

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-774

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 21-774

SUPPL #

HFD # 120

Trade Name Ambien CR

Generic Name Zolpidem tartrate

Applicant Name Sanofi-Synthelabo

Approval Date, If Known September 2, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-908

Ambien

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

EFC 4529

EFC 4530

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

YES

NO

Investigation #2

YES

NO

Investigation #1

!
!

YES

! NO

Explain:

! Explain:

Investigation #2

!
!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Renmeet Gujral, Pharm.D.

Title: Regulatory Project Manager

Date: 11/10/05

Name of Office/Division Director signing form: Russell Katz, M.D.

Title: Division Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Russell Katz
11/23/2005 07:13:06 AM

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA#s 10-155; 14-399; 19-908; 20-599; 21-774

sanofi-aventis U.S. LLC
Attention: Craig Audet
Vice President, US Regulatory Affairs Marketed Products
300 Somerset Corporate Boulevard
P.O. Box 6977
Bridgewater, NJ 08807-0977

Dear Mr. Audet:

We acknowledge receipt on January 25, 2006, of your January 23, 2006, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug applications (NDA):

<u>NDA #</u>	<u>Name of Drug Product</u>	<u>Name of New Applicant</u>	<u>Name of Previous Applicant</u>
10-155	Mytelase Tablets	sanofi-aventis U.S. LLC	Sanofi-Synthelabo Inc.
14-399	Norpramin	sanofi-aventis U.S. LLC	Aventis Pharmaceuticals Inc.
19-908	Ambien Tablets	sanofi-aventis U.S. LLC	Sanofi-Synthelabo Inc.
20-599	Rilutek Tablets	sanofi-aventis U.S. LLC	Aventis Pharmaceuticals Inc.
21-774	Ambien CR Tablets	sanofi-aventis U.S. LLC	Sanofi-Synthelabo Inc.

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate sanofi-aventis U.S. LLC as the sponsor of record for these applications.

All changes in the NDA from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your applications of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

NDA 10-155; 14-399; 19-908; 20-599; 21-774

Page 2

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call Katherine Needleman, Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Katherine Needleman
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Katherine Needleman
3/16/2006 09:22:11 AM



NDA 21-774

Sanofi-Synthelabo Research
9 Great Valley Parkway
Malvern, PA 19355

Attention: Daryl DeKarske, MPH
Director, Drug Regulatory Affairs

Dear Mr. De Karske:

Please refer to your new drug application (NDA) for Ambien (zolpidem tartrate) CR tablets.

The Agency has determined that modifications are needed in the class labeling for the sedative-hypnotic group. These changes will be applicable for all drug products that are indicated for the treatment of insomnia.

Accordingly, we request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

1. **WARNINGS:**

Modify the first two sentences to include bold and revised text as shown below:

~~Since~~ — sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. **The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness which** — should be evaluated.

2. **DRUG ABUSE AND DEPENDENCE:**

Add the following two paragraphs as the first two paragraphs to the Abuse and Dependence subsection:



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, fifteen of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected." 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.

In addition, we remind you that you must submit 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>

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

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/s/

Russell Katz
2/14/2006 08:44:54 AM

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD- 42 DDMAC Attention: Michael Brony		FROM: HFD-120/ Division of Neuropharmacological Drug Products		
DATE 6/14/05	IND NO.	NDA NO. 21-774	TYPE OF DOCUMENT Meeting Package	DATE OF DOCUMENT May 31, 2005
NAME OF DRUG Ambien CR (Zolpidem tartrate)12.5mg, 6.25mg tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Insomnia	DESIRED COMPLETION DATE Meeting is on 6/28/05
NAME OF FIRM: Sanofi Synthelabo				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This is a meeting package for Ambien CR used to treat insomnia. The internal meeting is June 27, 2005 and the meeting with the sponsor is on June 28, 2005. Please let me know if you have any further questions. You can contact me at gujralr@cder.fda.gov or at 301-594-5535. Thank you				
SIGNATURE OF REQUESTER Renmeet Gujral, Pharm.D. Regulatory Project Manager 301-594-5535 gujralr@cder.fda.gov		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Renmeet Gujral
6/14/05 04:16:20 PM



NDA 21-774

Sanofi Synthelabo Inc.
9 Great Valley Parkway
Malvern, PA 19355

Attention: Debra Gayda, PhD
Sr. Director, Drug Regulatory Affairs

Dear: Dr. Gayda,

Please refer to the meeting between representatives of your firm and FDA on May 10, 2005. The purpose of the meeting was to discuss the Agency's April 8, 2005, Approvable action for your NDA, and to discuss strategies for resubmission of your NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

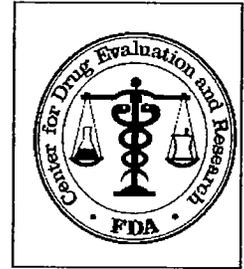
If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa E. Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure



MEETING MINUTES

Meeting Date: May 10, 2005

Location: Parklawn Building, Conference Room "C"

NDA/ Name: NDA 21-774/Ambien® CR

Sponsor: Sanofi Synthelabo Inc.

Type of Meeting: Post Action Meeting

Attendees:

Sanofi Synthelabo	Title
Werner Rein, MD	Clinical Development
Christina Soubrane, MD	Clinical Development
Christian L'Heritier, PhD	Biostatistics
Sylvain Durreleman, MD, PhD	VP, Clinical Operations; Biostatistics
Danielle Le Peuch	Project Direction
Jose Necciari, PhD	Preclinical Development
Estelle Weinling, PharmD	Clinical Metabolism & PK
Sol Rajfer, MD	International Development
Doug Greene, MD	Vice President, Global Head, Regulatory Affairs
Emmanuelle Magueur, PharmD	Regulatory Affairs
Debra Gayda, PhD	Regulatory Affairs
FDA	Title
Bob Rappaport, MD	Division Director, DAARP
Paul Andreason, MD	Team Leader, Psychiatry, DNNDP
Eric Bastings, MD	Team Leader, Neurology, DNNDP
Tom Permutt, PhD	Lead Mathematical Statistician, DAARP
D. Elizabeth McNeil, MD	Clinical Reviewer, DAARP
Joan Buenconsejo, PhD	Statistical Reviewer, DAARP
Lisa E. Basham-Cruz, MS	Regulatory Project Manager

Background: The NDA for Ambien CR (zolpidem tartrate extended-release) Tablets was received on June 8, 2004, and was filed on August 7, 2004, with a PDUFA date of April 8, 2005. On May 2, 2005, the review responsibility for the sedative-hypnotic drug class was transferred from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170) to the Division of Neuropharmacological Products (HFD-120). This Post-Action meeting included representation from both divisions. The representatives from HFD-170 provided an overview of their reasons for the April 8, 2005, Approvable action. The representatives from HFD-120 spoke to potential approaches to resubmission that may support approval of the NDA.

Meeting Minutes: Following introductions, Dr. Rappaport provided some opening remarks. He stated that HFD-170 and HFD-120 were in communication during review of the subject NDA and that his intent for the meeting was to provide the Applicant with a clear understanding of the reasons for HFD-170's approvable action, and for HFD-120 to communicate what they consider appropriate approaches for adequately addressing the deficiency. Sanofi expressed their gratitude for a face-to-face meeting and for our efforts to keep them informed during this period of restructuring.

Dr. McNeil presented a short slide presentation summarizing HFD-170's rationale for the approvable action. The content of the slides is shown below in bolded text. Discussion is presented in normal text.

Rationale for approvable decision

Study 4529 failed to meet the pre-specified primary endpoint which was to demonstrate improved sleep maintenance, by decreasing WASO, over 8 hours.

- **A decrease in WASO over 8 hours was adequately demonstrated when patients were evaluated on N1/N2.**
- **A decrease in WASO over 8 hours was not demonstrated when patients were evaluated on N15/16.**

Study 4530 met the pre-specified primary endpoint which was to demonstrate improved sleep maintenance, by decreasing WASO, over 6 hours.

- **A decrease in WASO over 6 hours was adequately demonstrated when patients were evaluated on N1/N2.**
- **A decrease in WASO over 6 hours was demonstrated when patients were evaluated on N15/16.**

We had only one study, #4530, which demonstrated efficacy on the pre-specified primary endpoint.

While study #4529 demonstrated efficacy on some secondary and exploratory endpoints, it did not demonstrate efficacy on the pre-specified primary endpoint, nor did it display persistence of effect which would be required for — (the latter issue was discussed at the EOP2 mtg).

With only one study that succeeded in demonstrating efficacy on the primary endpoint, we took an approvable action.

Referring to study 4529, the sponsor noted that the primary endpoint was to measure WASO at N1 and N2 and that this study was therefore successful. Dr. McNeil acknowledged that the primary endpoint was as stated, but noted that the sponsor was told at the EOP2 meeting that they would need to demonstrate persistence of effect for this formulation, i.e., efficacy at N15/N16, to obtain —. The sponsor inquired what labeling the data would support. Dr. Rappaport turned the meeting over to Dr. Andreason, who was speaking on behalf of Russell Katz, MD; Director, Division of Neuropharmacological Products.

Dr. Andreason began by apologizing about any misunderstanding related to the acceptability of measuring WASO at 6 versus 8 hours. He stated that the prior request from the company to measure at 6 hours was not understood to be a request as to whether 6 hours (rather than 8) is adequate to demonstrate sleep maintenance, but was interpreted as a request to perform an exploratory analysis. The sponsor inquired whether there exists such a claim as sleep maintenance over six hours. Dr. Andreason responded that sleep maintenance is generally measured over 8 hours. He added that he assumed that the drug would improve sleep onset, which it did not. The sponsor then claimed that the drug did, in fact, improve sleep onset. Dr. Buenconsejo noted that, in her analysis, this was not the case; the pre-specified ANOVA analysis did not result in demonstration of efficacy. The sponsor chose to switch to ANCOVA, which was not pre-specified, and thus, an invalid method. The sponsor responded that they had pre-specified ANCOVA as a conditional analysis, i.e., if there were heterogeneity problems at baseline, ANCOVA would be used. There was some discussion about the appropriateness of this approach. The sponsor stated that ANCOVA should be considered a pre-specified method of analysis, and that they will provide clarification on this issue.

— Dr. Andreason went on to discuss the change in current thinking regarding how sleep maintenance is measured, i.e., WASO or Wake Time During Sleep (WTDS). He said that, in the past, Total Sleep Time (TST) was the standard measurement of sleep duration. Today, WASO is the standard because it is more easily measured and parses out problems like LTPS affecting TST. This issue was revisited with the review of the Ambien CR NDA. —

—
— Dr. Rappaport clarified by saying that “sleep duration” is no longer considered an accurate descriptor of sleep maintenance. Dr. McNeil added that the controlled-release formulation was expected, in theory, to improve sleep by both decreasing LTPS (as the currently marketed Ambien does) and improving sleep maintenance.

Dr. Andreason suggested that the sponsor contact the Project Manager in HFD-120 to schedule a meeting with that division. The sponsor summarized what they expect to discuss in a meeting with HFD-120.

1. Whether a decrease in sleep latency was demonstrated in studies submitted to the Ambien CR NDA.
2. Ambien's indication and appropriateness of "sleep maintenance" claim given current thinking.
- 3.

Dr. Andreason advised the sponsor to focus on their argument that they have demonstrated a decrease in sleep latency and on whether they

The sponsor inquired whether there is any further guidance that the Agency can provide on measurement of sleep claims. Dr. Andreason responded that the Agency is not accepting claims of quality of sleep. Acceptable measures are PSG and patient reports of TST. Dr. Rappaport added that the Agency is generally requiring one study with objective measures and one study with subjective measures.

The Applicant summarized the key issues:

1. The sponsor will provide support for their belief that they met the secondary efficacy endpoint of Latency to Persistent Sleep in studies 4529 and 4530.
2. /
3. The Applicant and the Agency will consider whether a sleep latency claim is appropriate for Ambien CR.
4. /
5. The Applicant will schedule a meeting with the Division of Neuropharmacological Products.

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/s/

Lisa Basham-Cruz
5/27/05 01:59:22 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 2, 2005

TO: Robbin Nighswander
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
HFD-120

FROM: Parinda Jani
Chief, Project Management Staff
Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

SUBJECT: Transfer of the sedative/hypnotic drug class from HFD-170 to HFD-120
Comis Drug Class: #2020400

In line with the agreements reached at a meeting held between our Divisions on April 26, 2005, administrative responsibility for the Sedative/Hypnotic Drug Class is being transferred back to the Division of Neuropharmacological Drug Products (HFD-120). If you have any questions, call me at 301-827-7422.

I 025361 AT AMBIEN (ZOLPIDEM)

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 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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/s/

Jackie Ware
5/3/05 11:40:08 AM
For Robbin Nighswander

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 3/28/05

DESIRED COMPLETION DATE: 4/1/05

ODS CONSULT#:

DATE OF DOCUMENT: 3/18/05

PDUFA DATE: 4/8/05

03-0312-3

TO: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Lisa Basham-Cruz
Project Manager
HFD-170

PRODUCT NAME:

Ambien CR
(Zolpidem Tartrate Extended-release Tablets)
6.25 mg and 12.5 mg

NDA: 21-774

NDA SPONSOR:

Sanofi-Synthelabo Inc.

SAFETY EVALUATOR: Felicia Duffy, RN

DMETS RECOMMENDATIONS:

DMETS recommends implementation of the container label and carton labeling revisions outlined in the Section II of this review.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: April 1, 2005

NDA # 21-774

NAME OF DRUG: Ambien CR
(Zolpidem Tartrate Extended-release Tablets)
6.25 mg and 12.5 mg

NDA HOLDER: Sanofi-Synthelabo Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) to re-review the container labels and carton labeling of Ambien CR. The labeling for Ambien CR was previously reviewed in ODS consult #03-0312-1. This consult is in response to the labeling revisions outlined in the aforementioned consult.

Ambien (zolpidem tartrate) was approved on December 16, 1992 under NDA 19-908. Ambien is an immediate release formulation non-benzodiazepine hypnotic indicated for the use of short term insomnia. Ambien is also a schedule IV controlled substance and is available in 5 mg and 10 mg tablets. The usual adult dosage is 10 mg by mouth at bedtime.

Ambien CR is the extended-release formulation of the currently marketed Ambien. According to the sponsor, this new formulation will modify the release of the drug substance in order to maintain plasma concentrations of the drug in the middle of the night. Ambien CR has the same dosing interval as Ambien. Ambien CR is a schedule IV controlled substance and will be available in 6.25 mg and 12.5 mg tablets. The usual adult dosage will be 12.5 mg by mouth at bedtime. Elderly or debilitated patients may be especially sensitive to the effects of Ambien CR (zolpidem tartrate extended-release tablets). Patients with hepatic insufficiency do not clear the drug as rapidly as normal. A 6.25 mg dose is recommended in these patients. The total Ambien CR dose should not exceed 12.5 mg. Ambien CR is available in 6.25 mg and 12.5 mg strengths. The proposed packaging configuration is a 100 count and 500 count bulk bottles containing 6.25 mg or 12.5 mg, a blister package containing 30 tablets of Ambien 6.25 mg or 12.5 mg.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

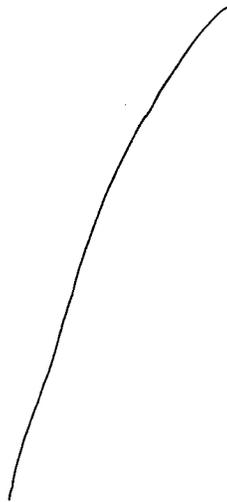
In the review of the “Ambien CR” container labels and carton labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENTS

In the USP monographs, dosage form descriptors are included as part of the established name. Therefore, to be consistent with the nomenclature in the USP, the dosage form indicator should be a part of the established name. We recommend the established name should appear as follows:

Ambien CR
(Zolpidem Tartrate Extended-release Tablets)
XX mg

B.



C. BLISTER LABEL (6.25 mg and 12.5 mg, 30 count)

1. See General Comment.
2. Although the statement “ — ” appears on the back of each blister, the product strength must also be included in conjunction with the proprietary and established names on each blister. Please revise accordingly.

D. CONTAINER LABEL (100 count and 500 count bottles)

1. See General Comment.
2. The net quantity of the 6.25 mg and 12.5 mg 100 and 500 count bottles appear more prominent as the product strength (e.g., bolded). Please decrease the font size, and debold the net quantity in order to avoid confusion.

3. The color used to express the 6.25 mg and 12.5 mg is identical. We recognize the sponsor differentiating the carton color; however, the actual strengths should be differentiated as well.



G. CARTON LABELING (6.25 mg and 12.5 mg: 3 cards of 10 tablets)

1. See General Comment.
- 2.



III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section II of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Felicia Duffy
4/6/05 09:22:16 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/6/05 09:25:36 AM
DRUG SAFETY OFFICE REVIEWER



INFORMATION REQUEST LETTER

NDA 21-774

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

Attention: Debra P. Gayda, Ph.D.
Director, Drug Regulatory Affairs

Dear Dr. Gayda:

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

We are reviewing the Chemistry, Manufacturing, and Controls 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. The in-process specifications for tablet dimensions include the tablet thickness but not the tablet diameter. Provide a limit on the tablet diameter.
2. Provide a calculation of the head space per tablet for the bottle configurations used in the primary stability studies (_____ 100 count-size and _____ /500 count-size) and for those proposed for marketing (100-ml/100 count-size, 175-ml/500 count-size).
3. Clarify whether the bottle supplier, the _____ or the proposed marketing configurations are the same as those for the container closures used in the primary stability studies.
4. Replace the term ' _____ with "debossed" on the "Appearance" specification and provide the revised specification sheet.

NDA 21-774

Page 2

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Ravi Harapanhalli, PhD
Chemistry Team Leader for the
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
3/30/05 03:51:23 PM
IR

REQUEST FOR CONSULTATION

TO (Division/Office):
**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM:
Bob Rappaport, MD; Director, DACCADP

DATE March 24, 2005	IND NO.	NDA NO. 21-774	TYPE OF DOCUMENT NDA: C&C Labeling	DATE OF DOCUMENT March 18, 2005
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NAME OF DRUG Ambien CR	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Sedative/hypnotic	DESIRED COMPLETION DATE April 1, 2005
---------------------------	------------------------------------	---	--

NAME OF FIRM: **Sanofi Synthelabo**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | Labeling: Carton & Container |

II. BIOMETRICS

- | | |
|---|--|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:
NDA 21-774, for Ambien CR, is in house with a PDUFA goal date of April 8, 2005. The sponsor has provided revised Carton & Container labels in response to our 2/25/05 discipline review letter. This letter contained comments from your prior 12/2/04 review of the C&C. The revised labeling can be found in the EDR, March 18, 2005 submission (BL).
Please contact Lisa Basham-Cruz (301-827-7420) with any questions.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND <input checked="" type="checkbox"/> DFS
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/s/

Lisa Basham-Cruz
3/24/05 03:15:18 PM
For Bob Rappaport, MD



INFORMATION REQUEST LETTER

NDA 21-774

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

Attention: Debra P. Gayda, Ph.D.
Director, Drug Regulatory Affairs

Dear Dr. Gayda:

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

We are reviewing the Chemistry, Manufacturing, and Controls 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. Provide a justification as to why the currently specified _____ of the drug substance is adequate to control the drug product performance.
2. Based on the pharmaceutical development experience, provide information on the _____ in the drug product and whether it is critical to the performance of the drug product.
3. Provide a purity factor calculation for zolpidem tartrate working standard batch CL-05278 → batch # 22023/B).
4. Provide supporting CoAs for the drug substance batch 230389 and the excipient batches used in the manufacturing of the _____ drug product batches 23047 and 23048.
5. Compendial testing of the excipients may not adequately assure their fitness for use in the product performance. Additional functional attributes such as _____ may need to be controlled. Provide such controls in the acceptance specifications for the excipients based on the pharmaceutical development experience or justify why such additional controls are not needed.

6.

7. Clearly define the term _____ and provide appropriate limits in the in-process parameters for the manufacturing operations of _____.

8.

9. Provide additional controls to assure the _____. These controls should be included in the "Controls of Critical Steps and Intermediates".

10.

11. Provide a brief description with justification for the sampling plans used in the in-process control of critical steps and intermediates.

12. Provide justification as to why testing _____ is sufficient to assure the performance of the finished (coated) tablets.

13. Provide information on the sampling plans used for the release testing and stability testing of the drug product.

14. Stability data indicates that the _____
_____ on stability. Revise the drug product specifications to include the _____

15. Specify the count-size (number of tablets) of the blisters used in the stability studies.

16. Revise the master batch records to adequately document the drug substance lot number and excipient lot numbers.

17. Provide an agreement that the finalized master blank batch record and a post validation executed batch record of the _____ production scale batch would be submitted to the NDA in an annual report.

18. The reasoning provided for the categorical exclusion from environmental assessment is inadequate. Provide additional calculations including the projected sales in the next five

years and the projected environmental introduction concentration (EIC) which is claimed to be < 1ppb.

If you have any questions, call Lisa E. Basham-Cruz, Regulatory Project Manager, at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Ravi Harapanhalli, PhD
Chemistry Team Leader for the
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
3/22/05 04:36:55 PM
IR



MAR 15 2005

Food and Drug Administration
Rockville MD 20857

Barbara Harris, Ph.D.
PsyPharma Clinical Research, Inc.
4045 E. Union Hills Drive, Ste #122
Phoenix, Arizona 85050

Dear Dr. Harris:

Between February 1 and 8, 2005, Ms. Sandra L. Shire, representing the Food and Drug Administration (FDA), conducted an inspection and met with you and members of your staff to review your conduct of two clinical investigations (protocols # EFC4529 entitled: "Comparison of efficacy and safety of Zolpidem-MR 12.5 mg and placebo in patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel-group study" and EFC4530 entitled: "Comparison of efficacy and safety of Zolpidem-MR 12.5 mg and placebo in elderly patients with primary insomnia. A double-blind, randomized, placebo-controlled, parallel-group study") of the investigational drug Ambien-CR (zolpidem-MR), performed for Sanofi-Synthelabo. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that, except for minor deficiencies, you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Shire 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,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

Page 2 – Barbara Harris, Ph.D.

CFN/FEI. ✓

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-170 Doc.Rm. NDA# 21-774

HFD-170 Review Div.Dir. (Rappaport)

HFD-170 MO (McNeil)

HFD-170 PM (Basham-Cruz)

HFD-46/47c/r/s/ GCP File #11426

HFD-46/47 (Currier)

HFR-PA252 DIB (Maxwell)

HFR-PA2565 Bimo Monitor (Koller)

HFR-PA2530 Field Investigator (Shire)

GCF-1 Seth Ray

r/d:cac: 3/10/05

reviewed:NK: 3/11/05

f/t:cac: 3/14/05

o:\cac\2005\Harris.Pdufa.N21774.AmbienCR.Ltr.NAI.doc

Reviewer Note to Rev. Div. M.O.

The inspection of Barbara Harris, Ph.D., was 1 of 2 inspections assigned to verify data supporting the pending NDA 21-774, Ambien-CR, submitted by Sanofi-Synthelabo

The current inspection covered her conduct of studies with protocols 4529 and 4530. Both protocols were designed to show the effectiveness of Ambien-CR in reducing the total time awake after sleep onset compared to placebo. Protocol 4529 was conducted in an adult population; 4530 in a geriatric population. 63 subjects were screened for protocol 4529 and 20 completed. 27 subjects were screened for 4530 and 15 completed. Study records, including source documents, lab reports, CRFs, and queries were reviewed during the inspection. Items reviewed for accuracy and completeness were I/E criteria, physical exams, medical histories, labs, drug dosing, WASO values, RAVLLT/DSST scores, AE/SAE reporting, and drug accountability records.

No major discrepancies were found in the conduct of the study, and no 483 was issued to the site. One subject technically did not meet eligibility criteria based on the BMI (limit was 32, subject's BMI was 32.3), and it appears that one subject incorrectly filled in a blank on the DSST test at

visit 6 and was allowed to re-do it. Also, one subject was 1 day out of limit for the next study visit. None of these problems appear to have clinical significance. There was nothing found during the inspection of the selected records that would preclude the data from Dr.Harris' site being used to support an approval decision for the NDA.

Of note, however is the inspection revealed a discrepancy between the mean screening WASO values calculated by the site to determine eligibility and those calculated from the same PSG readings by the Central Reader (CR). The site was to calculate mean WASOs only for screening nights 1 and 2, and the rest of the study nights' data was to be sent to the CR. However, the CR also calculated the screening night WASOs. The field investigator compared the site's screening WASOs with the CR's WASOs and found significant differences. Although variation in WASO scores is expected due to the inherent difficulty in assessing sleep stages from PSG readings, in at least 20 cases (both protocols), mean WASO values differed between 20 and 75 minutes. In the majority of the cases (16), the WASOs calculated by the study site were significantly greater than those calculated by the CR. In protocol 4529, 4 subjects (004, 005, 020, and 053) that were considered eligible for the study by the site were ineligible by the CR's calculations. (The significance of this finding is tempered by the fact that 4529 turned out to be a negative study.) In addition, it was discovered that the PSG reading program () employed by the study site allowed for multiple WASO interpretations without an audit trail, so it could not be determined if any WASO values had been re-calculated. This information about the WASO discrepancies and the PSG program is being reported for future evaluation of protocols employing these procedures.

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/s/

Ni Aye Khin

3/20/05 05:00:08 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 11, 2005
TO: NDA file
FROM: Lisa Basham-Cruz
SUBJECT: **Established name**
NDA 21-774, Ambien CR (zolpidem tartrate extended-release)
tablets

The following emails were exchanged between Debra Gayda, of Sanofi Synthelabo, and myself, on March 2; and March 11, 2005, respectively.

-----Original Message-----

From: debra.gayda@us.sanofi.com [mailto:debra.gayda@us.sanofi.com]
Sent: Wednesday, March 02, 2005 12:09 PM
To: Basham-Cruz, Lisa
Subject: RE: FW: Stability - N 21-774

Hi Lisa,

Thanks for the letter. We are working on providing a response (including new artwork) by the end of next week.

However, we have one question for the reviewer regarding their rationale for the request to revise the establish name from ' _____ to "extended release" (comment 1d). We understand that "extended release" is one of the two categories under modified release tablets. The term "extended release" may be confusing to a patient since this term is most frequently used for a once-a-day product effective for up to 24 hours. Therefore, we thought that _____ or _____ was more appropriate for a product to treat insomnia. If possible we would appreciate some further guidance from the reviewer on this question prior to submission of our formal response.

Thanks,
Debra

From: Basham-Cruz, Lisa
Sent: Friday, March 11, 2005 5:09 PM
To: 'debra.gayda@us.sanofi.com'
Subject: Established name for NDA 21-774

Debra,

Here is our response to your question regarding the established name.

We disagree with the proposed nomenclature of _____ and _____ in the established name of the drug product for the following reasons.

1. "Extended-release" is the term recognized in CDER Data Standards manual and in USP
2. "Extended-release" is the term used for products that have extended release profiles, rather than immediate release profiles, and is not necessarily restricted to the 24-h release profile only.
3. This term accurately describes the release profile of the drug product in question.
4. The policy of the CDER Labeling and Nomenclature Committee (LNC) is to implement standardized nomenclature for the established names.
5. There may have been some inconsistencies in the past, but they are being rectified.

Hope this clarifies things,

Lisa Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II; Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Lisa Basham-Cruz
3/11/05 05:18:33 PM
CSO

Office of Drug Safety

MEMO

To: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products, HFD-170

From: Laura Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Linda Kim-Jung, Pharm.D., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Date: March 1, 2005

Re: ODS Consult 03-0312-2, Ambien CR (Zolpidem Tartrate Extended-release Tablets)
6.25 mg and 12.5 mg; NDA 21-774

This memorandum is in response to a February 16, 2005 request from your Division for a final review of the proprietary name, Ambien CR. The proposed proprietary name Ambien CR was found acceptable by the Division of Medication Errors and Technical Support (DMETS) on March 31, 2004 (ODS Consult 03-0312). Subsequently, DMETS provided comments on the container label, carton, and insert labeling dated November 9, 2004 in ODS Consult 03-0312-1. Since the initial review, DMETS has identified two additional proprietary names that were thought to have the potential for confusion with Ambien CR. These products are listed in Table 1 (below) along with the dosage forms available and the usual dosage. Additionally, DMETS reiterates its concern that health practitioner education is necessary in advance to minimize confusion over this new dosage formulation.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Ambien CR	Zolpidem Tartrate Extended-release tablets: 6.25 mg and 12.5 mg	Adults: 12.5 mg daily at bedtime Elderly: 6.25 mg daily at bedtime	N/A
Ambi 10 Cream	Benzoyl Peroxide Cream: 10%	Adults (> 12 yo): use on the affected areas of the skin one or two times a day	SA, LA
Ambi Skin Discoloration Fade Cream	Hydroquinone Cream: 2%	Apply a thin layer only to affected areas of darkened, discolored skin. Use twice daily, or as directed by a doctor.	SA, LA

1. Look-alike or Sound-alike Concerns

- a. Ambi 10 Cream may sound and look similar to Ambien CR when pronounced or scripted. Ambi 10 Cream is an over-the-counter (OTC) topical preparation of benzoyl peroxide cream that is used for the treatment of acne. The names Ambi and especially Ambi 10 have some phonetic similarities to Ambien due to the shared prefix, 'ambi-', however the name Ambien is audibly longer with three syllables compared to the two syllables for Ambi. The names also have orthographic similarities, because they share the same prefix, however, the name Ambi is noticeably shorter than the name Ambien. If the word "cream" is abbreviated as "cr" (Ambi 10 cr), a written order for Ambi 10 Cream may be misinterpreted as an Ambien CR product. However, there are product characteristics that will help to distinguish the two products such as: dosage form (tablet vs. cream), prescription directions (take by mouth vs. apply or use), strength (6.25 mg or 12.5 mg vs. 10%), and classification

(prescription vs. non-prescription). Ambien CR is available in two different strengths (6.25 mg and 12.5 mg) therefore the strength will be likely indicated on a prescription; whereas Ambi 10 is available as one strength (10%), and the strength is communicated as part of the tradename (10) or not communicated at all. Thus these different product characteristics, such as strength, directions for use, and classification will help to minimize the potential for confusion between Ambi 10 cream and Ambien CR products.

ambien cr
ambi 10 cr

- b. The root of Ambi Skin Discoloration Fade Cream may sound and look similar to Ambien CR. Ambi Skin Discoloration Fade Cream is an OTC topical preparation of hydroquinone cream that is used to treat skin discoloration. An order for the product name "Ambi Skin Discoloration Fade Cream" is not likely to be confused with Ambien CR because of the additional modifiers in the product name. However, the root of the name, "Ambi Cream" does sound and look similar to Ambien CR. The two names have some phonetic similarities because they share the same prefix 'ambi-', however the name Ambien is audibly longer with three syllables compared to the two syllables for Ambi. The names also have some orthographic similarities due to the shared prefix, however the suffix '-en' for Ambien and the lack of a suffix for Ambi is a noticeable difference. As discussed previously for the product Ambi 10 cream, (see section a above) if Ambi Cream is abbreviated as "Ambi cr", a written order for Ambi Cream may be misinterpreted as an Ambien CR product. However, Ambien CR is available in two different strengths (6.25 mg and 12.5 mg) therefore the strength will be indicated on a prescription; whereas Ambi cream is available as one strength (2%), therefore the strength may be omitted on a prescription. Additionally, there are product characteristics that will help to distinguish the two products such as: dosage form (tablet vs. cream), prescription directions (take by mouth vs. apply or use), strength (6.25 mg or 12.5 mg vs. 2%), and classification (prescription vs. non-prescription). Thus the orthographic and phonetic differences along with the different product characteristics, such as strength, directions for use, and classification, will help to distinguish the two names, and will minimize the potential for confusion between Ambi Cream and Ambien CR products..

ambi cr
ambien cr

2. New Formulation Concerns

Upon the introduction of a new formulation into the marketplace, the potential for medication errors due to confusion between two products with the same root name often increases. The likelihood for confusion between Ambien and Ambien CR is likely in the event that the "CR" modifier is overlooked or omitted on a prescription. Additionally, both drugs have once daily dosage which may increase the potential for confusion. Therefore, DMETS reiterates its concern that the potential for confusion between these two products may occur, especially when Ambien CR is launched into the marketplace. DMETS encourages the sponsor to ensure that healthcare practitioners are educated about Ambien CR, before and during its launch into the marketplace.

In summary, DMETS has no objection to the use of the proprietary name, Ambien CR. We remind you of our label and labeling recommendations outlined in our November 9, 2004 consult. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, Ambien CR, acceptable from a promotional perspective. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Laura Pincock
3/23/05 12:59:24 PM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
3/23/05 02:52:47 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/24/05 12:33:49 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/24/05 12:43:37 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-774

DISCIPLINE REVIEW LETTER

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

Attention: Debra P. Gayda, Ph.D.
Director, Drug Regulatory Affairs

Dear Dr. Gayda:

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

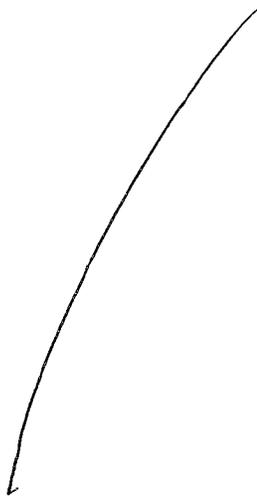
Our reviews of the carton and container labels are complete, and we have identified the following deficiencies:

1. General Comments:

- a. Provide the 30-count blister sheet (front and back).
- b.
- c. If the commercial bottles are to be marketed with carton containers, provide the carton drawings for all of the representative configurations, with strength and count size being the only difference.
- d. Revise the established name
to “(ZOLPIDEM TARTRATE EXTENDED-RELEASE) TABLETS.”
- e. The formulation descriptor should appear in conjunction with the established name. In addition, the strength should be presented in conjunction with the proprietary name and established name. For example:

Ambien CR
(Zolpidem Tartrate Extended-Release) XX-mg Tablets
- f. Boldface the font for “ZOLPIDEM TARTRATE” to increase the prominence of the established name. Increase the prominence of the rest of the established name, i.e., “EXTENDED-RELEASE TABLETS,” accordingly.

- g. The blue colored 12.5-mg strength is difficult to see when presented on the background of the product. Please revise the coloring of the strength so it does not blend with the background yet remains differentiated from the 6.25 strength.
 - h. The obscures the proprietary and established names along with the product strength on several display panels. In addition, the color scheme makes it difficult to clearly read the label. We recommend presenting the proprietary name, the established name, and the product strength on a in lieu of the for easier readability.
- 2.



3. Commercial

a. Blisters

i. Blister Flap (6.25 and 12.5 mg 30 tablet PAK)

Provide the following information in multiple places within the blister flap to ensure the integrity of needed information in the event blister flap becomes separated from the carton or is cut into unit-dose tablets:

Proprietary and established names
Strength and lot number
Expiration date
Dosing information

ii. Ambien CR Pak (6.25 mg and 12.5 mg; 30 tablets)

- (1) Relocate the product strength juxtaposed to the proprietary name and increase its prominence.
- (2) Relocate the net quantity away from the product strength and decrease its prominence as it appears almost as prominent as the product strength.

b. Bottles

The net quantity of the 6.25-mg and 12.5-mg 100-count bottle appears as prominent as the product strength. In addition, the boxing of the net quantity of the 500-count tablets on the 6.25-mg and 12.5- mg tablets causes the reader to focus on the net quantity rather than the product strength. Decrease the prominence of the net quantity and relocate it away from the product strength to avoid confusion.

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

Sincerely,

{See appended electronic signature page}

Parinda Jani
Supervisory CSO
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sara Stradley
2/25/05 04:04:04 PM
For Parinda Jani

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Controlled Substance Staff Attn: Corinne Moody HFD-009		FROM: Bob Rappaport, M.D. Division Director, Division of Anesthetic, Critical Care and Addiction Drug Products		
DATE January 10, 2005	IND NO.	NDA NO. 21-774	TYPE OF DOCUMENT: PACKAGE INSERT	DATE OF DOCUMENT June 8, 2004
NAME OF DRUG Ambien CR	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Sedative hypnotic	DESIRED COMPLETION DATE March 11, 2005	
NAME OF FIRM: Sanofi Synthelabo				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY			<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT	
			<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER:	
CSS specialty review for Pkg Insert				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Review of package insert. Please evaluate the package insert text from an abuse liability perspective. The electronic (WORD) label is available through the EDR (NDA 21-774, June 8,, 2004 submission), as well as the annotated PDF label. The PDUFA date is April 8, 2005. Please contact Lisa E. Basham-Cruz, Regulatory Project Manager, with any questions at 301-827-7420. Please cc any formal response to Lisa Basham-Cruz (basham!). Please display our consult tracking number prominently on the cover of your response: 2005.170.A.00003 Thank you!				
SIGNATURE OF REQUESTER Lisa E. Basham-Cruz		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND <input checked="" type="checkbox"/> DFS		

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/s/

Lisa Basham-Cruz
1/10/05 05:04:13 PM
For Bob Rappaport, MD

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 10/22/04
DATE OF DOCUMENT: 6/8/04

DESIRED COMPLETION DATE: 2/15/05
PDUFA DATE: 4/8/05

ODS CONSULT#:
03-0312-1

TO: Bob Rappaport, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH: Lisa Basham-Cruz
Project Manager
HFD-170

PRODUCT NAME:

Ambien CR
(Zolpidem Tartrate Extended-Release Tablets)
6.25 mg and 12.5 mg

NDA: 21-774

DACCADP TRACKING NUMBER: 2004.170.A.00091

NDA SPONSOR:
Sanofi-Synthelabo Inc.

SAFETY EVALUATOR: Felicia Duffy, RN

DMETS RECOMMENDATIONS:

DMETS recommends implementation of the container label and carton labeling revisions outlined in the Section II of this review.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: November 9, 2004

NDA # 21-774

NAME OF DRUG: Ambien CR
(Zolpidem Tartrate Extended-Release Tablets)
6.25 mg and 12.5 mg

NDA HOLDER: Sanofi-Synthelabo Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (DACCADP) to review the container labels, carton labeling, and package insert for possible interventions to minimize medication errors.

Ambien (zolpidem tartrate) was approved on December 16, 1992 under NDA 19-908. Ambien is an immediate release formulation non-benzodiazepine hypnotic indicated for the use of short term insomnia. Ambien is also a schedule IV controlled substance and is available in 5 mg and 10 mg tablets. The usual adult dosage is 10 mg by mouth at bedtime.

Ambien CR is the extended-release formulation of the currently marketed Ambien. According to the sponsor, this new formulation will modify the release of the drug substance in order to maintain plasma concentrations of the drug in the middle of the night. Ambien CR has the same dosing interval as Ambien. Ambien CR is a schedule IV controlled substance and will be available in 6.25 mg and 12.5 mg tablets. The usual adult dosage will be 12.5 mg by mouth at bedtime.

PRODUCT INFORMATION

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia. Ambien CR has been shown to in controlled clinical studies.

The recommended dose for adults is 12.5 mg immediately before bedtime. Elderly or debilitated patients may be especially sensitive to the effects of Ambien CR (zolpidem tartrate extended-release tablets). Patients with hepatic insufficiency do not clear the drug as rapidly as normal. 6.25 mg dose is recommended in these patients. The total Ambien CR dose should not exceed 12.5 mg. Ambien CR is available in 6.25 mg and 12.5 mg strengths. The proposed packaging configuration is a 100 count and 500 count bulk bottles containing 6.25 mg or 12.5 mg, a blister package containing 30 tablets of Ambien 6.25 mg or 12.5 mg,

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the "Ambien CR" container labels, carton labeling and package insert, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

A. GENERAL COMMENTS

1. _____
2. We recommend consulting Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC) on the correct designation of the established name as _____ is not an official dosage form recognized by USP.
3. We recommend including the formulation descriptor to appear in conjunction with the established name. In addition, the strength should be presented in conjunction with the proprietary name and established name. For example:

Ambien CR
(Zolpidem Tartrate Extended-Release Tablets)
XX mg

4. The blue colored 12.5 mg strength is difficult to see when presented on the _____ of the product. Please revise the coloring of the strength so it does not blend with the background yet remains differentiated from the 6.25 mg strength.
5. The background coloring obscures the proprietary and established names along with the product strength on several display panels. In addition, the _____ color scheme makes it difficult to clearly read the label. We recommend presenting the proprietary name, the established name and the product strength on _____ lieu of the _____ id for easier readability (see examples below).

B. BLISTER FOIL (6.25 mg and 12.5 mg samples)

1. See comments A2 and A3.

2.

3. On the back panel of the blister foil, revise "6.25 mg" to read as "6.25 mg/tablet" to enhance clarity.

4.

C. BLISTER FLAP (6.25 mg and 12.5 mg 30 tablet PAK)

1. A draft of the blister flap was not provided; therefore, it is not possible to fully assess the safety of the blister label. Please forward copies of the final printed blister flap when they are available.

2.

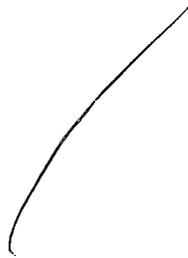
3. Please ensure the dosing instructions, lot number and expiration dates are expressed on each blister flap in the event the blister flap becomes separated from the carton, or cut into unit-dose tablets.
4. There are no instructions on the container, which inform patients how to remove the tablet from the container (e.g., Push through the foil). Additionally, it may be useful to continue using the circled numbers (e.g. ③ Push tablet through foil ... and ④ Fold flap and push) Revise accordingly.
5. Provide instructions on how to use the blister packaging in the event the blister flap becomes separated from the carton.

D. CONTAINER LABEL (100 count and 500 count bottles)

1. See comments A2 and A3.
2. The net quantity of the 6.25 mg and 12.5 mg 100 count bottle appears as prominent as the product strength. In addition, the boxing of the net quantity of the 500 count tablets on the 6.25 mg and 12.5 mg tablets causes the reader to focus on the net quantity rather than the product strength. Please decrease the prominence of the net quantity and relocate it away from the product strength to avoid confusion.

E.

F.



G. AMBIEN CR PAK (6.25 mg and 12.5 mg: 30 tablets)

1. See comments A1 through A3.
2. Relocate the product strength juxtapose to the proprietary name and increase its prominence.
3. Relocate the net quantity away from the product strength and decrease its prominence as it appears almost as prominent as the product strength.

H.



I. PACKAGE INSERT

1. In the "Information for Patients section", please include a statement about not chewing, crushing, or breaking the tablet since it is an extended-release product.
- 2.
3. Please address how health care providers are to switch patients from Ambien to Ambien CR and vice versa and if any precautions should be taken.

J. PATIENT PACAKGE INSERT

Please include a statement about not chewing, crushing, or breading the tablet since it is an extended-release product.

III. DMETS RECOMMENDATIONS:

DMETS recommends implementation of the labeling revisions outlined in Section II of this review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Felicia Duffy, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Felicia Duffy
12/2/04 08:52:30 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/2/04 09:05:41 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/2/04 10:45:39 AM
DRUG SAFETY OFFICE REVIEWER

D

9 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

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/s/

Lisa Basham-Cruz
10/21/04 01:54:13 PM
For Bob Rappaport, MD



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-774

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

Attention: Debra Gayda, PhD
Senior Director, Drug Regulatory Affairs

Dear Dr. Gayda:

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

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on August 7, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing 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.

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

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/s/

Rigoberto Roca
8/20/04 01:13:33 PM
for Bob Rappaport, M.D.



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 Geda, PhD
Senior Director, Drug Regulatory Affairs

Dear Dr. Geda:

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: Ambien CR (zolpidem tartrate — release), 6.25-mg and 12.5-mg Tablets

Review Priority Classification: Standard (S)

Date of Application: June 8, 2004

Date of Receipt: June 8, 2004

Our Reference Number: NDA 21-774

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 7, 2004, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be April 8, 2005.

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. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed, we will notify you whether we have waived the pediatric study requirement for this application.

NDA 21-774

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

Center for Drug Evaluation and Research
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at 301-827-7420.

Sincerely,

{See appended electronic signature page}

Lisa Basham-Cruz, MS
Regulatory Project Manager
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lisa Basham-Cruz
8/5/04 11:12:31 AM

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/s/

Lisa Basham-Cruz
7/1/04 03:39:07 PM

Is the application affected by the Application Integrity Policy (AIP)? YES NO
 If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

• Does the submission contain an accurate comprehensive index? YES NO

• Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

• Submission complete as required under 21 CFR 314.50? YES NO
 If no, explain:

• If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?
 All

Additional comments:

• If in Common Technical Document format, does it follow the guidance? N/A YES NO

• Is it an electronic CTD? N/A YES NO
If an electronic CTD, all certifications must be in paper and require a signature.
 Which parts of the application were submitted in electronic format?
 Modules 1, 2, 3, 5
 Certifications in paper.

Additional comments: (No Module 4 (Pharm/Tox))

• Patent information submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES, _____ years NO
 Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 25,361

- End-of-Phase 2 Meeting(s)? Date(s) 4/19/02 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) Comments sent NO
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES* NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES* NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? Schedule 4 per EOP2 minutes 4/19/04.
N/A YES NO
***planned**

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- | | | | |
|---|----------------|------------|----|
| • Did applicant request categorical exclusion for environmental assessment? | | <u>YES</u> | NO |
| If no, did applicant submit a complete environmental assessment? | | YES | NO |
| If EA submitted, consulted to Nancy Sager (HFD-357)? | | YES | NO |
| • Establishment Evaluation Request (EER) submitted to DMPQ? | pending | YES | NO |
| • If a parenteral product, consulted to Microbiology Team (HFD-805)? | | YES | NO |

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

YES	NO
-----	----
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

YES	NO
-----	----
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

YES	NO
-----	----
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

___ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

YES NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

YES NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A YES NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?)

N/A YES NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES

NO

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 16, 2004

BACKGROUND: NDA 19-908 for Ambien approved 12/16/92. This application is for a modified-release formulation. The proposed indication is for treatment of insomnia. The IR formulation is approved for short-term treatment of insomnia.

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Elizabeth McNeil
Secondary Medical:	
Statistical:	Joan Buenconsejo
Pharmacology:	Adam Wasserman
Statistical Pharmacology:	
Chemistry:	Danae Christodoulou
Environmental Assessment (if needed):	
Biopharmaceutical:	David Lee
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
Regulatory Project Management:	Lisa Basham-Cruz
Other Consults:	CSS: TBD DDMAC: TBD ODS: TBD

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO

CLINICAL MICROBIOLOGY NA X FILE _____ REFUSE TO FILE _____

STATISTICS FILE X REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA X FILE X REFUSE TO FILE

- GLP inspection needed: YES NO

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

X No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-170

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/s/

Lisa Basham-Cruz
8/10/04 02:40:02 PM
CSO

45 DAY MEETING CHECKLIST
(Answer Yes or No to the questions below)

FILEABILITY:

On initial overview of the NDA application: NDA-21774 (Zolpidem-MR) EFC4529 and EFC4530

STATISTICAL:

- (1) On its face, is the statistical section of the NDA organized in a manner to allow substantive review to begin? **YES**
- (2) Is the statistical section of the NDA indexed and paginated in a manner to allow substantive review to begin? **YES**
- (3) On its face, is the statistical section of the NDA legible so that substantive review can begin? **YES**
- (4) On its face, do there appear to be at least two adequate and well-controlled studies in the application? **YES**
- (5) Are the pivotal efficacy studies of appropriate design to meet the basic requirements for approvability of this product based on proposed draft labeling? **YES**
- (6) Are all the data sets for pivotal efficacy studies 'complete for all indications (infections) requested? **YES**
 - (a) Line listings by Center
 - (b) Intermediate analysis summary tables
 - (c) Pathogen listing
 - (d) Adverse events listing by Center
 - (e) Lost subject/patient tables by reason, time of loss, and center
- (7) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? **YES**
- (8) From a statistical perspective, is this NDA fileable? If "no", please state below why it is not. **YES**

Request to be conveyed to the sponsor: Submit SAS programs that generated the efficacy results

Joan Buenconsejo 06/29/04

Reviewing Statistician Date
Thomas Permutt, Ph.D. 06/29/04

Supervisory Statistician Date

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/s/

Joan Buenconsejo
6/29/04 04:51:23 PM
BIOMETRICS

Thomas Permutt
7/1/04 09:39:29 AM
BIOMETRICS
concur

NDA FILEABILITY CHECKLIST

NDA Number: 21-774

Applicant: Sanofi Synthelabo Inc.

Stamp Date: 6/08/04

1. **Drug Name:** AMBIEN™ CR (zolpidem tartrate) — release tablets, 12.5 mg (adults), 6.5 mg (elderly)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		Ambien CR (zolpidem tartrate — release tablets, 12.5 mg (adults), 6.5 mg (elderly) A new formulation
2	Is the section indexed and paginated adequately?	√		The submission is electronic in CTD format and appears to be very well written and complete.
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		<p>SANOFI WINTHROP INDUSTRIE 30-36 avenue Gustave Eiffel BP 27166 37100 Tours FRANCE</p> <ul style="list-style-type: none"> - Release of drug substance - Release of excipients and primary packaging components - Drug product manufacture - In-process testing of drug product - Packaging - Labeling - Release of drug product (bulk and packaged) - Stability testing • CFN: 9617678 (from EES) <p>SANOFI WINTHROP Inc. 6244 Lemay-Ferry Road Saint Louis, Missouri 63129 USA</p> <ul style="list-style-type: none"> - Receipt of bulk tablets - Packaging - Labeling - Final release of packaged products (P. 93/274) • CFN: 1931809 (from EES)
5	Is a statement provided that all facilities are ready for GMP inspection?		√	However, the product AMBIEN Tablets is currently marketed. Reference is made to NDA 19-806.
6	Has an environmental assessment report or categorical exclusion been provided?	√		Categorical exclusion is provided (Vol. 1, Item 1.2.1.9.)
7	Does the section contain controls for the	√		Drug Substance, Item 3.2.S – p. 3-7

	drug substance?			Reference is made to NDA 19-908, AMBIEN tablets, and DMF _____
8	Does the section contain controls for the drug product?	√		Specifications, Item 3.2.P.5.1 – p. 127-184
9	Has stability data and analysis been provided to support the requested expiration date?	√		_____ stability data are provided in the NDA and _____ data will be provided in 11/2004 as agreed in the pre-NDA meeting. The expiration date proposed is 18 months. (Stability, Item 3.2.P.5.6.4 – p. 185)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		Reference is made to the pre-NDA meeting of 11/18/2003 and IND 25,361. Stability data are provided as agreed in the pre-NDA meeting.
11	Have draft container labels been provided?	√		Vol. 1, Item 1.2.3
12	Has the draft package insert been provided?	√		Vol. 1, Item 1.2.2.2.1
13	Has an investigational formulations section been provided?	√		Pharmaceutical development Section, Item 3.2.P.2 – p.19 and Formulation development, Item 3.2.P.2.2.1 – p.27 are included.
14	Is there a Methods Validation package?	√		3.2.R.4 Method validation package (p. 5-52, electronic submission) Validation is included for the following analytical methods which are applied to 6.25 mg and 12.5 mg Zolpidem-MR tablets: - assay of zolpidem tartrate - degradation product: _____ - dissolution test. A summary of the validation results is given in Table (3.2.R.4.1) 1 and in Table (3.2.R.4.2) 1. Validation terms are those described in the current ICH guidelines for the validation of analytical procedures. Analytical Methods, Item 3.2.P.5.2 – p. 127 and Methods Validation, Item 3.2.P.5.3 – p.150 Sections have been provided also in the drug Product Section of the NDA.
15	Is a separate microbiological section included?		√	_____ are included in the specifications. Testing according to _____ (135/274)

Have all DMF References been Identified? YES

References are made to: NDA 19-908, AMBIEN Tablets

DMF Number	Holder	Description	LOA Included (Vol. 1, Item 1.2.1.7)	Status
_____	_____	_____	Yes	V. 2, 3/1998 Updated
Type II				

			12/10/2001
			Yes
Type III			Yes

Comments:

The NDA is fileable from a CMC perspective.

The proposed modified release formulation consists of a two-layer tablet that provides biphasic release of zolpidem: immediate followed by prolonged release. The new formulation is intended to modify drug substance release for sleep maintenance. The modified release formulation is based on the marketed immediate release formulation with similar excipients. Coatings and colors are different. New excipients in the AMBIEN CR Tablets are colloidal silicon dioxide and potassium bitartrate. Updated drug substance specifications have been approved in NDA 19-908/SCS-016. [redacted] is the manufacturer of the drug substance for both NDAs. The drug substance zolpidem bitartrate is referenced to [redacted]

[redacted] Specifications for AMBIEN CR Tablets include most of the testing for AMBIEN tablets and additional tests. The specifications for degradation products and dissolution are provided according to the ICH Guidelines. Batch analysis (release data for the drug product) are provided (3 primary batches for each strength, p. 153-156). Stability data are provided for [redacted] (normal and accelerated); the [redacted] data will be amended in November 2004. The proposed expiration dating is 18 months. AMBIEN CR Tablets will be marketed in bottles of 100 and 500-count for both strengths [redacted]

[redacted] are referenced to Type III DMFs. A claim for categorical exclusion from preparing an EA is provided. Proposed draft PI and container labels are provided. The trade name "AMBIEN CR" is acceptable by initial FDA review (Letter 5/14/2004, Vol. 1, p. 5/26). Sanofi-Synthelabo submitted Patent documentation with the filing of this NDA: US Patent # 6,54,531, Date of Issue 2/4/2004; Expiration 12/1/2019.

Review Chemist: D. Christodoulou, Ph.D.

Date: 7/13/04

Chemistry Team Leader: R. Harapanhalli, Ph.D.

Date:

cc:
Original NDA 21-774
HFD-170/Division File
HFD-170/LBasham-Cruz
HFD-170/DChristodoulou
HFD-170/RHarapanhalli
HFD-820/EDuffy

File: NDA21774FILEABILITY.DOC

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/s/

Danae Christodoulou
7/14/04 09:58:41 AM
CHEMIST

Ravi Harapanhalli
7/14/04 10:56:27 AM
CHEMIST