such as sleep driving (i.e. driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported with [redacted]. (b) (4)

The last sentence of this paragraph should be made a stand alone paragraph and should be altered to read as follows:

Worsening of depression, including suicidal thoughts and actions (including completed suicides) has been reported in association with the use of sedative hypnotics.

- In section 6.1, we note that you have deleted the heading "Incidence in controlled clinical trials". We ask that you reinstate this heading for 6.1.

- Final paragraph of section 7.1 CNS-active drug should become the initial paragraph in this section.

- The two paragraphs in section 7.2 should be reversed.

- The sentence "Ambien should not be administered with or immediately after a meal" should be included in the DOSAGE AND ADMINISTRATION section of the PI and in the SAFE USE OF SLEEPING MEDICINES section of the information for patients section.

- The subheading "non-teratogenic effects" in section 8.1 Pregnancy should be bolded.

- The pediatric use section of the label (section 8.4) should read as follows:

[redacted]: Safety and effectiveness [redacted] have not been established. In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder were treated with an oral solution of zolpidem. Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%). Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

(b) (4) (b) (4)

- The addition of the following sentences to the overdosage section (section 10.1) is acceptable:

1) In post marketing experience of overdose with zolpidem alone or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise and fatal outcomes have been reported, 2) however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions).

- In section 10.2, the subheading "poison control center" should be deleted.

- In section 12.3, the entire paragraph entitled "Postulated relationship between elimination rate of hypnotics and their profile of common untoward effects" should be deleted.

- In section 14.2, the references to the doses studied should be removed. While the section may continue to make reference to the findings with the 10 mg dose, all references to the 15 mg dose should be removed. The following sentence should be added to the end of this section:

  > Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with [redacted] (b) (4) [redacted] (b) (4) Ambien.

- The heading for section 17.1 should be changed to read: [redacted] (b) (4). The first sentence in this section, "Patient information is printed at the end of this insert" is to be deleted.

- In the subsection of section 6 entitled "Adverse events observed at an incidence of ≥ 1% in controlled trials," the first sentence should read: The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate and at a greater incidence than placebo in U.S. placebo-controlled trials.

- The tables in the adverse event section should be modified to read as follows:

Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials lasting up to 35 nights

(Percentage of patients reporting)		
Body System/ Adverse Event *	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-
Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1

Please note that we have attached to this letter labeling that includes the approved Medication Guide **(S-025)** and all of the additional revisions to the package insert (in ~~strikeout~~/redline format) discussed above. We ask that you submit final printed labeling (FPL) that is identical to this labeling.

Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

With regard to Supplemental Application S-024:

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

With regard to "approved" Supplemental Application S-025:

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplemental application NDA 19-908 S-025**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit revised content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

Supplemental Application S-020:

We note that you provided a complete response to our December 4, 2006 approvable letter to supplemental application **S-020** on March7, 2007. However, we also note that all of the proposed changes included in that submission were approved in our action letter sent to NDA **19-908/S-022** on March 28, 2007. Therefore, we will not complete a review of this supplemental application and it will be retained in our files with no further action.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Cathleen Michaloski, MPH, Regulatory Project Manager, at 301-796-1123.

Sincerely,

{See appended electronic signature page}
Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert including Medication Guide

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

/s/

Russell Katz

10/4/2007 04:40:30 PM