CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21774Orig1s003

Trade Name: AMBIEN CR

Generic or Proper Name: zolpidem tartarte

Sponsor: Sanofi Aventis

Approval Date: 12/20/2007

Indication:

Ambien CR is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-774/S-003/S-004/S-005/S-007/S-008

Sanofi Aventis U.S., LLC
300 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Attention: Qinghua (Sarah) Ji, M.D.
Assistant Director, Regulatory Development

Dear Dr. Ji:

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

Application	Submitted on:	Received on:	Provides for:
S-003	February 20, 2007	February 20, 2007	Efficacy Supplement for increase duration of use (6 months) of Ambien CR 12.5 mg (adults) and 6.25 mg (elderly)
S-004	March 7, 2007	March 8, 2007	"Changes Being Effected" Supplement; revisions to Warnings and Precautions section
S-005	April 17, 2007	April 18, 2007	"Changes Being Effected" Supplement; revisions to Warnings and Precautions section and Overdosage section
S-007	August 14, 2007	August 15, 2007	"Prior Approval" Supplement; Medication Guide
S-008	September 20, 2007	September 20, 2007	"Prior Approval" Supplement; Drug-Drug Interaction

We also acknowledge receipt of your amendments to these applications dated April 17, 2007, May 23, 2007, August 28, 2007 and September 20, 2007.

We have completed our review of supplemental new drug applications **S-003 and S-007**, and they are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling and medication guide text.

Content of Labeling

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the Medication Guide). Upon receipt, we will transmit that version to the

National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 21-774/S-003."

Fulfillment of Pediatric Research Equity Act (PREA) Study Requirements

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 are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that Ambien (zolpidem) would be ineffective or unsafe in all pediatric age groups. Our determination is based upon data submitted and reviewed as part of the pediatric studies for exclusivity submitted for your Ambien immediate-release product. That information has been described in the pediatric use section of labeling.

Promotional Materials

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the enclosed product labeling and has determined that it contains significant new risk information relating to your drug product. Therefore, we are hereby informing you that all promotional materials that include representations about Ambien CR should be revised to include the new risk information immediately. These revisions should include prominent disclosure of the important new information described in the WARNINGS and PRECAUTIONS sections that appear in the revised package labeling. If you have any questions about the promotion of your drug products, please contact DDMAC by facsimile at (301)796-9878 or at the address provided below.

In addition, please send one copy to the Division of Neurology Products and two copies of both the promotional materials and the proposed package insert directly to:

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

Dear Healthcare Professional Letter

We note that, on March 14, 2007, you issued a Dear Health Care Professional Letter (DHCP) that informed healthcare professional about the risks of sleep-driving and anaphylaxis. If you have not yet done so, we request that you submit a copy of the letter to this NDA and a copy to the following address:

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

Supplemental Applications S-004, S-005 and S-008

We note that additional supplemental applications **(S-004, S-005 and S-008)**, submitted on March 8, 2007, April 17, 2007, and September 20, 2007 respectively, have been superseded by supplemental applications **S-003** and **S-007**. Therefore we will not review supplemental applications **S-004, S-005** and **S-008**, but they will be retained for our files.

Other

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

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology
Office of New Drugs 1
Center for Drug Evaluation and Research

Enclosure: Package Insert (incl Medication Guide)

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

/s/

Russell Katz

12/20/2007 03:50:15 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Ambien CR safely and effectively. See full prescribing information for Ambien CR.

Ambien CR (zolpidem tartrate extended-release) tablets Ⓒ
Initial U.S. Approval: 1992

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2007
Warnings and Precautions	
Severe anaphylactic and anaphylactoid reactions (5.2)	03/2007
Abnormal thinking and behavioral changes (5.3)	03/2007
Special populations (5.6)	04/2007

----------INDICATIONS AND USAGE----------
Ambien CR is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

----------DOSAGE AND ADMINISTRATION----------
- Adult dose: 12.5 mg once daily immediately before bedtime (2.1)
- Elderly/debilitated/hepatically impaired patients: 6.25 mg once daily immediately before bedtime (2.2)
- Tablets to be swallowed whole, not to be crushed, divided or chewed. Should not be taken with or immediately after a meal (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
6.25 mg and 12.5 mg extended-release tablets. Tablets not scored (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation (4)

----------WARNINGS AND PRECAUTIONS----------
- Need to evaluate for co-morbid diagnoses: Revaluate if insomnia persists after 7 to 10 days of use (5.1)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur (5.2)
- Abnormal thinking, behavioral changes, complex behaviors: May include "sleep-driving" and hallucinations. Immediately evaluate any new onset behavioral changes (5.3)
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose (5.3, 5.6)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation (5.4, 9.2)
- CNS depressant effects: Use can impair alertness and motor coordination. If used in combination with other CNS depressants, dose reductions may be needed due to additive effects. Do not use with alcohol (2.3, 5.5)
- Elderly/debilitated patients: Use lower dose due to impaired motor, cognitive performance and increased sensitivity (2.2, 5.6)
- Patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, mild to moderate sleep apnea: Use with caution and monitor closely (5.6)

----------ADVERSE REACTIONS----------
Most commonly observed adverse reactions (> 10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- CNS depressants: Enhanced CNS-depressant effects with combination use. Use with alcohol causes additive psychomotor impairment (7.1)
- Imipramine: Decreased alertness observed with combination use. (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed with combination use (7.1)
- Rifampin: Combination use decreases exposure to and effects of zolpidem (7.2)
- Ketoconazole: Combination use increases exposure to and effect of zolpidem (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Crosses the placenta. No studies in pregnant women. (8.1)
- Nursing mothers: Infant exposure via breast milk (8.3)
- Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7.4%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder (5.6, 8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised 12/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) in duration *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

The dose of Ambien CR should be individualized.

2.1 Dosage in adults

The recommended dose of Ambien CR for adults is 12.5 mg once daily immediately before bedtime. The total Ambien CR dose should not exceed 12.5 mg per day.

2.2 Special populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. The recommended dose of Ambien CR in both of these patient populations is 6.25 mg once daily immediately before bedtime *[see Warnings and Precautions (5.6)]*.

2.3 Use with CNS depressants

Dosage adjustments may be necessary when Ambien CR is combined with other CNS depressant drugs because of the potentially additive effects *[see Warnings and Precautions (5.5)]*.

2.4 Administration

Ambien CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of Ambien CR may be slowed by ingestion with or immediately after a meal.

3 DOSAGE FORMS AND STRENGTHS

Ambien CR is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

Ambien CR 6.25 mg tablets are pink, round, bi-convex, and debossed with A~ on one side.

Ambien CR 12.5 mg tablets are blue, round, bi-convex, and debossed with A~ on one side.

4 CONTRAINDICATIONS

Ambien CR is contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation. Observed reactions include anaphylaxis and angioedema *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Need to evaluate for co-morbid diagnoses

Because 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 that should be evaluated.** Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem.

5.2 Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

5.3 Abnormal thinking and behavioral changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g. aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation and depersonalization. In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations *[see Use in Specific Populations (8.4)]*.

Complex behaviors such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported with sedative-hypnotics, including zolpidem. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” may occur with Ambien CR alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien CR appears to increase the risk of such behaviors, as does the use of Ambien CR at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien CR should be strongly considered for patients who report a “sleep-driving” episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with “sleep-driving”, patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably.

In primarily depressed patients, worsening of depression, including suicidal thoughts and actions including completed suicides), have been reported in association with the use of

sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.4 Withdrawal effects

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs *[see Drug Abuse and Dependence (9)]*.

5.5 CNS depressant effects

Ambien CR, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, Ambien CR should only be taken immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien CR. Ambien CR showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Ambien CR is administered with such agents because of the potentially additive effects.

5.6 Special populations

Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended Ambien CR dosage is 6.25 mg in such patients to decrease the possibility of side effects *[see Dosage and Administration (2.2)]*. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with Ambien CR (zolpidem tartrate) in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien CR in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with an immediate-release formulation of zolpidem tartrate (10 mg) when compared to placebo. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be taken if Ambien CR is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received.

Ambien CR should be used with caution in patients with sleep apnea syndrome or myasthenia gravis.

Data in end-stage renal failure patients repeatedly treated with an immediate-release formulation of zolpidem tartrate (10 mg) did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required; however, these patients should be closely monitored *[see Clinical Pharmacology (12.3)]*.

A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with Ambien CR 6.25 mg in patients with hepatic compromise, and they should be closely monitored *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

Use in patients with depression: As with other sedative/hypnotic drugs, Ambien CR should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Use in pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD given an immediate-release oral solution of zolpidem tartrate, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Serious anaphylactic and anaphylactoid reactions *[see Warnings and Precautions (5.2])*
- Abnormal thinking, behavior changes, and complex behaviors *[see Warnings and Precautions (5.3)]*
- Withdrawal effects *[see Warnings and Precautions (5.4)]*
- CNS-depressant effects *[see Warnings and Precautions (5.5)]*

6.1 Clinical trials experience

Associated with discontinuation of treatment: In 3-week clinical trials in adults and elderly patients (> 65 years), 3.5% (7/201) patients receiving Ambien CR 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as compared to 0.9% (2/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with Ambien CR was somnolence (1%).

In a 6-month study in adult patients (18-64 years of age), 8.5% (57/669) of patients receiving Ambien CR 12.5 mg as compared to 4.6% on placebo (16/349) discontinued treatment due to an adverse reaction. Reactions most commonly associated with discontinuation of Ambien CR

included anxiety (anxiety, restlessness or agitation) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo, and depression (depression, major depression or depressed mood) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo.

Data from a clinical study in which selective serotonin reuptake inhibitor- (SSRI-) treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

Most commonly observed adverse reactions in controlled trials: During treatment with Ambien CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of Ambien CR were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating Ambien CR 12.5 mg, the adverse reaction profile was consistent with that reported in short-term trials, except for a higher incidence of anxiety (6.3% for Ambien CR versus 2.6% for placebo).

Adverse reactions observed at an incidence of ≥1% in controlled trials: The following tables enumerate treatment-emergent adverse reaction frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following tables were derived from results of two placebo-controlled efficacy trials involving Ambien CR. These trials involved patients with primary insomnia who were treated for 3 weeks with Ambien CR at doses of 12.5 mg (Table 1) or 6.25 mg (Table 2), respectively. The tables include only adverse reactions occurring at an incidence of at least 1% for Ambien CR patients and with an incidence greater than that seen in the placebo patients.

Table 1. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Adults (percentage of patients reporting)

Body System/Adverse Reaction *	Ambien CR 12.5 mg (N = 102)	Placebo (N = 110)
Infections and infestations		

Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
Metabolism and nutrition disorders		
Appetite disorder	1	0
Psychiatric disorders		
Hallucinations **	4	0
Disorientation	3	2
Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0
Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
Nervous system disorders		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders ***	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
Eye disorders		
Visual disturbance	3	0
Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
Ear and labyrinth disorders		
Vertigo	2	0
Tinnitus	1	0
Respiratory, thoracic and mediastinal disorders		
Throat irritation	1	0
Gastrointestinal disorders		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux disease	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		

Rash	1	0
Skin wrinkling	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0
Reproductive system and breast disorders		
Menorrhagia	1	0
General disorders and administration site conditions		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
Investigations		
Blood pressure increased	1	0
Body temperature increased	1	0
Injury, poisoning and procedural complications		
Contusion	1	0
Social circumstances		
Exposure to poisonous plant	1	0

*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.
**Hallucinations included hallucinations NOS as well as visual and hypnogogic hallucinations.
***Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Table 2. Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Elderly (percentage of patients reporting)

Body System/Adverse Reaction *	**Ambien CR 6.25 mg (N=99)**	**Placebo (N=106)**
Infections and infestations		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
Nervous system disorders		
Headache	14	11

Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders **	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		
Flatulence	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system and breast disorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.
**Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Dose relationship for adverse reactions: There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Other adverse reactions observed during the premarketing evaluation of Ambien CR: Other treatment-emergent adverse reactions associated with participation in Ambien CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed During the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate:

Immediate-release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Ambien, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic nervous system: Frequent: dry mouth. Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole: Frequent: asthenia. Infrequent: chest pain, edema, falling, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system: Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, insomnia, lethargy, lightheadedness, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime

dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system: Infrequent: infection. Rare: abscess herpes simplex herpes zoster, otitis externa, otitis media.

Liver and biliary system: Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal system: Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

Reproductive system: Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system: Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages: Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

Special senses: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

Urogenital system: Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence. Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

7 DRUG INTERACTIONS

7.1 CNS-active drugs

Since the systematic evaluations of zolpidem in combination with other CNS-active drugs have been limited, careful consideration should be given to the pharmacology of any CNS-active drug to be used with zolpidem. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem.

An immediate-release formulation of zolpidem tartrate was evaluated in healthy subjects in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated *[see Warnings and Precautions (5.5)]*.

A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following five consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

7.2 Drugs that affect drug metabolism via cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes has not been carefully evaluated.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female subjects between five consecutive daily doses of rifampin (600 mg) and a single dose of an immediate-release formulation of zolpidem tartrate (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

A randomized double-blind crossover interaction study in twelve healthy subjects showed that co-administration of a single 5 mg dose of immediate-release zolpidem tartrate with ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased Cmax of zolpidem by a factor of 1.3 and increased the total AUC of zolpidem by a factor of 1.7 compared to zolpidem alone and prolonged the elimination half-life by approximately 30% along with an increase in the pharmacodynamic effects of zolpidem. Caution should be used when ketoconazole is given with zolpidem and consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together. Patients should be advised that use of Ambien CR with ketoconazole may enhance the sedative effects.

7.3 Other drugs with no interaction with zolpidem

A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in normal subjects.

7.4 Drug-laboratory test interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of Ambien CR in pregnant women. Ambien CR should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Oral studies of zolpidem in pregnant rats and rabbits showed adverse effects on the development of offspring only at doses greater than the maximum recommended human dose (MRHD of 12.5 mg/day). These doses were also maternally toxic in animals. A teratogenic effect was not observed in these studies. Administration to pregnant rats during the period of organogenesis produced dose-related maternal toxicity and decreases in fetal skull ossification at doses 20 to 100 times the MRHD. The no-effect dose for embryo-fetal toxicity was 4 times the MRHD. Treatment of pregnant rabbits during organogenesis resulted in maternal toxicity at all doses studied and increased post-implantation embryo-fetal loss and under-ossification of fetal sternebrae at the highest dose (30 times the MRHD). The no-effect level for embryo-fetal toxicity was approximately 8 times the MRHD. Administration to rats during the latter part of pregnancy and throughout lactation produced maternal toxicity and decreased pup growth and survival at doses approximately 20 to 100 times the MRHD. The no-effect dose for offspring toxicity was approximately 4 times the MRHD.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hypnotic drugs during pregnancy.

8.2 Labor and delivery

Ambien CR has no established use in labor and delivery *[see Pregnancy (8.1)*].

8.3 Nursing mothers

Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal subjects (2.6 ± 0.3 hr). Between 0.004% and 0.019% of the total administered dose is excreted into milk. The effect of zolpidem on the nursing infant is not known. Caution should be exercised when Ambien CR is administered to a nursing mother.

8.4 Pediatric use

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) *[see Warnings and Precautions (5.6)]*. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

FDA has not required pediatric studies of Ambien CR in the pediatric population based on these efficacy and safety findings.

8.5 Geriatric use

A total of 99 elderly (≥ 65 years of age) received daily doses of 6.25 mg Ambien CR in a 3-week placebo-controlled study. The adverse reaction profile of Ambien CR 6.25 mg in this population was similar to that of Ambien CR 12.5 mg in younger adults (≤ 64 years of age). Dizziness was reported in 8% of Ambien CR-treated patients compared with 3% of those treated with placebo.

The dose of Ambien CR in elderly patients is 6.25 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs *[see Warnings and Precautions (5.6)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled substance

Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

9.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg effects were difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

9.3 Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The following adverse events, which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal, were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. Post-marketing reports of abuse, dependence and withdrawal have been received.

10 OVERDOSAGE

10.1 Signs and symptoms

In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise and fatal outcomes have been reported.

10.2 Recommended treatment

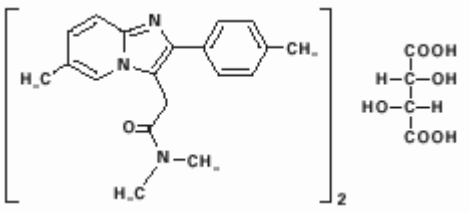
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

11 DESCRIPTION

Ambien CR contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Ambien CR (zolpidem tartrate extended-release tablets) is available in 6.25 mg and 12.5 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.
Ambien CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content. The 6.25 mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide. The 12.5 mg Ambien CR tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate,

microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

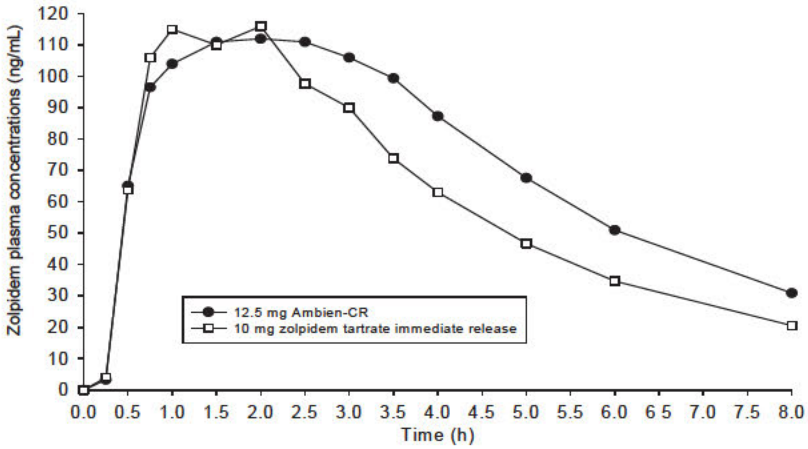
Subunit modulation of the $GABA_A$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the $GABA_A$ receptor complex is located on its alpha (α) subunit and is referred to as the benzodiazepine (BZ) receptor.

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines, or other drugs with known hypnotic properties. In contrast to the benzodiazepines, which nonselectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the $alpha_1/alpha_5$ subunits. The BZ_1 receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the BZ_1 receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

12.3 Pharmacokinetics

Ambien CR exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond three hours after administration. A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of Ambien CR 12.5 mg and of an immediate-release formulation of zolpidem tartrate (10 mg). The terminal elimination half-life observed with Ambien CR (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg). The mean plasma concentration-time profiles are shown in Figure 1.

Figure 1: Mean plasma concentration-time profiles for Ambien CR (12.5 mg) and immediate-release zolpidem tartrate (10 mg)



In adult and elderly patients treated with Ambien CR, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

Absorption:
Following administration of Ambien CR, administered as a single 12.5 mg dose in healthy male adult subjects, the mean peak concentration (C_{max}) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/ml) occurring at a median time (T_{max}) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy subjects compared the pharmacokinetics of Ambien CR 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 23% and 30%, respectively, while median T_{max} was increased from 2 hours to 4 hours. The half-life was not changed. These results suggest that, for faster sleep onset, Ambien CR should not be administered with or immediately after a meal.

Distribution:
Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL.

Metabolism:
Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination:
When Ambien CR was administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

Special Populations

Elderly:
In 24 elderly (≥ 65 years) healthy subjects administered a single 6.25 mg dose of Ambien CR, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (T_{max}) of 2.0 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

Hepatic Impairment:
Ambien CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency *[see Dosage and Administration (2.2) and Warnings and Precautions (5.6)]*.

Renal Impairment:
Ambien CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl_{Cr} = 6.5 ± 1.5 mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally-impaired patients. No dosage adjustment is necessary in patients with compromised renal function. However, as a general precaution, these patients should be closely monitored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis:
Zolpidem tartrate was administered to CD-1 mice and Sprague-Dawley rats for two years at dietary dosages of 4, 18, and 80 mg/kg/day. No evidence of carcinogenic potential was observed in either mice or rats at doses up to 80 mg base/kg/day (40 and 80 times the maximum recommended human dose [MRHD] of Ambien CR 12.5 mg [10 mg zolpidem base], respectively, on a mg/m^2 basis).

Mutagenesis:
Zolpidem did not have mutagenic activity in several tests including an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* mammalian gene forward mutation assay in mouse lymphoma cells, and an *in vitro* unscheduled DNA synthesis in rat hepatocytes. Zolpidem was not clastogenic in an *in vitro* chromosomal aberration assay in human lymphocytes or in an *in vivo* micronucleus test in mice.

Impairment of fertility:
Zolpidem tartrate was administered by oral gavage to Sprague-Dawley rats at doses of 4, 20, or 100 mg base/kg/day. Treatment of males began 71 days prior to mating and continued through mating while treatment of females began 14 days prior to mating and continued through mating, gestation, and weaning which occurred on post partum Day 25. Zolpidem administered at 100 mg base/kg was associated with irregular estrus cycles and prolonged pre-coital intervals, but did

not produce a decline in fertility. The no-effect dose was 20 mg base/kg/day (20 times the MRHD of Ambien CR on a mg/m^2 basis).

14 CLINICAL STUDIES

14.1 Controlled clinical trials

Ambien CR was evaluated in three placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

Adult outpatients (18-64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo. Ambien CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Ambien CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment. Ambien CR 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

Elderly outpatients (≥ 65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Ambien CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment. Ambien CR 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, in patients treated with Ambien CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

In a 24-week double-blind, placebo controlled, randomized study in adult outpatients (18-64 years) with primary insomnia (N=1025), Ambien CR 12.5 mg administered as needed (3 to 7 nights per week) was superior to placebo over 24 weeks, on patient global impression regarding aid to sleep, and on patient-reported specific sleep parameters for sleep induction and sleep maintenance with no significant increased frequency of drug intake observed over time.

14.2 Studies pertinent to safety concerns for sedative/hypnotic drugs

Next-day residual effects: In five clinical studies [three controlled studies in adults (18-64 years of age) administered Ambien CR 12.5 mg and two controlled studies in the elderly (≥ 65 years of age) administered Ambien CR 6.25 mg or 12.5 mg], the effect of Ambien CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with Ambien CR 12.5 mg and 6.25 mg using self-ratings of sedation.

During the 3-week studies, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg Ambien CR versus 2% of the placebo group; next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg Ambien CR versus 5% of the placebo group *[see Adverse Reactions (6)]*. In a 6-month study, the overall incidence of next-day somnolence was 5.7% in the Ambien CR group as compared to 2% in the placebo group.

Rebound effects: Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two 3-week placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of Ambien CR. On the second night, there was no worsening compared to baseline in the Ambien CR group.

In a 6-month placebo-controlled study in which Ambien CR was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

Ambien CR 6.25 mg tablets are composed of two layers* and are coated, pink, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5501-31	bottle of 100
0024-5501-50	bottle of 500
0024-5501-10	carton of 30 unit dose
0024-5501-34	carton of 100 unit dose

Ambien CR 12.5 mg tablets are composed of two layers* and are coated, blue, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5521-31	bottle of 100
0024-5521-50	bottle of 500
0024-5521-10	carton of 30 unit dose
0024-5521-34	carton of 100 unit dose

*Layers are covered by the coating and are indistinguishable.
Store between 15°-25° C (59°-77°F). Limited excursions permissible up to 30° C (86°F)

17 PATIENT COUNSELING INFORMATION

Prescribers or other healthcare professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics, should counsel them in its appropriate use, and should instruct them to read the accompanying Medication Guide *[see Medication Guide (17.4)]*.

17.1 Severe anaphylactic and anaphylactoid reactions

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

17.2 Sleep-driving and other complex behaviors

There have been reports of people getting out of bed after taking a sedative-hypnotic and driving their cars while not fully awake, often with no memory of the event. If a patient experiences such an episode, it should be reported to his or her doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when Ambien CR is taken with alcohol or other central nervous system depressants *[see Warnings and Precautions (5.3)]*. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events.

In addition, patients should be advised to report all concomitant medications to the prescriber. Patients should be instructed to report events such as "sleep-driving" and other complex behaviors immediately to the prescriber.

17.3 Administration instructions

Patients should be counseled to take Ambien right before they get into bed and only when they are able to stay in bed a full night (7-8 hours) before being active again. Ambien CR tablets should not be crushed, divided, or chewed, and should not be taken with or immediately after a meal. Advise patients NOT to take Ambien CR when drinking alcohol.

17.4 Medication Guide

MEDICATION GUIDE
AMBIEN CR® (ām'bē-ən see ahr**) C-IV**
(*zolpidem tartrate extended-release tablets*)

Read the Medication Guide that comes with AMBIEN CR before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about AMBIEN CR?

After taking AMBIEN CR, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with AMBIEN CR. Reported activities include:

- driving a car ("sleep-driving")
- making and eating food
- talking on the phone
- having sex

- sleep-walking

Call your doctor right away if you find out that you have done any of the above activities after taking AMBIEN CR.

Important:
1. Take AMBIEN CR exactly as prescribed

- Do not take more AMBIEN CR than prescribed.
- Take AMBIEN CR right before you get in bed, not sooner.

2. Do not take AMBIEN CR if you:

- drink alcohol
- take other medicines that can make you sleepy. Talk to your doctor about all of your medicines. Your doctor will tell you if you can take AMBIEN CR with your other medicines.
- cannot get a full night's sleep

What is AMBIEN CR?
AMBIEN CR is a sedative-hypnotic (sleep) medicine. AMBIEN CR is used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep
- waking up often during the night

AMBIEN CR is not for children.

AMBIEN CR is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep AMBIEN CR in a safe place to prevent misuse and abuse. Selling or giving away AMBIEN CR may harm others, and is against the law. Tell your doctor if you have ever abused or have been dependent on alcohol, prescription medicines or street drugs.

Who should not take AMBIEN CR?
Do not take AMBIEN CR if you are allergic to anything in it. See the end of this Medication Guide for a complete list of ingredients in AMBIEN CR.

AMBIEN CR may not be right for you. Before starting AMBIEN CR, tell your doctor about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant, or breastfeeding

Tell your doctor about all of the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects. **Do not take AMBIEN CR with other medicines that can make you sleepy.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take AMBIEN CR?

- Take AMBIEN CR exactly as prescribed. Do not take more AMBIEN CR than prescribed for you.
- **Take AMBIEN CR right before you get into bed.**
- **Do not take AMBIEN CR unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**
- Swallow AMBIEN CR Tablets whole. Do not chew or break the tablets. Tell your doctor if you cannot swallow tablets whole.
- For faster sleep onset, AMBIEN CR should NOT be taken with or immediately after a meal.
- Call your doctor if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much AMBIEN CR or overdose, call your doctor or poison control center right away, or get emergency treatment.

What are the possible side effects of AMBIEN CR?

Serious side effects of AMBIEN CR include:

- **getting out of bed while not being fully awake and do an activity that you do not know you are doing.** (See "What is the most important information I should know about AMBIEN CR?)
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN CR.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using AMBIEN CR.

The most common side effects of AMBIEN CR are:

- headache
- sleepiness
- dizziness
- You may still feel drowsy the next day after taking AMBIEN CR. **Do not drive or do other dangerous activities after taking AMBIEN CR until you feel fully awake.**

After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as: trouble sleeping, nausea, flushing, lightheadedness, uncontrolled crying, vomiting, stomach cramps, panic attack, nervousness, and stomach area pain.

These are not all the side effects of AMBIEN CR. Ask your doctor or pharmacist for more information.

How should I store AMBIEN CR?

- Store AMBIEN CR at room temperature, 59° to 77°F (15° to 25° C).
- **Keep AMBIEN CR and all medicines out of reach of children.**

General Information about AMBIEN CR

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use AMBIEN CR for a condition for which it was not prescribed.
- Do not share AMBIEN CR with other people, even if you think they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about AMBIEN CR. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about AMBIEN CR that is written for healthcare professionals. For more information about AMBIEN CR, call 1-800-633-1610 or visit www.ambiencr.com.

What are the ingredients in AMBIEN CR?

Active Ingredient: Zolpidem tartrate

Inactive Ingredients: The 6.25 mg tablets contain: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide. The 12.5 mg tablets contain: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

Rx Only

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

December 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	003
Submission Code	ES
Letter Date	February 20 2007
Stamp Date	February 20 2007
PDUFA Goal Date	December 21 2007
Reviewer Name	D. Elizabeth McNeil, MD
Review Completion Date	November 13, 2007
Established Name	Zolpidem tartrate controlled release tablets
(Proposed) Trade Name	Ambien CR
Therapeutic Class	Sedative-hypnotic
Applicant	sanofi
Priority Designation	S
Formulation	Controlled release tablets
Dosing Regimen	One po QHS
Indication	Insomnia
Intended Population	Adults with primary insomnia

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

I recommend approval of this efficacy supplement.

The dosage and indication section should include the information that the long term studies were done in adults only.

The initial studies of Ambien CR demonstrated that the immediate increase in sleep maintenance benefit may be expected to last up to 6 (elderly) or 7 hours (adults). When objectively evaluated by polysomnography after a fortnight of use, the sleep maintenance benefit decreases to 4 hours (elderly) or 5 hours (adults), however, there seems to be a sustained subjective benefit in the adult population as evidenced by the results from this study.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There is no recommended risk management activity for this product.

1.2.2 Required Phase 4 Commitments

There are no required Phase 4 commitments for this product.

In light of the safety findings from the trial of zolpidem in pediatric patients, I recommend a waiver of the PREA requirement for testing of zolpidem-MR in pediatric patients. It is unclear that the potential benefit could outweigh the risk of psychiatric adverse events.

1.2.3 Other Phase 4 Requests

There are no optional or recommended Phase 4 requests for this product.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zolpidem tartrate is an imidazopyridine class hypnotic currently marketed by Sanofi as an immediate release formulation under the trade name Ambien (NDA 19-908) and as Ambien CR (NDA 21-774), a bilayer formulation which is intended to produce immediate as well as sustained release of zolpidem.

The sponsor submitted a Phase III study, LTE 5407, a double-blind, randomized, placebo-controlled, parallel group study which used a subjective endpoint to evaluate the efficacy of zolpidem-MR 12.5 mg used on a chronic intermittent basis by adults aged 18 to 64 years old.

[*Reviewer's note: This study specifically excluded elderly patients so we cannot comment on the potential for long-term benefit in persons who are 65 years old or older*.]

1.3.2 Efficacy

The sponsor demonstrated that Ambien CR provided subjective improvement in sleep induction and sleep maintenance in patients with chronic primary insomnia at the end of 12 weeks, which was the pre-specified primary study endpoint.

The sponsor's analysis, with which we concurred, showed that the effect remained statistically significant throughout the double blind study period of 24 weeks.

1.3.3 Safety

While there may be an increased risk of anxiety with long-term use, consistent with the development of physical dependence, this study did not otherwise reveal any new safety concerns with long-term use of Ambien CR. However, it is of interest that 4 of the 25 reported SAEs involved perforated viscera, either appendix or colonic diverticulum. This is an unexpected finding and of unclear relation to use of zolpidem-MR.

During this 6-month study, 57 of the 238 active-drug recipients who discontinued did so due to an adverse event. While the adverse event profile was similar to that seen in the original NDA submission, it was notable that the incidence of anxiety was higher at 6.3% in the active treatment group as compared to 2.6% for the placebo group.

1.3.4 Dosing Regimen and Administration

The proposed dose of Ambien-MR is based upon the known pharmacokinetic/pharmacodynamic activity of zolpidem as well as the data from a double-blind, placebo-controlled, 10-way crossover phase I study (PDY 4054) which compared the pharmacodynamic effects of eight formulations of zolpidem-MR to the currently marketed immediate release form of zolpidem. [*Reviewer's note: This study was discussed in the initial review for Ambien CR; the interested reader is referred to that review for further details*.]

Oral administration of this product is appropriate.

1.3.5 Drug-Drug Interactions

The sponsor assessed drug-drug interactions between zolpidem–MR and concomitantly used cytochrome 450 inhibitors during the two Phase 3 studies done for the initial approval. The current label addresses interactions seen with CNS-active drugs as well as cimetidine, ranitidine, and digoxin.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolpidem tartrate is an imidazopyridine class hypnotic with an affinity for the benzodiazepine (BZ_1) receptor of $GABA_A$.

Sanofi currently markets an immediate release form of zolpidem (Ambien) as well as this modified release formulation, Ambien CR. Various generic manufacturers also market zolpidem in an immediate release formulation.

The sponsor proposes that this product, Ambien CR, be used for the treatment of chronic insomnia, recommending one tablet be taken at bedtime. This medication is for use in the adult population, including the elderly. This formulation has not been studied in pediatric patients.

2.2 Currently Available Treatment for Indications

Currently there are six FDA approved products indicated for the treatment of chronic insomnia: Halcion (triazolam); Prosom (estazolam); Ambien (zolpidem); Sonata (zaleplon); Lunesta (eszopiclone); Rozerem (ramelteon).

A number of other products are used off-label to treat chronic insomnia e.g. tricyclic antidepressants, anxiolytics, and antihistamines.

2.3 Availability of Proposed Active Ingredient in the United States

Zolpidem tartrate is currently being marketed by Sanofi as Ambien (an immediate-release formulation) and as Ambien CR.

There have been recent labeling changes for this product:

- February 2006: The Division requested that all manufacturers of sedative hypnotics modify their indications section to clearly state the duration of the efficacy trials performed while removing the "short-term" language from the indication. Additionally changes were made to the drug abuse and dependence section to more clearly reflect our current thinking.
- December 2006: The Division requested that all manufacturers of sedative-hypnotics modify their labels to include information on severe anaphylactic/anaphylactoid reactions as well as complex sleep related behaviors, including "sleep-driving." Sanofi, and other manufacturers of sedative-hypnotics were told that they should issue a Medication Guide for provision to patients.
- August 2007: Sponsors of sedative-hypnotic products were asked to make changes to the WARNINGS section to address worsening of depression and suicide.

2.4 Important Issues With Pharmacologically Related Products

The safety concerns associated with the hypnotics include next-day residual effects as well as neuropsychiatric adverse events such as confusion, amnesia, hallucinations, and worsening of psychiatric disorders, especially when the medications are not taken immediately before bedtime.

The next-day residual effects on attention and vigilance are evaluated during the development plan for drugs in the sedative/hypnotic group. Some sponsors are beginning to develop methods to specifically evaluate next-day driving ability.

The known neuropsychiatric adverse events are predominantly handled through labeling. These labels for these drugs all specify that the drug is to be taken at bedtime. When people do not take the drug immediately before bed, they may experience confusion as well as lacunar amnesia for their actions between ingestion of the pill and actually falling asleep.

Ambien has been reported (http://www.erowid.org/pharms/zolpidem/zolpidem.shtml) to provide the following sensations when used at a time other than right before going to sleep: a transient sense of "social togetherness", loss of inhibition, thinking difficulties, balance difficulties, loss of motor control, amnesia, heightened sense of relaxation, dissociation, distorted depth perception and visual/auditory hallucinations. [*Reviewer's note: These reports are spontaneous accounts of off-label use.]*

2.5 Presubmission Regulatory Activity

There was no presubmission regulatory activity for this application other than that which was described in section 2.3.

2.6 Other Relevant Background Information

Prior to completion of this review there were two supplemental labeling request amendments for this product:

SLR 004 [redacted] (b) (4) because the changes recommended for the Ambien immediate release product had to be incorporated into the label for this product. Those recommended changes have been incorporated into the current labeling recommendations for this action.

SLR 007 which provided a medication guide based upon the most recent approved labeling. The medication guide can receive an approval action.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC review was performed by Dr. Nallaperumal Chidambaram of ONDQA/DPE/Branch VII. He reports that there was no new CMC information "other than some minor editorial changes to the how supplied section of the labeling and a carton of 100 count unit dose packaging configuration." He deemed the proposed changes acceptable.

3.2 Animal Pharmacology/Toxicology

There was no new pharmacology/toxicology information submitted with this efficacy supplement.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source for clinical data was the material submitted by the sponsor in support of this application. Additional data was derived from sponsor-supplied annual reports of adverse events as well as post-marketing data from the AERS database.

4.2 Tables of Clinical Studies

Table 1: Clinical studies

	Study population	**PK/PD data**	**Efficacy data**	**Safety data**
LTE 5407	Adults with insomnia		X	X

4.3 Review Strategy

The sponsor's submission was emphasized in this review.

I, Dr. D. Elizabeth McNeil, was responsible for the synthesis and documentation of the overall conclusions of this application. As both Team Leader and primary reviewer for this submission, this review represents both the clinical review as well as the CDTL review as mandated by GMRP.

The formal biometrics analyses of the efficacy data were performed by Dr.Ohidul Siddiqui, of the Office of Biostatistics.

The CMC review was performed by Dr. Nallaperumal Chidambaram of ONDQA/DPE/Branch VII.

There was no new pharmacokinetics information submitted with this efficacy supplement.

There was no new pharmacology/toxicology information submitted with this efficacy supplement.

4.4 Data Quality and Integrity

We did not select any sites for DSI inspection in association with this efficacy supplement.

4.5 Compliance with Good Clinical Practices

The sites appear to have been in compliance with good clinical practices (GCP).

4.6 Financial Disclosures

We obtained financial disclosure information from the principal and sub-investigators for study LTE 5407.

The sponsor submitted certification of the absence of disclosable interests (form 3454) for the majority of the Principal Investigators and their sub-investigators.

The sponsor disclosed a financial agreement with the following investigator (form 3455):

- (b) (6) (b) (6). He received payments "in excess of $25,000 for participation as a member of the (b) (4) for sanofi-aventis." His site enrolled (b) (6) of the 1025 randomized patients.

Reviewer's summary
The submitted financial information is complete.

The payments made to (b) (6) were unlikely to have influenced study outcome.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following is taken from my initial NDA review of this product:

> When a single 12.5 dose was administered to healthy adult males, Ambien CR was found to have the following pharmacokinetic parameters: C_{max} was 134 ng/ml (range: 68.9 to 197 ng/ml) ; T_{max}, 1.5 hours; mean AUC, 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL); mean zolpidem elimination half-life, 2.8 hours (range: 1.62 to 4.05 hr).
>
> When a single 6.25 dose was administered to healthy elderly patients, Ambien CR was found to have the following pharmacokinetic parameters: C_{max} was 70.6 ng/ml (range: 35

to 161 ng/ml) ; T_{max}, 2.0 hours; mean AUC, 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL); mean zolpidem elimination half-life, 2.9 hours (range: 1.59 to 5.50 hrs).

A food effect study revealed that when Ambien was taken with food, the mean AUC was decreased by 23%, the C_{max} was decreased by 30% with an increase in median T_{max} from 2 to 4 hours. The mean half-life was not changed.

In adult and elderly patients who were treated with Ambien CR, zolpidem plasma concentrations were measured on day 1 and day 15 approximately 9 hours post dose. Zolpidem concentrations remained stable. There was no evidence of drug accumulation after up to 15 days of use.

5.2 Pharmacodynamics

Zolpidem, though not a benzodiazepine, shares some of the pharmacological properties of the benzodiazepines. It interacts with the GABA-BZ receptor complex, preferentially binding the (ω1) receptor. This receptor is present in the substantia nigra (pars reticulata), ventral thalamic complex, pons, and globus pallidus, among other places.

5.3 Exposure-Response Relationships

Exposure-response relationships were not investigated as part of this efficacy supplement.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor proposes the following indication for this product:
Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks) and 24 weeks (using patient-reported assessment up to 24 weeks) in duration (See Section 14 Clinical Studies).

6.1.1 Methods

[*Reviewer's note: The interested reader is referred to the review by Dr. Ohidul Siddiqui of the Office of Biostatistics for detailed discussion of the statistical analysis.*]

The intent to treat (ITT) population was defined as all patients who were randomized, took at least one dose of double-blind study medication and provided at least one post baseline efficacy notation. The ITT population was compared, active vs. placebo, on the results for PGI-Item-1 at week 12. The specific statistical analysis was a Cochran-Mantel-Haenzel test with rank scores.

Week 16 data was used if the data from Week 12 was missing for a given patient. If data from both week 12 and week 16 were missing, the data from Week 8 was used.

6.1.2 General Discussion of Endpoints

This study used the following primary endpoint, patient's Global Impression (PGI)-Item 1, as assessed after 12 weeks of double blind treatment

This item is "aid to sleep" scored as follows:

- 1-helped me sleep,
- 2-did not affect my sleep or
- 3-worsened my sleep.

Reviewer's comments:
This long term study used a subjective endpoint to assess long term efficacy. The original submission had demonstrated a gradual decrease in objective efficacy with time. It is unclear whether there is any objective evidence that efficacy returns to Night 1/2 levels or stabilizes at day 15/16 levels.

The secondary endpoints are enumerated and discussed in appendix 10.1.

6.1.3 Study Design

This was a multi-center, Phase 3, randomized, double-blind, placebo-controlled, parallel group study in patients with primary chronic insomnia who were instructed to self-administer Ambien CR on an as needed basis (3 to 7 times/week) for up to 24 weeks.

6.1.4 Efficacy Findings

The sponsor found, after analysis of the primary endpoint in this subjective study, that the study drug was statistically superior to placebo "as an aid to sleep ($p<0.0001$)" when evaluated after 12 weeks of double-blind treatment .

Table 2: (taken from the study report section 8.1.1.1)

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Aid to sleep	N	251	558
	Mean (SD)	1.5 (0.6)	1.1 (0.3)
	Median	1.0	1.0
	Help for sleeping [n (%)]	129 (51.4)	501 (89.8)
	Not affect [n (%)]	111 (44.2)	51 (9.1)
	Worsened [n (%)]	11 (4.4)	6 (1.1)
	p-value		<.0001

PGM = SL80075023/LTE5407/CSR 01/BS/PGM RPT/C26 pgi.sas OUT= OUTPUT/C26 PGI CMH1 1.html (19JUN2006 - 9:49)
Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: P-value comes from CMH test with rank score
Note: SD=Standard deviation

6.1.5 Clinical Microbiology

This section is not applicable to this efficacy supplement.

6.1.6 Efficacy Conclusions

Statistician's comments:
(The following is taken verbatim from Dr. Siddiqui's review)

"The statistical findings support the efficacy of long-term zolpidem-MR treatment in patients with chronic insomnia, Zolpidem-MR 12.5 mg was effective in improving sleep induction and sleep maintenance in patients with chronic primary insomnia at the end of 12 weeks…"

Clinical reviewer's comments:
This long term study used a subjective primary endpoint to assess long term efficacy. The original submission had demonstrated a gradual decrease in objective efficacy with time. It is unclear whether there is any objective evidence that efficacy returns to Night 1/2 levels or stabilizes at week 15/16 levels.

The study results were internally consistent. The advantage of study drug was demonstrated in almost all secondary endpoints when measured at 4 week intervals up to and including Week 24.

The use of study drug was fairly constant throughout the study: the active group took 18.9 (mean) tablets during Month 1 and 19.6 tablets during Month 6, the placebo group took 16.5 (mean) tablets during Month 1 and 17.9 (mean) tablets during Month 6.

Since the sponsor wanted a 24 week claim (as evidenced by their proposed changes to the indication statement) it would have been appropriate to use 24 weeks as the primary efficacy endpoint instead of 12 weeks.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

One death was reported during this trial.

Patient #005407840035008
A 52-year-old man, whose past medical history was significant for arterial hypertension and hypercholesterolemia, was randomized to the zolpidem-MR treatment group. He was lost to follow-up on Day 3 of the double-blind treatment group. He was found dead in his home on Day 20. In section 9.3.1 of the study report, the sponsor reports that "the cause of death was unknown

and an autopsy was performed. All efforts to obtain the cause of death and autopsy report failed…"

[*Reviewer's comment: We are not provided with sufficient information to determine whether use of zolpidem-MR played any role in the patient's demise.*]

7.1.2 Other Serious Adverse Events (SAE)

There were no consistent patterns noted among the reported SAEs. However, it is of interest that 4 of the 25 reported SAEs involved perforated viscera, either appendix or colonic diverticulum. This is an unexpected finding and of unclear relation to use of zolpidem-MR.

Placebo arm

Patient # 005407840014019

This 26 year old female was hospitalized with **"lower abdominal pain**" on Day 29. She was discovered to be 5 weeks **pregnant** at that time and was withdrawn from the study.

Patient # 005407840014020

This 21 year old female was hospitalized with **"food poisoning**" on Day 9. She discontinued study participation on Day 35 due to investigator/subject request. This adverse event was probably not associated with the use of study drug.

Patient # 005407840037005

This 55 year old female was diagnosed with **possible breast cancer** one month after the end of the study. The biopsy done on Day 204 showed no evidence of malignancy.

Patient # 005407840063051

This 32 year old male was hospitalized for treatment of **dehydration** on Day 3 of the post study treatment period. He had stopped use of study drug on Day 1.

Patient # 005407840066020

This 45 year old male was hospitalized for treatment of a **cardiac stent occlusion** on Day 111. On Day 115 he had an episode of angina pectoris. He completed the study.

Patient # 005407840067008

This 52 year old male was hospitalized for treatment of **depression** on Day 12. He was noted to have had an "extensive history of mental illness including multiple suicide attempts." He "admitted to drinking 3 packs of beer or more 3 times per week, smoking marijuana, and crack cocaine. [*Reviewer's note: It is unclear why this person was not excluded from the study because of his substance abuse.*]

Patient # 005407840067010

This 59 year old male was hospitalized for treatment of **coronary artery disease** on Day 126. He discontinued on Day 131.

Zolpidem-MR treatment arm

Patient #005407840005009

This 51 year old female with no significant past medical history was discontinued from the study on Day 136 due to the discovery of possible **bladder cancer**. She was subsequently lost to follow-up. This adverse event was probably not associated with the use of study drug.

Patient # 005407840014019

This 52 year old male with no reported prior psychiatric history had a **myocardial infarction** on Day 30. He was withdrawn from the study on Day 30. He also noted daytime sedation beginning on Day 2 and lasting for 14 days. While the myocardial infarction cannot be causally linked to the use of study drug, the sedation can be.

Patient # 005407840035009

This 52 year old male was hospitalized with a **"perforated appendix**" on Day 91. While causality can not be definitively determined, it is unclear that this is completely unrelated to the use of study drug.

Patient # 005407840037005

This 54 year old male with insulin dependent diabetes had **headache related to hyperglycemia** on Day 51. This adverse event was probably not associated with the use of study drug.

Patient # 005407840048021

This 53 year old female was hospitalized with a **"perforated appendix**" on Day 86. She also had suicidal ideation reported as a NSAE. She discontinued the study on Day 86 as a result. While causality can not be definitively determined, it is unclear that this is completely unrelated to the use of study drug.

Patient # 005407840049020

This 39 year old female was struck by an automobile and had a **traumatic hematoma, a traumatic intracranial hemorrhage as well as a retroperitoneal hemorrhage** on Day 11. She discontinued study drug on Day 44 due to "investigator/patient request." While causality can not be definitively determined, it is unclear that this is completely unrelated to the use of study drug.

Patient # 005407840052008

This 61 year old female noted **orthostatic hypotension and ataxia** on Day 169, which was the day that she completed the study period. This persisted and she was hospitalized on Day 172. While causality can not be definitively determined, it is unclear that this is completely unrelated to the use of study drug.

Patient # 005407840053014

This 60 year old male had four days of **gastrointestinal bleeding**, beginning on Day 128, for which he was hospitalized. He completed the study treatment period. While causality

can not be definitively determined, it is unclear that this is completely unrelated to the use of study drug.

Patient # 005407840058001

This 64 year old female had a **worsening of her coronary artery disease** on Day 177, during the post study treatment period. She completed the treatment period on Day 164. This adverse event was probably not associated with the use of study drug.

Patient # 005407840058012

This 36 year old female was hospitalized for an emergent **cholecystectomy** on Day 128. She completed the study treatment period.

Patient # 005407840058014

This 56 year old female was hospitalized for treatment of **rectal bleeding due to a diverticulum of the colon** on Day 10. She stopped use of study drug on Day 100 "due to investigator/patient request."

Patient # 005407840058015

This 25 year old male was hospitalized for evaluation of **elevated hepatic enzymes** on day 22: ALT of 53 (1.4 x ULN) and AST of 83 (1.3 x ULN). Use of the study drug was stopped that day. On Day 50, which was 28 days after last ingestion of study drug, he suffered a **ruptured colonic diverticulum**.

Patient # 005407840061057

This 60 year old male was hospitalized for treatment of **anxiety** in association with nausea, chest tightness and elevated blood pressure on Day 44.

Patient # 005407840064001

This 21 year old female was hospitalized for treatment of **kidney stones** on Day 86. This adverse event was probably not associated with the use of study drug.

Patient # 005407840065039

This 52 year old female was hospitalized for treatment of **hypertension and alcoholic gastritis** on Day 39. She reported drinking wine, vodka and approximately 16 ounces of beer daily. She also used cannabis and cocaine. She discontinued study drug on Day 70 due to poor compliance. [*Reviewer's note: It is unclear why this person was not excluded from the study because of his substance abuse.*]

Patient # 005407840079001

This 39 year old male was hospitalized for treatment of **herpes zoster** on Day 138. This adverse event was probably not associated with the use of study drug.

Patient # 005407840079012

This 49 year old female was hospitalized for treatment of **bronchitis** on Day 40. She discontinued use of study drug on Day 42. This adverse event was probably not associated with the use of study drug.

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7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The following table, (7.1) 2, was taken directly from the study report.

Table 3: Disposition of study patients

population

	Placebo (N=351) n (%)	Zolpidem-MR 12.5 mg (N=674) n (%)	Overall (N=1025) n (%)
Treated patients	349 (99.4)	669 (99.3)	1018 (99.3)
Completed study treatment period	184 (52.4)	436 (64.7)	620 (60.5)
Study treatment discontinuation	167 (47.6)	238 (35.3)	405 (39.5)
Main reason for treatment discontinuation:			
Lack of efficacy/disease progression	82 (23.4)	32 (4.7)	114 (11.1)
Adverse event	16 (4.6)	57 (8.5)	73 (7.1)
Poor compliance to protocol	15 (4.3)	27 (4.0)	42 (4.1)
Subject's request	21 (6.0)	63 (9.3)	84 (8.2)
Subject lost to follow-up	27 (7.7)	50 (7.4)	77 (7.5)
Other reason	6 (1.7)	9 (1.3)	15 (1.5)
Completed Run-out period	221 (63.0)	465 (69.0)	686 (66.9)
Main reason for run-out period discontinuation:			
Adverse event	8 (2.3)	40 (5.9)	48 (4.7)
Poor compliance to protocol	8 (2.3)	20 (3.0)	28 (2.7)
Subject's request	60 (17.1)	78 (11.6)	138 (13.5)
Subject lost to follow-up	35 (10.0)	59 (8.8)	94 (9.2)
Other reason	19 (5.4)	12 (1.8)	31 (3.0)
Completed study treatment and run-out period	180 (51.3)	431 (63.9)	611 (59.6)

7.1.3.2 Adverse events associated with dropouts

The incidence of discontinuation due to adverse events was almost twice as high in the zolpidem arm (8.5%0 as in the placebo group (4.6%). Of those patients who discontinued due to an adverse event, 7% (5/73) in the zolpidem arm and <1% (1/57) of the placebo group discontinued due to memory impairment, coded as either memory impairment or amnesia. While none of the patients in the placebo group discontinued due to next-day somnolence as an adverse event, 11% (8/73) of the patients in the zolpidem group did so. In the zolpidem group, 14% of the patients who discontinued (10/73) discontinued due to anxiety, restlessness or agitation; an equivalent percentage discontinued due to depression, major depression or depressed mood. In the placebo group, <1% of those who discontinued did so for these specific adverse events.

Those patients who discontinued due to an SAE are not included in the listings below as they were previously discussed. Unless otherwise noted, the involved patients were receiving

zolpidem-MR. While there were many reasons for discontinuation, I have chosen to report adverse events only.

- Patient # 005407840007019
  This 43 year old female with no reported prior psychiatric history noted **depression** on Day 44. She was withdrawn from the study on Day 56. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840010003
  This 33 year old male with no reported prior psychiatric history noted **anxiety** on Day 27. He was withdrawn from the study on Day 56. This was coded as withdrawn due to investigator/patients request. His concomitant complaints of anxiety, agitation and hyperacusis resolved within 60 days after onset. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient #005407840013012
  This 46 year old female whose past medical history was notable for stress related depression noted "**decrease in concentration"** on Day 61. She was permanently withdrawn form study medication as a result of that symptom along with the asthenia, blurred vision, nausea, myalgia, headaches which she was also experiencing.

- Patient # 005407840015003
  This 61 year old female with no reported prior psychiatric history noted **anxiety** on Day 51. She was withdrawn from the study on Day 56. This was coded as off study due to investigator/patients request. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840015005
  This 49 year old female noted **anxiety and depression** on Day 30. She was withdrawn from the study on Day 49. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840016016
  This 42 year old female noted **anxiety** on Day 32 **and "disturbance in attention"** on Day 54. On the latter day she reported the following symptoms which contributed to her decision to stop taking the study drug: tremor, anorexia, agitation, diarrhea, vomiting, nausea, asthenia, paresthesia and dizziness. While she also reported memory impairment, derealization and depersonalization these were not considered contributory to the decision to discontinue. She was withdrawn from the study on Day 54. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840016019
  This 45 year old female noted **anxiety** on Day 99. She was withdrawn from the study on Day 106. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840025005
  This 52 year old male noted **anxiety and irritability** on Day 29. He noted depression on Day 36. He was withdrawn from the study on Day 46. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug. This was coded as off study due to investigator/patients request.

- Patient # 005407840025018
  This 50 year old female noted **anxiety, irritability and emotional volatility** on Day 7. She was withdrawn from the study on Day 28. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840029014
  This 58 year old female noted **decreased concentration and lack of coordination** on Day 2. She also noted dizziness, nausea, morning somnolence, and vomiting. She was withdrawn from the study on Day 2. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840029021
  This 49 year old female, with a past medical history significant for a major depressive episode, noted **depression** on Day 57. She was withdrawn from the study on Day 85. She also reported headache and morning somnolence. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840031006
  This 36 year old male noted **disturbance in attention** on Day 39. He also noted headache, irritability, depersonalization, fatigue and restlessness. He had noted morning somnolence beginning on Day 24 and withdrew from the study on Day 49 due to that symptom. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840031011
  This 50 year old male noted **disturbance in attention** on Day 88. He had noted headaches and **forgetfulness** beginning on Day 1 and withdrew from the study on Day 89 due to the latter symptom. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840031012
  This 42 year old male noted **disturbance in attention** as well as morning somnolence on Day 2. He withdrew from the study on Day 13 due to an exacerbation of insomnia which had begun on Day 3. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840035001
  This 56 year old female noted **disturbance in attention** as well as asthenia, depersonalization, dizziness, headache, myalgia, agitation, restlessness, diaphoresis, memory impairment, anorexia, derealization, and paresthesiae on Day 1. She noted

decreased cognitive functioning on Day 16. She withdrew from the study on Day 21 due to the persistence of these symptoms. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840036013
  This 55 year old female noted **disturbance in attention** on Day 2. She also noted fatigue, and poor coordination. She withdrew from the study on Day 2 due to "investigator/patient request." While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840037001
  This 61 year old male noted **depression** on Day 40. He withdrew from the study on Day 66 due to this adverse event. While there is not a clear causal connection, it is not possible to completely rule out an association with study drug.

- Patient # 005407840037013 (placebo)
  This 52 year old female, with a past medical history significant for depression, noted **anxiety** on Day 16. She was withdrawn from the study on Day 35.

- Patient # 005407840037015
  This 62 year old female noted **anxiety** on Day 2. She was withdrawn from the study on Day 20 due to this event.

- Patient # 005407840042007
  This 40 year old female noted **amnesia** on Day 11. She was withdrawn from the study on Day 12 due to this event. It should be noted that the patient thought that she might have taken the medication in the middle of the night as opposed to before bed.

- Patient # 005407840043042
  This 44 year old female noted **difficulty with concentration** on Day 3 and **anxiety** on Day 5. She was withdrawn from the study on Day 28 due to these events.

- Patient # 005407840043058
  This 59 year old female noted **depression** on Day 108, following "the last intake of the investigational product. She was withdrawn from the study on Day 108 due to these events.

- Patient # 005407840046025
  This 61 year old male noted **anxiety** on Day 5. He began noting fatigue on Day 6. He discontinued the study drug on Day 23.

- Patient # 005407840053024
  This 44 year old male noted **anxiety and dyspnea** on Day 20. He had also noted morning fatigue/somnolence beginning on Day 10. He stopped use of investigational product on Day 20 due to these symptoms.

- Patient # 005407840061055 (placebo)
  This 49 year old female noted **disturbance in attention** on Day 3 as well as depressed mood, anxiety, vivid dreams, morning somnolence on Day 4. Due to the attention disturbance, she withdrew from the study on Day 27.

- Patient # 005407840062006
  This 51 year old male noted **depression** on Day 47. the depression was related to the death of one of his parents. He stopped taking study drug on Day 112 as he wished to begin using an anti-depressant.

- Patient # 005407840063014
  This 51 year old female noted **depression** on Day 2. He stopped taking study drug on Day 7 due to this symptom.

- Patient # 005407840066014
  This 53 year old female noted **disturbance in attention** as well as memory impairment on Day 49. She withdrew from the study on Day 15.

- Patient # 005407840066031
  This 60 year old female noted **depressed mood** on Day 5. She withdrew from the study on Day 9.

- Patient # 005407840066033
  This 60 year old female noted **anxiety** on day 3. She noted lethargy and **depressed mood** on Day 4. She withdrew from the study on Day 16.

- Patient # 005407840074016
  This 48 year old female noted **disturbance in attention** as well as dizziness, poor coordination, irritability, lethargy, agitation, muscular weakness, and headache, on Day 114. She withdrew from the study on Day 127.

- Patient # 005407840074022
  This 36 year old female noted **anxiety** as well as **depression,** fatigue and anorexia on Day 121. She withdrew from the study on Day 133.

- Patient # 005407840075005
  This 25 year old female noted **amnesia (on awakening)** and morning somnolence **on Day 43.** On Day 59, she had memory impairment, depersonalization, difficulty concentrating, asthenia, poor coordination, dizziness on Day 59. She withdrew from the study on Day 58.

- Patient # 005407840076013
  This 51 year old female noted **amnesia on Day 74.** She took her last dose on Day 73 on Day73.

7.1.3.3 Other significant adverse events

Falls

Zolpidem-MR treatment arm

- Patient # 005407840001018
  This 56 year old man, whose past medical history was notable for Type II diabetes, peripheral neuropathy and cataract surgery, slipped on ice and **fell** on Day 169 (December 15 2005). On the same day he was noted to have contusions of the back and buttocks. By report he recovered from this incident within 24-48 hours. He also reported an instance of nasopharyngitis and an instance of influenza while participating in the study. He completed the entire study including the follow-up period.

- Patient # 005407840001020
  This 60 year old man, whose past medical history was notable for arthritis, slipped on ice and **fell** on Day 168, the day he completed the study period. He recovered from said fall within 24-48 hours. He also reported a sore throat, sneezing and rhinorrhea on Day 101 as well as a upper respiratory infection on Day 161.

- Patient # 005407840002015
  This 54 year old female **fell** on Day 142, abrading her left knee. She had also fallen on Day 51 after slipping on a banana peel. She sustained an abrasion above her left eyebrow as a result of that earlier fall. On Day 81, she had complained of non-cardiac chest pain. All of these complaints resolved within 24 hours.

- Patient # 005407840006008
  This 52 year old female slipped on a wet floor and **fell** on Day 121, breaking **multiple teeth**. Her study course was notable for a 24 hour period (Day 30) of acute right ear deafness. She also had an episode of headache, as well as a upper respiratory infection.

- Patient # 005407840029016
  This 49 year old female complained of rebound insomnia on Day 168. On Day 169, she had poor coordination with a resultant contusion to her head, irritability, restlessness, fatigue and difficulty concentrating.

Placebo treatment arm

- Patient #005407840002024
  This 55 year old female, whose past medical history was notable for anal cancer with subsequent radiotherapy, sustained a **toe fracture due to a fall** on Day 28. She healed from this incident within 20 days. She noted constipation on Day 44 and burning eyes with white mucoid discharge on Day 57. On Day 168, she complained of lethargy, poor coordination, lack of energy, fatigue, difficulty with remembering, and difficulty concentrating. Most of these complaints resolved within 14 days.

7.1.4 Other Search Strategies

No other search strategies were used in the review of this application.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Spontaneously reported or investigator observed adverse events were recorded for participants at the initial screening, on screening nights 1 & 2, at baseline and at study visits.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Treatment emergent adverse events (TEAE) were defined as events which occurred or worsened during study treatment, defined as the time between the first intake and up to 24 hours after the last study drug intake. The adverse event categorization and preferred terms used were appropriate in most instances.

7.1.5.3 Incidence of common adverse events

The adverse events reported with the highest incidence were headache (10.5% in the 12.5mg treatment arm, 9.5% in the placebo treatment arm), somnolence/sedation (6.9% in the 12.5mg treatment arm, 2.6% in the placebo treatment arm), dizziness (4.8% in the 12.5mg treatment arm, 2% in the placebo treatment arm).

These findings are consistent with the adverse events reported from the initial trials submitted in support of approval.

It should be noted that one of the most frequent adverse event constellations for discontinuation was the constellation of psychiatric events including anxiety and depression.

7.1.5.4 Common adverse event tables

The following is a reproduction of table (9.2.2)2 in the study report which summarizes those TEAE which both occurred at a rate of at least 1% in the zolpidem-MR population and had an incidence in that population which was greater than placebo.

Table 4: Common adverse events

Preferred term	Placebo (N=349) n (%)		Zolpidem-MR 12.5 mg (N=669) n (%)	
Headache	33	(9.5)	70	(10.5)
Anxiety	9	(2.6)	42	(6.3)
Somnolence	7	(2.0)	38	(5.7)
Dizziness	7	(2.0)	32	(4.8)
Fatigue	11	(3.2)	30	(4.5)
Disturbance in attention	6	(1.7)	29	(4.3)
Irritability	10	(2.9)	25	(3.7)
Nausea	8	(2.3)	23	(3.4)
Sinusitis	3	(0.9)	22	(3.3)
Back pain	8	(2.3)	17	(2.5)
Asthenia	7	(2.0)	16	(2.4)
Hypertension	1	(0.3)	14	(2.1)
Urinary tract infection	1	(0.3)	13	(1.9)
Vomiting	0	(0)	13	(1.9)
Influenza	6	(1.7)	12	(1.8)
Paraesthesia	4	(1.1)	12	(1.8)
Agitation	3	(0.9)	12	(1.8)
Anorexia	3	(0.9)	12	(1.8)
Contusion	2	(0.6)	10	(1.5)
Depressed mood	0	(0)	10	(1.5)
Fall	3	(0.9)	9	(1.3)
Restlessness	2	(0.6)	8	(1.2)
Sedation	2	(0.6)	8	(1.2)
Coordination abnormal	1	(0.3)	8	(1.2)
Dyspepsia	1	(0.3)	8	(1.2)
Gastroenteritis viral	1	(0.3)	8	(1.2)
Amnesia	0	(0)	8	(1.2)
Constipation	2	(0.6)	7	(1.0)

7.1.5.5 Identifying common and drug-related adverse events

The following adverse events, as may be seen in the table above, showed a consistent difference from control in the adult population studied:

- Anxiety
- Somnolence (with possible dose/response effects as shown in the initial studies)
- Dizziness
- Disturbance in attention

7.1.5.6 Additional analyses and explorations

No additional analyses or explorations were done since the adverse events listed in 7.1.5.5 are well described in the literature on zolpidem.

7.1.6 Less Common Adverse Events

Hallucinations (visual and auditory) have been described as an associated adverse event with this product.

It is of interest that 4 of the 25 reported SAEs involved perforated viscera, either appendix or colonic diverticulum. This is an unexpected finding and of unclear relation to use of zolpidem-MR.

7.1.7 Laboratory Findings

Laboratory testing was not performed as part of this clinical study.

7.1.8 Vital Signs

Vital signs were obtained at baseline at and each of the study visits. There were no notable abnormalities detected.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not performed as part of this clinical study.

7.1.10 Immunogenicity

There was no data provided to assess the impact of immunogenicity on safety, efficacy, clinical pharmacokinetics or pharmacology.

7.1.11 Human Carcinogenicity

The following text is taken directly from the currently approved label for Ambien CR:

> "Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m2 basis, respectively.
>
> No evidence of carcinogenic potential was observed in mice.
>
> Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/ day dose. Incidence

> rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence."

7.1.12 Special Safety Studies

Rebound effect:
The sponsor used WASO and TST data from the patient morning questionnaire (PMQ) to evaluate rebound both in the treatment and the post-treatment phase.

The sponsor specifically evaluated rebound during nights off-drug during the treatment period since the drug was to be taken on a chronic intermittent basis, as well as during the first 3 consecutive nights after treatment discontinuation. While a worsening of total sleep time was noted on "off-drug" night during the first month, this was not seen during subsequent months or at final discontinuation. The use of study drug was stable throughout the 24 weeks.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The following information comes from my review of the initial NDA submission for this product:

> "Withdrawal phenomena in the form of rebound effects on WASO, and SE occur on the first night after abrupt discontinuation of this drug. Rebound effects on LPS were seen in adults (EFC 4529) but not in the elderly (EFC 4530). When evaluated by the criteria used for diagnosis of drug withdrawal according to DSM-IV, hypertension (n=1) anxiety (n=2) and nausea (n=3) were seen in the group which received 12.5 mg zolpidem-MR and tremor (n=1) was seen in the group which received 6.25 mg zolpidem-MR though not in the placebo group."

In this study, increased anxiety was noted with long term use; this may represent a withdrawal effect as the level wears off during the day. Additionally, the label currently notes that "…the following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. "

This class IV controlled substance has abuse potential due to its neuropsychiatric effects.

7.1.14 Human Reproduction and Pregnancy Data

There was a single pregnancy report during this study. Patient #005407840071015, who took additional doses of study drug on Day 30, and Day 45. She was discovered to be pregnant on Day 165, the day that she completed the study period. No further information was available..

Zolpidem tartrate is currently pregnancy category C. Studies to assess the effects of zolpidem on human reproduction and development have not been conducted. Studies to assess the effects of in utero zolpidem exposure on children have not been conducted. Studies in rats showed a trend

to dose-related delay in ossification of the skull bones. The no-effect dose for fetal toxicity (rabbits) was 4 mg base/kg or 7 times the maximum human dose on a mg/m2 basis.

Studies in lactating mothers indicate that between 0.004% and 0.019% of the total administered dose is excreted into the milk. The effect of this level of exposure on the receiving infant has not been formally assessed.

7.1.15 Assessment of Effect on Growth

The effect on growth was not evaluated for this NDA as this product is not approved for use in the pediatric population.

7.1.16 Overdose Experience

There were three cases of overdose, all of which occurred during the double-blind treatment period. The cases all apparently resolved without sequelae.

- Case 1: a 20 year old female who took 2 doses on Days 31 and 46
- Case 2: a 46 year old female with an intentional overdose on Day 13 and an accidental overdose on Day 21
- Case 3: a 30 year old female, who was withdrawn from the study when it was discovered that she was intentionally overdosing by taking an extra tablet seven times between days 0 and 25.

The currently approved label for Ambien CR notes that zolpidem's sedative hypnotic effect may be reversed by administration of flumazenil.

7.1.17 Postmarketing Experience

This will be discussed in section 7.2.2.2.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter, phase IIIb clinical study to evaluate the long-term efficacy and safety of zolpidem-MR 12.5 mg compared to placebo, when administered over 6 months "as needed" to patients with chronic primary insomnia.

Eligible patients were to have had a 7-day screening run in period in which they were to take no medication. However, they were expected to complete morning questionnaires via an interactive voice recording system (IVRS), and could be excluded for non compliance.

After randomization, patients were to begin a 24-week double-blind treatment period, during which they were instructed to take 3 to 7 tablets a week on an "as needed basis." Patients were to be seen every 4 weeks, i.e. week 4, week 8 etc. The study was to end with a 7-night run-out period.

7.2.1.2 Demographics

Table 5: Demographics (study report, tables (7.4.1) 1 and (7.4.1) 2)

		Placebo (n=349)	Zolpidem-MR 12.5 mg (n=669)
Gender	Male	139 (39.8%)	256 (38.3%)
	Female	210 (60.2%)	413 (61.7%)
Ethnicity	White	230 (65.9%)	432 (64.6%)
	Black	63 (18.1%)	120 (17.9%)
	Asian	4 (1.1%)	10 (1.5%)
	Other	52 (14.9%)	107 (16%)
Age (years)	n	349	669
	Mean (SD)	45.0 (11.5)	46.0 (10.8)
	Min-Max	18-64	18-64

7.2.1.3 Extent of exposure (dose/duration)

All participants were supposed to receive a 6-month double-blind period during which they could take study drug on an as needed basis.

The following is a reproduction of the table found in appendix 14.2.5.1.1.1 of the study report, showing the maximal duration of consecutive days with study drug.

Table 6: Maximal duration of consecutive days with study drug

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=669)	Overall (N=1018)
Overall	N	349	667	1016
	Mean (SD)	14.3 (16.5)	19.5 (22.0)	17.7 (20.4)
	Median	8.0	12.0	11.0
	Min; Max	0; 123	0; 171	0; 171
Actual month 1	N	349	667	1016
	Mean (SD)	8.0 (6.8)	9.2 (7.0)	8.8 (6.9)
	Median	6.0	7.0	6.0
	Min; Max	0; 28	0; 28	0; 28
Actual month 2	N	277	589	866
	Mean (SD)	8.1 (7.1)	9.8 (7.5)	9.2 (7.4)
	Median	5.0	7.0	7.0
	Min; Max	0; 28	0; 28	0; 28
Actual month 3	N	234	538	772
	Mean (SD)	8.0 (6.7)	9.5 (7.1)	9.1 (7.0)
	Median	6.0	7.0	7.0
	Min; Max	1; 28	0; 28	0; 28
Actual month 4	N	212	498	710
	Mean (SD)	8.0 (7.0)	9.4 (7.0)	9.0 (7.1)
	Median	5.0	7.0	6.0
	Min; Max	0; 28	0; 28	0; 28
Actual month 5	N	204	467	671
	Mean (SD)	7.9 (6.6)	10.3 (7.7)	9.6 (7.5)
	Median	5.5	8.0	7.0
	Min; Max	0; 28	0; 28	0; 28
Actual month 6	N	188	448	636
	Mean (SD)	8.4 (7.0)	10.0 (7.7)	9.6 (7.5)
	Median	6.0	7.0	7.0
	Min; Max	0; 28	1; 28	0; 28

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

There were no additional studies reviewed in support of this application.

7.2.2.2 Postmarketing experience

In order to assess the post marketing experience for zolpidem in the marketed formulation, I reviewed the periodic safety update reports submitted to the Ambien NDA (#19-908) as well as the Ambien CR NDA (#21-774) since 2005.

One finding of clinical significance was the number of reports of visual hallucinations, although tactile and auditory hallucinations were also described. I observe that most of these spontaneous reports came from people who took ≥2 times the recommended dose for age. This observation would lead me to postulate that there may be a dose-response relationship: if the medicine is taken at ≥2 times the recommended dose for age, the risk of hallucination increases. We know from the controlled studies that there is a baseline risk of hallucination, even when taking the recommended dose.

I would also note that there were not infrequent complaints of withdrawal-type symptoms and of memory impairment after use of Ambien.

7.2.2.3 Literature

The sponsor provided an adequate selection of references from the sleep literature for this review.

7.2.3 Adequacy of Overall Clinical Experience

In addition to the data accrued during drug development, the agency has amassed post-marketing data on zolpidem since the approval of Ambien in December 1992 and Ambien CR in August 2005.

Although I would question the exclusion of the elderly, a population which is known to make frequent use of sedative/hypnotics, this application exposed an adequate number of adult subjects. The gender ratio was appropriate. While it may have been desirable to achieve greater ethnic diversity in the population studies, that is a problem endemic to clinical trials and not specific to this development program. Overall the inclusion/exclusion criteria were appropriate. Patients with severe or chronically progressive renal or hepatic disease would have been excluded but we already have data indicating that dose reduction is not necessary in the former group and is necessary in the latter to decrease the risk of adverse events. Patients with severe or unstable respiratory insufficiency were excluded from study participation.

The doses and durations of exposure were adequate to assess safety for the intended use of this product.

The sponsor appropriately evaluated participants for next-day residual and rebound effects which have been associated with use of the sedative/hypnotics

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

There was no new preclinical data provided for review in support of this submission. The available preclinical data comes from the NDA for Ambien.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing was limited to vital sign assessment and efforts to assess adverse events. The methods and questionnaires that the sponsor used were adequate and the assessments were done at an appropriate frequency.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The information on zolpidem tartrate metabolism, clearance and drug-drug interaction comes primarily from pre- and post-marketing experience with Ambien. The currently approved Ambien CR label contains information on the enzymatic pathways responsible for drug clearance. The label also includes information on significant drug-drug interactions for drugs such as digoxin, fluoxetine, rifampin and itraconazole.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The class specific adverse events of concern are the next-day residual effects and the rebound effect after abrupt drug discontinuation. The sponsor adequately assessed the study participants for these effects as detailed in section 7.1.12. In summary, there was no next-day residual effect seen in the adult participants. Rebound effects were seen on the first night after discontinuation but not the second night.

7.2.8 Assessment of Quality and Completeness of Data

The data provided appears to be complete and of excellent quality.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions reviewed in support of this application.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

A single study in adults was submitted in support of this efficacy supplement so there was no pooling of data done by this reviewer. The sponsor performed analyses in which this study population was combined with the adult study population used for the initial NDA submission.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

This study used a single dose so no explorations for dose dependency were performed.

7.4.2.2 Explorations for time dependency for adverse findings

Headache and morning somnolence were most pronounced, in both groups, during the first month but stabilized or decreased thereafter. The complaints of memory impairment/amnesia increased steadily in the zolpidem group to reach 5% by the end of the study.

Table 7: Time dependency for selected adverse events

	Month 1		**Months 2/3**		**Months 4/5/6**	
	Placebo N= 349	**Zolpidem N=669**	Placebo N= 314	**Zolpidem N=637**	Placebo N= 232	**Zolpidem N=529**
Headache of any sort	16 (5%)	**35(5%)**	12(4%)	**24(4%)**	11 (5%)	**30 (6%)**
Somnolence/sedation/lethargy	6 (2%)	**37(6%)**	3(<1%)	**11(2%)**	2(<1%)	**7 (1%)**
Anxiety/agitation/nervousness	1 (<1%)	**6(<1%)**	1(<1%)	**6 (<1%)**	3(1%)	**3 (<1%)**
Memory impairment/amnesia	2 (<1%)	**16 (2%)**	2(<1%)	**14(2%)**	8(3%)	**27 (5%)**
Depression of any sort	1 (<1%)	**0**	1(<1%)	**8 (1%)**	4(2%)	**8 (2%)**

7.4.2.3 Explorations for drug-demographic interactions

The susceptibility to adverse effects of sedative/hypnotic agents is known to correlate with age. In light of this the sponsor recommends using reduced doses in the elderly, as was done in the development program. There were no elderly participants in this study.

7.4.2.4 Explorations for drug-disease interactions

This submission did not contain sufficient information on concomitant diseases to allow meaningful explorations for drug-disease interactions. Although not assessed during this development program, the approved labeling for Ambien and Ambien CR notes that this product should be used with caution in patients with compromised respiratory function. The approved label also states that no dosage adjustment is needed in patients with renal dysfunction though reduced doses should be used in persons with hepatic dysfunction.

7.4.2.5 Explorations for drug-drug interactions

Explorations for drug-drug interactions were not done as part of this efficacy supplement.

7.4.3 Causality Determination

Zolpidem, as demonstrated in pre-marketing studies and post-marketing data from Ambien as well as in the studies done with zolpidem-MR may fairly be considered capable of producing the following adverse effects:

- Psychomotor retardation
- Somnolence (with possible dose/response effects)
- Dizziness
- Nausea
- Memory impairment (with possible time dependency)
- Hallucinations

There are other adverse events which have been reported but the causality is less clear in those cases.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The approved dose of Ambien-MR is based upon the known pharmacokinetic/pharmacodynamic activity of zolpidem as well as the data from study PDY 4054, a study done as part of the development program for the initial NDA. Study PDY 4054 was a double-blind, placebo-controlled, 10-way crossover phase I study which compared the pharmacodynamic effects of eight formulations of zolpidem-MR to the immediate release form of zolpidem. Formulation E (12.5 mg) was chosen since it reduced the number of awakenings for up to 5 hours post-dose without statistically significant evidence of next-day residual effects. Elderly patients are known, from experience with Ambien, to be sensitive to lower doses of zolpidem. The sponsor decided to use a half-dose (6.25 mg) in the elderly.

Once daily oral administration of this product on “an as needed (PRN)” basis is an appropriate dosing regimen for long-term use.

8.2 Drug-Drug Interactions

The sponsor evaluated for drug-drug interaction between zolpidem–MR and concomitantly used cytochrome 450 inhibitors during the two Phase 3 studies submitted for the original NDA. No pharmacodynamic effects due to use of the combinations were seen in either study.

The current label addresses interactions seen with CNS-active drugs as well as cimetidine, ranitidine, and digoxin.

8.3 Special Populations

Gender
The percentage of adult females (65.9%) who reported adverse events was similar to the percentage reported by adult males (59%).

Age
Elderly patients were not evaluated as part of this study.

Ethnicity
The number of non-Caucasian participants was too small to make any comments on possible interactions of drug and ethnicity.

Although not assessed during this development program, the approved labeling for Ambien CR notes that this product should be used with caution in patients with compromised respiratory function. The label also states that no dosage adjustment is needed in patients with renal compromise while patients with hepatic impairment should be given a reduced dose and should be monitored closely.

8.4 Pediatrics

This product is not indicated for use in children.

A study of zolpidem (Ambien IR) for the treatment of insomnia in children with ADHD failed to demonstrate efficacy but did show an increased risk of psychiatric adverse effects.

8.5 Advisory Committee Meeting

The Agency did not convene an advisory committee meeting related to use of this product in the adult population.

8.6 Literature Review

A comprehensive literature review was not done for this product.

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan proposed for this product..

8.8 Other Relevant Materials

There were no other relevant materials reviewed for this submission.

9 OVERALL ASSESSMENT

9.1 Conclusions

Efficacy
The initial studies of Ambien CR demonstrated that the immediate increase in sleep maintenance benefit may be expected to last up to 6 (elderly) or 7 hours (adults). When objectively evaluated by polysomnography after a fortnight of use, the sleep maintenance benefit decreases to 4 hours (elderly) or 5 hours (adults), however, there seems to be a sustained subjective benefit in the adult population as evidenced by the results from this study.

Safety
This controlled release product has a similar safety profile to the immediate release product currently being marketed. Withdrawal-type symptoms are seen in a minority of patients. Rebound effects on sleep are seen on the first night after drug cessation. Like the withdrawal effects, the rebound effects appear to be short lived. There is a relatively high incidence of morning somnolence reported as an adverse event. Anxiety is also a clearly associated adverse event. I would argue that there may be an association with depression.

The incidence of perforated viscera, while causality has not been proven, is worthy of future monitoring.

9.2 Recommendation on Regulatory Action

I recommend approval of this efficacy supplement.

The dosage and indication section should include the information that the long term studies were done in adults only.

9.3 Recommendation on Postmarketing Actions

There are no recommended risk management activities for this product, no required Phase 4 commitments, and no other Phase 4 requests for this product.

Since a study of zolpidem (Ambien IR) for the treatment of insomnia in children with ADHD failed to demonstrate efficacy but did show an increased risk of psychiatric adverse effects, a

waiver should be granted for this product. No study of Ambien CR should be required in the pediatric population.

9.4 Labeling Review

Changes were made to the following sections:

- Highlights
- 1 Indications and usage
- 2.1 Dosage and administration
- 4 Contraindications
- 5 Warnings and precautions
- 7 Drug interactions
- 8 Use in special populations

9.5 Comments to Applicant

None

10 APPENDICES

10.1 Review of Individual Study Report: LTE 5407

This study began on 31 August 2004. The last patient completed the study on 06 January 2006.

The one protocol amendment, dated 15 July 2004 prior to the screening of the first patient, made protocol clarifications which have been incorporated below without further comment since this amendment preceded patient enrollment.

Title:
Evaluation of the long-term efficacy and safety of zolpidem-MR 12.5 mg compared to placebo, when both are administered over a long-term period "as needed," in patients with chronic primary insomnia.: A randomized, double-blind, placebo-controlled, parallel group, multi-center, phase IIIb clinical study.

Objectives

- To evaluate the hypnotic efficacy of a 12.5 dose of zolpidem modified release (zolpidem-MR) compared with placebo, on an "as needed (PRN)" basis in patients with chronic primary insomnia
- To evaluate long term drug taking behavior
- To evaluate the safety of zolpidem-MR 12.5 mg in comparison to placebo administered PRN over a long term period
- To evaluate potential rebound and withdrawal effects after discontinuation of chronic intermittent use of zolpidem-MR 12.5 mg as compared to placebo
- To assess the consequences on job performance and healthcare consumption of chronic insomniac patients treated with zolpidem-MR 12.5 mg in comparison to placebo, when both are administered on a chronic intermittent basis over a long term

Expected Population
1000 adult patients with primary insomnia based upon DSM-IV and PSG criteria

Inclusion criteria

1. Adults aged 18 to 64 years inclusive
2. Females of childbearing potential (i.e. less than 2 years post-menopausal or not surgically sterile) had to be using acceptable contraception, as defined by the protocol, during the entire study period. Additionally these women had to have a negative serum pregnancy test at screening.
3. History of primary insomnia consisting of difficulty in initiating sleep, difficulty in maintaining sleep or non-restorative sleep for at least three months preceding the study visit and clinically significant distress or impairment in social, occupational or other important areas of functioning
4. Patient had to complain of at least one hour of wakefulness after sleep onset for at least 4 nights per week over the preceding month

5. Patient had to spend at least 6.5 hours and not more than 8.5 hours in bed each night over the 2 preceding weeks
6. Based on a sleep questionnaire during the run-in phase, patients had to have a mean wake time after sleep onset (WASO) $\geq$ 40 minutes and total sleep time (TST) of between 3 and 6.5 hours
7. Written, signed and dated informed consent must be given by the patient

Exclusion criteria

1. History of hypersensitivity to zolpidem, its excipients, or related compounds
2. Pregnancy or lactation
3. Night or shift workers
4. Persons who took a nap (defined as intentional sleep of more than 20 minutes) 3 or more times per week over the preceding month
5. Consumption of xanthine-containing beverages comprising more than 5 cups or glasses/day
6. Patients who were unable to participate for the entire duration of the study or those who in the opinion of the investigator had the potential to be non-compliant with the obligations inherent in trial participation
7. Participation in another clinical trial in the 2 months before the screening visit
8. Any of the following conditions based upon medical history and/or PSG: primary hypersomnia, narcolepsy, breathing-related sleep disorder, circadian rhythm sleep disorder, parasomnia, dyssomnia not otherwise specified
9. Severe psychiatric disorder by DSM IV criteria
10. Mental retardation
11. Dementia of Alzheimer's or vascular type
12. History of substance abuse or dependence within the last year
13. Myasthenia gravis
14. Severe or unstable respiratory insufficiency
15. Severe hepatic insufficiency
16. Use of any OTC or prescription sleep medication, including hypnotics, sedatives, and /or anxiolytics within 2 weeks or 5 half-lives (whichever was longer) prior to screening
17. Use of any substance with psychotropic effects or properties known to affect sleep/wake including but not limited to anti-psychotics, morphine/opioid derivatives, sedative antihistamines, stimulants, antidepressants, clonidine within 1 week to 5 half-lives prior to screening (whichever was longer)

Study duration

The study duration was approximately 6 months per patient.

Study Conduct

Study medications
Zolpidem-MR 12.5 mg po
Placebo

The investigational product was to be taken at least 3 nights a week.

Eligible patients were to have had a 7-day screening run in period in which they were to take no medication. However, they were expected to complete morning questionnaires via an interactive voice recording system (IVRS), and could be excluded for non compliance.

After screening patients were to be scheduled for a baseline visit at which morning questionnaire data was reviewed to assess eligibility, and the clinical global impression-severity section(CGI-S) as well the resource utilization questionnaire (RUQ) was to be completed by the investigator. At this visit, the patients completed an Epworth sleepiness scale (ESS) and a work limitation questionnaire (WLQ). Eligible patients were to be randomized using the IVRS.

After randomization, patients were to begin a 24-week double-blind treatment period, during which they were instructed to take 3 to 7 tablets a week on an "as needed basis." Patients were to be seen every 4 weeks, i.e. week 4, week 8 etc. At each interim visit, they would be expected to complete an ESS as well as the WLQ. The investigator was responsible for the CGI-improvement questionnaire as well as the RUQ. The patient was to complete morning questionnaires using the IVRS throughout this period.

The study was to end with a 7-night run-out period. Patients would be seen again at Visit 9, week 25 for final evaluations. At the termination visit, the PGI, the CGI-improvement, the RUQ and the physician's withdrawal checklist were completed.

Study results

Description of patients

Of the 1701 patients screened, 1025 patients were eligible for study participation. There were no significant imbalances in the two treatment groups in terms of baseline insomnia criteria or demographic characteristics.

Table8: Demographics (study report, tables (7.4.1) 1 and (7.4.1) 2)

		Placebo (n=349)	Zolpidem-MR 12.5 mg (n=669)
Gender	Male	139 (39.8%)	256 (38.3%)
	Female	210 (60.2%)	413 (61.7%)
Ethnicity	White	230 (65.9%)	432 (64.6%)
	Black	63 (18.1%)	120 (17.9%)
	Asian	4 (1.1%)	10 (1.5%)
	Other	52 (14.9%)	107 (16%)
Age (years)	n	349	669
	Mean (SD)	45.0 (11.5)	46.0 (10.8)
	Min-Max	18-64	18-64

Protocol violations

The sponsor excluded 7 patients from the intent-to-treat (ITT) population as they did not meet inclusion exclusion criteria:

- 2 patients in the placebo group-1 due to poor compliance, 1 due to "other reasons"
- 7 patients in the zolpidem group-1 due to poor compliance, 2 due to subject's request, 2 due to "other reasons," 2 due to loss to follow-up with no available post-baseline efficacy data

The sponsor excluded 119 placebo patients and 198 zolpidem patients from the per protocol population, see Table 9 below.

Table 9: Exclusions from the per protocol population (table 7.2.1.2 1 from the study report)

	Placebo (N=349) n (%)	Zolpidem-MR 12.5 mg (N=667) n (%)	Overall (N=1016) n (%)
Any deviation	119 (34.1)	198 (29.7)	317 (31.2)
Any deviation before inclusion	7 (2.0)	7 (1.0)	14 (1.4)
Intake of prohibited medication	6 (1.7)	7 (1.0)	13 (1.3)
Related to exclusion criteria	1 (0.3)	0 (0)	1 (<0.1)
Any deviation after inclusion	117 (33.5)	195 (29.2)	312 (30.7)
Dosing irregularity	0 (0)	1 (0.1)	1 (<0.1)
Intake of prohibited medication	38 (10.9)	68 (10.2)	106 (10.4)
No treatment compliance for actual month M1-M3	72 (20.6)	91 (13.6)	163 (16.0)
No treatment compliance for actual month M4-M6	46 (13.2)	79 (11.8)	125 (12.3)
No treatment compliance for the entire randomized period	72 (20.6)	91 (13.6)	163 (16.0)

PGM= SL80075023/LTE5407/CSR 01/BS/PGM RPT/C22 deviat.sas OUT= OUTPUT/C22 deviat 2.html (16JUN2006 - 15:02)

Efficacy

[*Reviewer's notes:*
The sponsor pre-specified three populations for efficacy analyses:

- *The treated population (n=1018) which included all patients who took at least one dose of double-blind study drug. This population was to be used for the safety analyses.*
- *The Intent To Treat population (n=1016) which included all patients who took at least once dose of study drug and who had at least one efficacy assessment post-baseline.*
- *The per protocol population (n=699) which included all patients in the ITT population who did not have a major protocol deviation leading to exclusion. The sponsor used this, the per protocol population, for analysis of the primary efficacy and main secondary endpoints. The analyses were therefore done on 669 randomized patients (68.2% of those randomized, including 66% of the patients who had been randomized to placebo and 70% of those who had been randomized to active treatment)*

The primary efficacy endpoints and all main secondary endpoints (as prioritized by the sponsor) were analyzed at 12 weeks of double-blind treatment.]

Primary endpoint

- Patient's Global Impression (PGI)-Item 1, as assessed after 12 weeks of double blind treatment

  This item is "aid to sleep" scored as follows:
  - 1-helped me sleep,
  - 2-did not affect my sleep or
  - 3-worsened my sleep.

  The results for this pre-specified primary endpoint have been discussed in detail in Section 6 of this review.

Secondary and exploratory endpoints

- PGI-items 1, 2, 3 and 4 at week 12
  This was a pre-specified secondary endpoint.
  The PGI used patient's reports (on a 3 point scale) for efficacy of sleep aid, sleep induction, sleep duration and medication strength. In all three areas, patients who received active drug reported significant improvement as compared to those who received placebo. The advantage in the active treatment arm was seen at all time points assessed (weeks, 4, 8, 12, 16, 20 and 24).

  Table 10: PGI items (taken from study report Table 8.1.2.1 2)

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Time to fall asleep	N	251	558
	Mean (SD)	1.7 (0.6)	1.3 (0.6)
	Median	2.0	1.0
	Shortened [n (%)]	101 (40.2)	397 (71.1)
	No change [n (%)]	135 (53.8)	135 (24.2)
	Lengthened [n (%)]	15 (6.0)	26 (4.7)
	p-value[a]		<.0001
Total amount of sleep	N	251	558
	Mean (SD)	1.6 (0.5)	1.2 (0.4)
	Median	2.0	1.0
	Lengthened [n (%)]	114 (45.4)	464 (83.2)
	No change [n (%)]	131 (52.2)	88 (15.8)
	Shortened [n (%)]	6 (2.4)	6 (1.1)
	p-value[a]		<.0001
Medication strength	N	251	558
	Just right [n (%)]	103 (41.0)	388 (69.5)
	Too strong [n (%)]	6 (2.4)	39 (7.0)
	Too weak [n (%)]	142 (56.6)	131 (23.5)
	p-value[b]		<.0001

PGM = SL80075023/LTE5407/CSR 01/BS/PGM RPT/C26 pgi.sas OUT= OUTPUT/C26 PGI CMH2 1.html (19JUN2006 - 9:49)
Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: [a] P-values come from CMH test with rank score
Note: [b] P-value comes Chi-2 square test comparing % of favorable responses between groups

- Morning sleepiness
  This was a pre-specified exploratory endpoint. An advantage was seen in the active treatment arm at all time points assessed (months 1, 2, 3, 4, 5 and 6).

- Ability to concentrate in the morning
  This was a pre-specified exploratory endpoint. An advantage was seen in the active treatment arm at all time points assessed (months 1, 2, 3, 4, 5 and 6).

- Daytime sleepiness using the Epworth Sleepiness Scale
  This was a pre-specified exploratory endpoint. The ESS is an eight item scale with each item rated from 0 (never) to 3 (high chance).

The advantage in the active treatment arm was seen at weeks 8, 12, 16, 20 and 20, but not at week 4 or week 24. When the sponsor analyzed the "ESS total score baseline adjusted mean change at endpoint," there was no statistically significant difference between the groups.

Table 11: ESS total score change from baseline to endpoint (Table 8.1.2.2 19 from the study report)

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Baseline	N	331	630
	Mean (SD)	7.5 (4.7)	7.5 (5.0)
Change from baseline	LS Mean (SE)	-1.66 (0.18)	-2.13 (0.13)
Difference vs placebo	LS Mean (SE)	-	-0.47 (0.23)
	95% CI	-	(-0.92 to -0.02)
	p-value	-	0.0386

PGM = SL80075023/LTE5407/CSR 01/BS/PGM RPT/I26 epworthlv.sas OUT= OUTPUT/I26 epworthlv 1.html (19JUN2006 - 9:46)
Note: Epworth sleepiness scale is composed of 8 items ranging from 0 (=would never) to 3 (=high chance)
Note: P-values come from a centered baseline adjusted analysis of covariance
CI = Confidence Interval - SD=Standard deviation- SE=Standard error

- Clinician Global Impression-Improvement (CGI-I) at week 12
This was a pre-specified secondary endpoint. The scale ranges from 1 (very much improved) to 7 (very much worse). The sponsor analyzed results from the ITT population in week 12, with scores of 1 or 2 defined as a favorable response and all other scores deemed unfavorable. The advantage in the active treatment arm was seen at all time points assessed (weeks, 4, 8, 12, 16, 20 and 24).

Table 12: CGI improvement (taken from study report Table 13.2.1 1)

		Placebo (N=349)		Zolpidem-MR 12.5 mg (N=667)	
Improvement scale	N	253		560	
	Favorable response [a]: [n (%)]	94	(37.2)	420	(75.0)
	Unfavorable response [b]: [n (%)]	159	(62.8)	140	(25.0)

PGM = SL80075023/LTE5407/CSR 01/BS/PGM RPT/C26 cgifavo.sas OUT= OUTPUT/C26 cgifavo 1.html (16JUN2006 - 15:08)
Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: CGI improvement scale ranging from 1 (very much improved) to 7 (very much worse)
[a] :Very much or much improved
[b] : Minimally improved or no change or minimally, much or very much worse.

- Sleep parameters from the morning questionnaire
  - Total sleep time (TST)
  - Wake time After Sleep Onset (WASO)
  - Sleep onset latency (SOL)
  - Number of nocturnal awakenings (NAW)
  - Quality of sleep

This was a pre-specified secondary endpoint. Zolpidem was significantly superior to placebo in all five areas when evaluated in the ITT population at week 12. The advantage in the active treatment arm was seen at all time points assessed (months 1, 2, 3, 4, 5 and 6) for all parameters with the exception of NAW. In the latter case, no significant difference was seen in Month 1 though a significant difference was appreciated in the subsequent months.

- Drug utilization
  This was a pre-specified secondary endpoint. As per the study report (p.92/547), the "overall mean number of days with [study drug] during the study were 86.3 and 112.2 for the placebo and zolpidem-MR 12.5-mg treatment groups, respectively. During each actual month of treatment, the mean number of days with [study drug] was less in the placebo group compared with the zolpidem-MR 12.5mg group."

Safety
A detailed analysis of the safety results may be found in Section 7 of this review, Integrated Review of Safety.

Rebound during the double-blind phase was evaluated using TST and WASO for no pill nights which followed 4 consecutive pill nights for each 4-week period, in comparison to baseline values. During the post-treatment phase, the potential rebound after final treatment discontinuation was assessed on TST and WASO during the run-out phase in comparison to baseline.

Withdrawal was assessed using the physician withdrawal checklist.

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/s/

Dawn McNeil
11/30/2007 01:16:15 PM
MEDICAL OFFICER

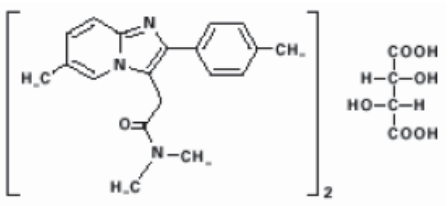
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1

1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 21-774	
3. NAME AND ADDRESS OF APPLICANT (*City and State*) Sanofi-Aventis US LLC 55 Corporate Drive Bridgewater, NJ 08807		4. AF NUMBER	
		5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG Ambien CR	7. NONPROPRIETARY NAME Zolpidem tartrate extended-release tablets	SE1-003	2-20-2007
8. SUPPLEMENT PROVIDES FOR: Treatment of insomnia, characterized by sleep onset and/ or sleep maintenance.		9. AMENDMENTS DATES 8-28-2007	
10. PHARMACOLOGICAL CATEGORY Treatment of Insomnia	11. HOW DISPENSED RX ✓ OTC	12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets	14. POTENCY 6.25 mg and 12.5 mg		
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: N,N,6-trimethyl-2-p-tolyl-imidazo[1,2-α]-pyridine-3-acetamide L-(+)-tartrate(2:1) $(C_{14}H_{21}N_3O)_2 . C_4H_6O_6$ 764.88 		16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	

17. COMMENTS

This long-term efficacy supplement provides for the use of Ambien CR in the treatment of insomnia, characterized by sleep onset and/ or sleep maintenance. The applicant has not provided any new CMC information other than some minor editorial changes to how supplied section of the labeling, and add a carton of 100 count unit dose packaging configuration. The proposed change is found to be acceptable. The applicant has submitted a claim for categorical exclusion from filing an environmental assessment document under 21 CFR 25.31 (b) and has indicated that based upon marketing estimates for the next five years, the estimated quantity of the active moiety that is expected to enter the aquatic environment will be below 1 part per billion. The applicant's claim is found to be acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS

Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Nallaperumal Chidambaram, Ph.D.		09-28-2007

DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: C. Michaloski HFD-120	Branch Chief: James Vidra Ph.D.

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/s/

Nallaperumal Chidambaram
9/28/2007 12:32:15 PM
CHEMIST

Jim Vidra
9/28/2007 12:48:33 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	NDA 21-774
Drug Name:	Zolpidern-MR 12.5 mg
Indication(s):	Chronic primary insomnia
Applicant:	Sanofi-Aventis
Date of Document:	Feb 20, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 1 (HFD-710)
Statistical Reviewer:	Ohidul Siddiqui, Ph.D
Concurring Reviewers:	Kun Jin, Ph.D; James Hung, Ph.D / Kooros Mahjoob, Ph.D
Medical Division:	HFD-120
Project Manager:	Cathleen Michaloski

Keywords: *NDA review, endpoint analysis, multi-center, CMH test*

Table of Contents

1. EXECUTIVE SUMMARY

The sponsor submitted efficacy findings of a study to support hypnotic efficacy of zolpidem-MR 12.5 mg, when administered over a long-term period on an "as needed" basis, in patients with chronic primary insomnia. The study was a USA, multicenter, Phase 3b, randomized, double-blind, placebo-controlled, 2 parallel groups study in patients with chronic primary insomnia. A total of 1025 patients were randomized (unbalanced 2:1 randomization scheme) in the study.

1.1. Conclusions and Recommendations

The statistical findings support the efficacy of long-term zolpidem-MR treatment in patients with chronic insomnia. Zolpidem-MR 12.5 mg was effective in improving sleep induction and sleep maintenance in patients with chronic primary insomnia at the end of 12 weeks double-blind period.

1.2. Brief Overview of Reviewed Clinical Study

1.2.1. Pivotal Study

The sponsor submitted efficacy findings of a study entitled "Evaluation of the long-term efficacy and safety of zolpidem-MR12.5 mg compared to placebo, when both are administered over a long-term period 'as needed' in patients with chronic primary insomnia" to seek approval to include a long-term efficacy of zolpidem-MR12.5 mg data in the current approved Ambien CR package.

The hypnotic efficacy of zolpidem-MR 12.5-mg was assessed by the patient's global impression (PGI-item1) at 12 weeks of double-blind treatment.

Statistical analyses of the primary outcome measure PGI Item-1 "aid to sleep" and secondary outcome measures CGI-I and PGI-Items 2, 3, and 4 were based on the data observed "at Week 12" in the intent-to-treat (ITT) population, using the following rules for missing data replacement: if data at Week 12 were missing, non-missing data at Week 16 was to be used, otherwise, non-missing data at Week 8 was to be used. No other replacement was performed.

Cochran-Mantel-Haenszel test with rank score was the primary statistical method to analyze CGI-I and PGI-Items 1, 2, and 3. Patient's global impression-Item 4 "medication strength" was analyzed using a Chi-square test on "favorable" response.

1.3 Statistical Issues and Findings

No statistical issues are found.

2. INTRODUCTION

2.1. Overview

The sponsor submitted a supplemental new drug application (sNDA) to seek approval to include a long-term efficacy of zolpidem-MR12.5 mg data in the current approved Ambien CR package based on the findings of one study. The title of the submitted study is "Evaluation of the long-term efficacy and safety of zolpidem-MR12.5 mg compared to placebo, when both are administered over a long-term period 'as needed' in patients with chronic primary insomnia".

2.2. Data Sources

The study report and SAS data sets of the study are available at \\CDSESUB1\N21774\N-000\2007-02-20.

3. STATISTICAL EVALUATION

3.1. Study reviewed

3.1.1. Study LTE5407

The study was a USA, multicenter, Phase 3b, randomized, double-blind, placebo-controlled, 2 parallel groups study in patients with chronic primary insomnia. A total of 1025 patients were randomized (unbalanced 2:1 randomization scheme) into this study. The study was to last approximately 6 months for each patient and consisted of the 3 phases: (i) a run-in period; (ii) randomized treatment period; and (iii) a run-out period. Table 1 lists the study design.

Table 1: Study design

Run-in Period	Randomized Treatment Period	Run-out Period
7 days ± 3 days	24 weeks ± 3 days	7 days ± 3 days
D -8 to D -1	W4, W8, W12, W16, W20, and W24	W25
Visit 1 to Visit 2	Visit 3 to Visit 8	Visit 9
Washout period and checking eligibility for randomization	Assessment of the efficacy and safety criteria	Assessment of safety, rebound effects, and any withdrawal symptoms following abrupt discontinuation of investigational product.
No investigational product	*Double-blind* zolpidem-MR 12.5 mg or placebo As needed (3 to 7 tablets per week)	No investigational product

D = day; W = week; MR = modified release.
Source: study report.

Primary Objective

Primary objective of the study was to evaluate the hypnotic efficacy of zolpidem-MR 12.5-mg in comparison to placebo, when administered over a long-term period, on an "as needed" basis, in patients with chronic primary insomnia.

Primary and secondary efficacy measures

The hypnotic efficacy of zolpidem-MR 12.5-mg in comparison to placebo administered over a long-term period was assessed on the patient's global impression (PGI-item1) over 12 weeks of double-blind treatment period.

Secondary measures were CGI-I (CGI improvement, assessed by the investigator), Patient's Global Impression (PGI items 2, 3 and 4), and Sleep parameters from patient's morning questionnaire collected daily through IVRS: Total Sleep Time (TST), Wake time After Sleep Onset (WASO), Sleep Onset Latency (SOL), Quality of sleep (QOS), and Number of nocturnal awakenings (NAW).

Analysis Population

The primary efficacy population was the Intent-to-treat (ITT) population --all randomized patients with at least one post-baseline efficacy data.

Sponsor also conducted statistical analysis on the Per-Protocol (PP) population as secondary analyses. The PP population corresponded to patients from the ITT population without a major protocol deviation.

Primary Statistical Method:

Statistical analyses of the primary variable PGI Item-1 "aid to sleep" and the main secondary variables related to CGI-I and to PGI-Items 2, 3, and 4 were based on the data observed **"at Week 12"** in the intent-to-treat (ITT) population, using the following rules for missing data replacement: if data at Week 12 were missing, non-missing data at Week 16 was to be used, otherwise, non-missing data at Week 8 was to be used. No other replacement was performed.

Cochran-Mantel-Haenszel test with rank score was the primary statistical method to analyze the outcome measures CGI-I and PGI-Items 1, 2, and 3. Patient's global impression-Item 4 "medication strength" was analyzed by using a Chi-square test on "favorable" response.

The mean changes from baseline for each PMQ derived parameter (TST, WASO, SOL, QOS, and NAW averaged over Week 9 to Week 12 were analyzed using an analysis of covariance (ANCOVA) model. The ANCOVA model included treatment group as fixed factor and the baseline value centered on the grand mean (i.e., subtracting the overall baseline mean value of the population) as a covariate.

Sponsor's Findings:

Patient disposition and demographics

Table 2 lists the patient disposition of the randomized patients. A total of 351 patients were randomized in the placebo group and 674 patients were randomized in the zolpidem-MR 12.5-mg group. Among the randomized patients, 52.4% patients in the placebo group and 64.7% patients in the zolpidem-MR 12.5-mg group completed the study treatment period. That is, about 47% patients from placebo group and 35% patients from zolpidem-MR 12.5-mg group discontinued the study during the study treatment period. The main reasons for discontinuation were "lack of efficacy/disease progression" for the placebo group (23.4% patients), and "subject's request" for the zolpidem-MR 12.5-mg group (9.3% patients).

Table 2: Summary of Patient Disposition

	Placebo (N=351) n (%)	Zolpidem-MR 12.5 mg (N=674) n (%)	Overall (N=1025) n (%)
Treated patients	349 (99.4)	669 (99.3)	1018 (99.3)
Completed study treatment period	184 (52.4)	436 (64.7)	620 (60.5)
Study treatment discontinuation	167 (47.6)	238 (35.3)	405 (39.5)
Main reason for treatment discontinuation:			
Lack of efficacy/disease progression	82 (23.4)	32 (4.7)	114 (11.1)
Adverse event	16 (4.6)	57 (8.5)	73 (7.1)
Poor compliance to protocol	15 (4.3)	27 (4.0)	42 (4.1)
Subject's request	21 (6.0)	63 (9.3)	84 (8.2)
Subject lost to follow-up	27 (7.7)	50 (7.4)	77 (7.5)
Other reason	6 (1.7)	9 (1.3)	15 (1.5)

Source: Study report.

Two patients from the placebo group and 7 patients from the zolpidem-MR 12.5-mg group were excluded from the ITT population. Table 3 lists the reasons for exclusion of these patients from the ITT sample.

Table 3: Exclusion from ITT population

	Placebo (N=351) n (%)	Zolpidem-MR 12.5 mg (N=674) n (%)	Overall (N=1025) n (%)
Any Reason	2 (0.6)	7 (1.0)	9 (0.9)
Not exposed	2 (0.6)	5 (0.7)	7 (0.7)
Poor compliance to protocol	1 (0.3)	1 (0.1)	2 (0.2)
Subject's request	0 (0)	2 (0.3)	2 (0.2)
Other reason	1 (0.3)	2 (0.3)	3 (0.3)
No post baseline efficacy data	0 (0)	2 (0.3)	2 (0.2)
Subject lost to follow-up	0 (0)	2 (0.3)	2 (0.2)

Source: Study Report

Table 4: Summary of demographic characteristics (gender and race) at baseline

		Placebo (N=349)		Zolpidem-MR 12.5 mg (N=669)		Overall (N=1018)	
Gender [n (%)]	N	349		669		1018	
	Female	210	(60.2)	413	(61.7)	623	(61.2)
	Male	139	(39.8)	256	(38.3)	395	(38.8)
Race [n (%)]	N	349		669		1018	
	Asian / Oriental	4	(1.1)	10	(1.5)	14	(1.4)
	Black	63	(18.1)	120	(17.9)	183	(18.0)
	Caucasian	230	(65.9)	432	(64.6)	662	(65.0)
	Other	52	(14.9)	107	(16.0)	159	(15.6)

Demography

Table 4 lists the demographic characteristic (gender and race) of the ITT patients. The distributions of the randomized patients into two groups were similar with respect to gender and race. Mean age was 45.7 years; mean weight was 80.3 kg, and BMI 28.1. The two groups were also similar with respect to age, weight, and BMI. The reported sleep parameters at baseline were also comparable between treatment groups.

Treatment Compliance

Table 5 summarizes the treatment compliance during the treatment period. The observed treatment compliance was superior for patients from the zolpidem-MR 12.5-mg group compared with patients from the placebo group.

Table 5: Summary of treatment compliance during randomized treatment period

		Placebo (N=349) n (%)		Zolpidem-MR 12.5 mg (N=669) n (%)		Overall (N=1018) n (%)	
Compliance [n (%)]	Overall	144	(41.3)	336	(50.2)	480	(47.2)
	Actual month 1	242	(69.3)	520	(77.7)	762	(74.9)
	Actual month 2	180	(51.6)	459	(68.6)	639	(62.8)
	Actual month 3	163	(46.7)	433	(64.7)	596	(58.5)
	Actual month 4	145	(41.5)	413	(61.7)	558	(54.8)
	Actual month 5	138	(39.5)	366	(54.7)	504	(49.5)
	Actual month 6	136	(39.0)	352	(52.6)	488	(47.9)

Source: Study report.

Efficacy results

Primary efficacy measure

Table 6 lists the findings of statistical analyses of primary efficacy variable (PGI-Item 1 “aid to sleep”). As an “aid to sleep” (PGI-Item 1), at Week 12 zolpidem-MR 12.5 mg was significantly superior ($p<0.0001$) to placebo for the ITT population. About 90% of patients from the zolpidem-MR 12.5-mg group versus 51% of patients from the placebo group declared that the medication helped them sleep.

Table 6: Patient's global impression - item-1 - aid to sleep at Week-12 - ITT population

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Aid to sleep	N	251	558
	Mean (SD)	1.5 (0.6)	1.1 (0.3)
	Median	1.0	1.0
	Help for sleeping [n (%)]	129 (51.4)	501 (89.8)
	Not affect [n (%)]	111 (44.2)	51 (9.1)
	Worsened [n (%)]	11 (4.4)	6 (1.1)
	p-value		<.0001

Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: P-value comes from CMH test with rank score
Note: SD=Standard deviation
Source: Study Report.

Secondary efficacy variables

A summary of the CGI-I at Week 12 in the ITT population is presented in Table 7. The percentage of patients who were reported as "very much improved" or "much improved" by the Investigators were 37.1% versus 75% in the placebo and zolpidem-MR 12.5 mg treatment groups, respectively.

Table 7: CGI - improvement scale at Week 12 - ITT population

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Improvement scale	N	253	560
	Mean (SD)	2.9 (1.2)	2.0 (1.1)
	Median	3.0	2.0
	Very much improved [n (%)]	41 (16.2)	208 (37.1)
	Much improved [n (%)]	53 (20.9)	212 (37.9)
	Minimally improved [n (%)]	52 (20.6)	75 (13.4)
	No change [n (%)]	103 (40.7)	53 (9.5)
	Minimally worse [n (%)]	4 (1.6)	9 (1.6)
	Much worse [n (%)]	0 (0)	2 (0.4)
	Very much worse [n (%)]	0 (0)	1 (0.2)
	p-value		<.0001

Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: P-value comes from CMH test with rank score
Note: SD=Standard deviation
Source: Study report

Table 8 lists a summary of Patient's Global Impression (PGI) Items 2, 3, and 4 at Week 12 for the ITT population. The percentage of patients with improved "time to fall asleep," and "total amount of sleep" was significantly superior for the zolpidem-MR 12.5-mg group compared with the placebo group.

Table 8: PGI items 2, 3, and 4 at Week-12 - ITT population

		Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Time to fall asleep	N	251	558
	Mean (SD)	1.7 (0.6)	1.3 (0.6)
	Median	2.0	1.0
	Shortened [n (%)]	101 (40.2)	397 (71.1)
	No change [n (%)]	135 (53.8)	135 (24.2)
	Lengthened [n (%)]	15 (6.0)	26 (4.7)
	p-value[a]		<.0001
Total amount of sleep	N	251	558
	Mean (SD)	1.6 (0.5)	1.2 (0.4)
	Median	2.0	1.0
	Lengthened [n (%)]	114 (45.4)	464 (83.2)
	No change [n (%)]	131 (52.2)	88 (15.8)
	Shortened [n (%)]	6 (2.4)	6 (1.1)
	p-value[a]		<.0001
Medication strength	N	251	558
	Just right [n (%)]	103 (41.0)	388 (69.5)
	Too strong [n (%)]	6 (2.4)	39 (7.0)
	Too weak [n (%)]	142 (56.6)	131 (23.5)
	p-value[b]		<.0001

Note: Values come from Week-12 or from Week-16 if Week-12 missing or from Week-8 if Week-16 missing
Note: P-value comes from CMH test with rank score ; Note: SD=Standard deviation;
Source: Study report

Table 9: Patient's morning questionnaire - mean change from baseline within month 3 - ITT population

			Placebo (N=349)	Zolpidem-MR 12.5 mg (N=667)
Total sleep time (min)	Baseline	N	265	579
		Mean (SD)	295.2 (47.4)	296.1 (48.5)
	Change from baseline	LS Mean (SE)	70.10 (3.64)	101.09 (2.46)
	Difference vs placebo	LS Mean (SE)	-	30.99 (4.40)
		95% CI	-	(22.36 to 39.62)
		p-value	-	<.0001
Time spent awake after falling asleep (min)	Baseline	N	265	579
		Mean (SD)	98.4 (46.9)	99.4 (47.8)
	Change from baseline	LS Mean (SE)	-44.03 (2.30)	-62.20 (1.55)
	Difference vs placebo	LS Mean (SE)	-	-18.16 (2.77)
		95% CI	-	(-23.61 to -12.72)
		p-value	-	<.0001
Sleep onset latency (min)	Baseline	N	265	579
		Mean (SD)	77.7 (48.2)	73.3 (46.5)
	Change from baseline	LS Mean (SE)	-25.69 (1.80)	-32.77 (1.22)
	Difference vs placebo	LS Mean (SE)	-	-7.08 (2.18)
		95% CI	-	(-11.36 to -2.81)
		p-value	-	0.0012
Quality of sleep	Baseline	N	265	579
		Mean (SD)	3.2 (0.4)	3.2 (0.4)
	Change from baseline	LS Mean (SE)	-0.66 (0.03)	-0.94 (0.02)
	Difference vs placebo	LS Mean (SE)	-	-0.29 (0.04)
		95% CI	-	(-0.37 to -0.21)
		p-value	-	<.0001
Number of nocturnal awakenings	Baseline	N	265	579
		Mean (SD)	2.9 (4.4)	3.2 (7.6)
	Change from baseline	LS Mean (SE)	-1.17 (0.09)	-1.72 (0.06)
	Difference vs placebo	LS Mean (SE)	-	-0.55 (0.10)
		95% CI	-	(-0.75 to -0.35)
		p-value	-	<.0001

Note: All described variables are mean calculated over actual month 3 or over actual month 4 if actual month 3 missing or over actual month 2 if month 4 missing ;
Note: 4 degrees Likert scale (1=excellent to 4=poor) used for quality of sleep
Note: P-values come from a centered baseline adjusted analysis of covariance. CI= Confidence Interval; SD=Standard deviation; SE=Standard error;
Source: Study Report.

A summary of the Patient's Morning Questionnaire (PMQ) mean change from baseline within Month 3 in the ITT population is listed in Table 9. Zolpidem-MR 12.5 mg was significantly superior to placebo on the sleep outcome measures TST, WASO, SOL, QOS, and NAW.

Observed cases (OC) analyses on other secondary efficacy measures

At Weeks 4, 8, 12, 16, 20, and 24, each of the following measures was significantly superior for the zolpidem-MR 12.5-mg group compared with the placebo group: PGI-Item 1 (aid to sleep), (ii) PGI-Item 2 (time to fall asleep), (iii) PGI-Item 3 (total sleep time), (iv) PGI-Item 4 (medication strength), and (v) Clinical global impression (CGI).

Similarly, at actual Months 1, 2, 3, 4, 5, and 6, the baseline adjusted mean change was significantly superior for the zolpidem-MR 12.5-mg group compared with the placebo group for the following measures: (i) Patient's Morning Questionnaire Total sleep time (TST), (ii) Wake time after sleep onset (WASO), (iii) Sleep onset latency (SOL), and (iv) Quality of sleep (QOS).

FDA Reviewer's Data Analyses and Comments

This reviewer re-analyzed the submitted datasets according to the protocol specified analyses, and was able to reproduce the sponsor's findings for both the primary and secondary efficacy measures. Based on the sponsor's analyses as well as this reviewer's analyses, the hypnotic efficacy of zolpidem-MR 12.5 mg was present, when the drug was administered over a long-term period, on an "as needed" basis, in patients with chronic primary insomnia.

4. Subgroup Analyses

4.1. Subgroup Analyses

Subgroup analyses on the primary efficacy measure were performed to evaluate the uniformity of treatment effect within patient subgroup (gender and race group). Subgroup analyses showed no substantial differences in efficacy of Zolpidem MR 12.5 mg across the subgroups.

Table 10. Subgroup Analysis - Patient's global impression - item-1 - aid to sleep at Week-12 - ITT population

	Placebo		Zolpidem_MR 12.5 mg
		N (%)	N (%)
Gender : Female	Help for Sleeping	85 (54%)	323 (92%)
	Not affect	64 (41%)	24 (7%)
	Worsened	7 (4%)	3 (1%)
	P-value		<.0001
Male	Help for Sleeping	44 (46%)	178 (85%)
	Not affect	47 (49%)	27 (13%)
	Worsened	4 (4%)	3 1%)
	P-value		<.0001

Race:	Black	Help for Sleeping	30 (70%)	89 (92%)
		Not affect	10 (23%)	7 (7%)
		Worsened	3 (7%)	-
		P-value		.0003
	Caucasian	Help for Sleeping	68 (42%)	328 (88%)
		Not affect	88 (55%)	40 (11%)
		Worsened	5 (3%)	5 (1%)
		P-value		<.0001
	Other	Help for Sleeping	31 (66%)	84 (94%)
		Not affect	13 (28%)	4 (4%)
		Worsened	3 (6%)	1 (1%)
		P-value		<.0001

5. SUMMARY AND CONCLUSIONS

5.1. Collective Evidence of Efficacy

Based on the primary analysis of efficacy on the ITT sample, zolpidem-MR 12.5 mg was significantly superior to placebo ($p<0.0001$) regarding the aid to sleep, when it was administered on an as needed basis for 3 months. About 90% of patients from the zolpidem-MR 12.5-mg group versus 51% of patients from the placebo group declared that the medication helped them sleep.

The statistical analyses of following secondary endpoints also showed that zolpidem-MR 12.5 mg administered as needed was significantly superior to placebo:

- time to fall asleep (PGI-Item 2): the percentage of patients who considered that zolpidem-MR 12.5 mg decreased the time to fall asleep was 71% at the study endpoint, versus 40% for placebo;

- total amount of sleep (PGI-Item 3): the percentage of patients who considered that zolpidem-MR 12.5 mg increased the total amount of sleep was 83% at the study endpoint, versus 45% for placebo;

- medication strength (PGI-Item 4): the percentage of patients who considered that the strength of zolpidem-MR 12.5 mg was “just right” was 70% at the study endpoint, versus 41% for placebo.

- the percentage of patients who were considered by the investigators “much or very much improved” in CGI was significantly greater at each 4-week interval of the treatment period ($p<0.0001$ at all time points) in the zolpidem-MR 12.5-mg group (66.7% at Week 4 and 84.3% at Week 24) compared with the placebo group (24.5% at Week 4 and 48.1% at Week 24).

Analysis of the patient's morning questionnaires showed that, at the study endpoint, zolpidem-MR 12.5 mg administered as needed, significantly improved patient-reported measures of TST, SOL, WASO and QOS in comparison with placebo. The endpoint analyses of PGI and CGI also confirm superiority of the zolpidem-MR 12.5-mg group in improving sleep induction and sleep maintenance in patients with chronic primary insomnia throughout 24 weeks, as compared to the placebo group.

5.3. Conclusions and Recommendations

The statistical findings support the efficacy of long-term zolpidem-MR treatment, and support the clinical utility of long-term "as needed" pharmacotherapy in patients with chronic insomnia. The study drug zolpidem-MR 12.5 mg (to be taken at a dose of no more than 1 tablet per day, 3 to 7 tablets per week) was effective in improving sleep induction and sleep maintenance in patients with chronic primary insomnia for a long-term period.

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/s/

Ohidul Siddiqui
9/6/2007 08:57:13 AM
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Kun Jin
9/6/2007 11:50:15 AM
BIOMETRICS

James Hung
9/6/2007 01:18:58 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	21-774 (SE-003)
Brand Name:	Ambien CR
Generic Name:	Zolpidem
Type of Dosage Form:	Extended Release Tablet
Strengths:	6.25 and 12.5 mg
Indications:	Insomnia
Type of Submission:	Efficacy Supplement
Sponsor:	Sanofi-Synthelabo, Inc.
Submission Date:	2/20/07 5/23/07 8/28/07
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCP Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates clinical pharmacology sections of the labeling submitted with this long-term efficacy supplement. The Supplement included study LTE5407 to evaluate long-term efficacy and safety of Ambien CR 12.5 mg (vs placebo) beyond 3 weeks and up to 6 months of treatment in patients with chronic insomnia. Clinical pharmacology and biopharmaceutics data were not included in the submission.

The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology sections of the proposed label that is in the PLR format. The sections that have been reviewed are as follows:

- Highlights
- Section 2 (Dosage and Administration)
- Section 4 (Contraindications)
- Section 5 (Warnings and Precautions)
- Section 7 (Drug Interactions)
- Section 8 (Use in Specific Populations)
- Section 12 (Clinical Pharmacology)

1.1 Recommendations and Comments to Sponsor

OCP recommends changes to the "Highlights" section of the labeling and editorial changes to Section 5.6 and to 12.3. Please refer to Section 3 of this review (page 3).

Sally Usdin Yasuda, MS, PharmD
Senior Reviewer, Neurology Drug Products, DCP I
Office of Clinical Pharmacology

Concurrence: Ramana Uppoor, PhD
Team Leader, Neurology Drug Products, DCP I
Deputy Director, DCP I
Office of Clinical Pharmacology

cc: HFD-120 NDA 21-774, E. McNeil
CSO/C. Michaloski
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DCPI/M. Mehta

2. Table of Contents

3. OCP Changes to Sponsor's Proposed Labeling

OCP recommends the following changes (in track changes, beginning on page 4) to the "Highlights" section of the labeling and editorial changes to Section 5.6 and to 12.3. Only the Clinical Pharmacology sections have been reviewed.

25 Pages of Draft Labeling have been Withheld in Full immdeiately following this page.

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

/s/

Sally Yasuda
11/8/2007 05:12:15 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
11/8/2007 05:20:55 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

OTHER REVIEW(S)

MEMORANDUM

To: **Cathleen Michaloski, BSN, MPH**
Division of Neurology Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **November 8, 2007**

Re: **Comments on draft labeling for Ambien CR (zolpidem tartrate extended release tablets)**
NDA 21-774/S-003

We have reviewed the proposed label for Ambien CR (FDA's 11-6-07 version) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

GENERAL COMMENTS

- Please ensure that all cross-references in the Full Prescribing Information (FPI) follow the preferred formatting for PLR labels, e.g., "*[see Clinical Pharmacology (12.3)]*" (and not "*[see Pharmacokinetics (12.3]).*" Note that the cross-reference should name the main section heading, but use the appropriate subsection number in parentheses.

- For the Medication Guide, the sponsor has the option of having the Medication Guide appear immediately at the end of the label (i.e., making it one long document). If this is the case, then the Medication Guide would be subsection 17.2. Alternatively, the Medication Guide can "accompany" the label, but remain a separate document that would not have a subsection number. Please confirm the sponsor's intentions as it has implications for label formatting.

HIGHLIGHTS

- When reviewing Highlights, please keep in mind the requirement that Highlights be limited to ½ page in length. Only if all efforts to streamline the information have failed, should we then consider granting a waiver for the ½ page requirement. The current presentation is well over the ½ page limit.

- *"Ambien CR® (zolpidem tartrate extended release) tablets for oral administration* ℃ *"*

Please insert a hard return before this line, separating it from the "See full prescribing information…" sentence with white space.

Please delete the "®" symbol from this line. If the sponsor objects, they may be allowed to use the symbol upon the first use of the trade name in the FPI.

The presentation of the controlled substances symbol is currently interfering with the line spacing. Please revise or ask the sponsor for an alternative presentation.

Initial U.S. Approval Date

- This date should reflect the introduction of zolpidem tartrate to the market, not the Ambien CR formulation.

Recent Major Changes

- Please ensure that this section includes all changes made in the last 12 months to the following sections of the label: Contraindications, Warnings and Precautions, Indications and Usage, and Dosage and Administration. Please also ensure that the text in the FPI that corresponds to each of these changes has a vertical line in the left margin.
- [redacted] (b) (4)
- The text in this section should not be in bolded type. Please revise.
- For changes to a numbered subsection of the label, the subsection title should be included in the listing. For example, the listing for the change to section 5.3 would be:

  Warnings and Precautions, Abnormal Thinking and Behavioral Changes (5.3) XX/2007

- Please delete the extra white space from the end of this section.

Dosage and Administration

- [redacted] (b) (4)

  To preserve lines in Highlights (to keep to the ½ page limit), we suggest revising this bullet slightly. The recommendation on total daily dose is not essential for Highlights, and can be addressed by adding "once daily" to the first sentence. We suggest:

  Adults: 12.5 mg once daily immediately before bedtime (2.1)

  We would then recommend that "once daily" also be added to the next bullet for elderly/debilitated/hepatically impaired patients for consistency.

- *"Tablets to be swallowed whole,* [redacted] (b) (4) *be crushed, divided or chewed. Should not be taken with or immediately after a meal*

To avoid its being overlooked and to clarify that these recommendations apply to all patients taking Ambien CR, we suggest that this information appear first in this section, without a bullet preceding it.

Warnings and Precautions

- We note that this section currently includes (b) (4) Once the ordering of the Warnings and Precautions has been finalized in the FPI, then a decision can be made about how many of the topics warrant inclusion in Highlights.

- In Highlights, each bulleted warning/precaution should impart a complete piece of information, i.e., state what the problem is, and how to manage it. We can assist with revision of this section. For example, the bullet on abnormal thinking and behavioral changes could read as:

  Abnormal thinking and behavioral changes: May include "sleep-driving," hallucinations, and worsening depression. Immediately evaluate any new onset behavioral changes. (5.3)

Adverse Reactions

- (b) (4)

  We recommend streamlining this sentence to say:

  Most commonly observed adverse reactions (>10% in either adult or elderly patients) are: headache, somnolence, and dizziness (6.1)

  Note that we changed (b) (4) to "adverse reactions."

  In addition, this sentence should be left-justified within the column, not indented.

- (b) (4)

  We recommend deletion of this sentence from Highlights. It does not seem to be critical information for Highlights, and the recommended dosing of Ambien CR does not include wide dose ranges. The discussion of this issue in the Adverse Reactions section of the FPI is adequate.

- (b) (4)

  (b) (4) Is this information critical for Highlights? It is unusual to present (b) (4) section under Adverse Reactions in Highlights. Please also consider space considerations for Highlights, as we strive to keep the section to ½ page.

Drug Interactions

- As with Warnings and Precautions, the discussion of drug interactions in the FPI should be properly ordered by importance first, and then a decision should be made about which to include in Highlights.

- Please ensure that the formatting in this section is consistent. In general, it is preferred to name the drug (followed by a colon), and then describe the interaction and what the clinician should do (e.g., adjust doses, stagger administration times). The current presentation is inconsistent among the bulleted items.

Use in Specific Populations

- Please delete the extra white space at the beginning of this section.

- [redacted (b) (4)]

  Because this statement gives no critical information, we recommend its deletion from Highlights.

- *"Nursing mothers:* [redacted (b) (4)]

  Please see this reviewer's comments on section "8.3 Nursing Mothers" in the FPI for proposed changes to the wording of this section.

- *"Pediatric use: Safety and effectiveness* [redacted (b) (4)] *not* [redacted (b) (4)] *established."*

  Please consider if we need to say more here. Perhaps something about the lack of effectiveness and risk of adverse reaction in these patients?

- [redacted (b) (4)]

  We suggest that this item be deleted from Highlights. [redacted (b) (4)] The same topic should not be presented multiple times in Highlights due to space concerns.

[redacted (b) (4)]

- [redacted (b) (4)]

  Because this product has a Medication Guide, this line should read "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."

Revision Date

- The date appearing at the end of Highlights must be presented as: "Revised: XX/2007," in bolded type, right-justified within the column.

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.

- If the Highlights and Contents will not fit on one page, we suggest that Highlights appear alone on page 1 and Contents appear in its entirely on page 2, rather than splitting it up between pages.

FULL PRESCRIBING INFORMATION

2.1 (b) (4)

- (b) (4)

  This sentence can be deleted because a similar sentence already appears under "2.3 Administration" about how to properly take the drug. There is no need to repeat this information twice and we want to ensure that it is clear that this recommendation applies to all patients taking Ambien CR, not just this population.

2.2 Special Populations

(b) (4)

In order to clarify that this dosing recommendation applies to both elderly/debilitated patients and those with hepatic insufficiency, we recommend revising this sentence to, "The recommended dose of Ambien CR in both of these patient populations is …"

The cross-reference at the end of this sentence should be to a particular subsection or subsections (e.g., 5.X) instead of to "5 Warnings and Precautions."

2.3 (b) (4)

- We recommend changing the title of this subsection to "Use with CNS depressants" to better describe the content of the section and to avoid confusion with the next section describing general administration instructions.

2.4 Administration

- Please unbold the text in this section. In addition, please correct the formatting for the beginning of section 3 that now appears within 2.4 inadvertently.

3 Dosage Forms and Strengths

- This section in the FPI must include a description of the appearance of the product (e.g., tablet color, imprinting, etc.). This information is presented twice in labels – here and in How Supplied/Storage and Handling.

4 Contraindications

- The cross-reference to section 5.2 should be rewritten in the preferred PLR format described above and used throughout the label.

5 Warnings and Precautions

- Please review this section to ensure that these warnings/precautions are in decreasing order of public health significance (i.e., the most important ones should appear first). Any reordering done here should also be reflected in Contents and Highlights.

5.1 (b) (4)

- We are discouraging the use of vague section titles such as (b) (4) in labeling. Instead, we suggest a title that better describes the section content. We suggest, "Assessment of insomnia and response" or something similar.
- (b) (4)

  This sentence seems out of place under a discussion of insomnia evaluation/ reevaluation. The increased sensitivity of some patients to the drug is adequately discussed in Dosage and Administration and does not seem to fit here.

5.3 Abnormal Thinking and Behavioral Changes

- *"A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics."*

  This sentence used the phrase "associated with," which is currently being discouraged in labeling because it is vague and has legal implications when included in labels. While we realize that this language is part of a class labeling initiative for sedative/hypnotics, please consider rewording here and throughout the label.

- *"In a clinical trial, 7.4 % of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations. (See section 8.4: Pediatric Use)"*

  Please revise the cross-reference at the end of this sentence to the preferred formatting.

- *"In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics."*

As noted above, please consider rewording to avoid use of “in association with.”

5.5 CNS depressant effects

- We suggest that the discussion here about additive effects when used with alcohol include a cross-reference to the Drug Interactions section.

5.6 Special Populations

- The section on “Use in patients with concomitant illness” is presented as one long paragraph, making it difficult to read. We suggest breaking it into four paragraphs: an introductory one consisting of the first two sentences, one on patients with respiratory compromise, one for patients with renal impairment, and one for patients with hepatic impairment.
- (b) (4)

  Can the phrase, “precautions should be observed” be rewritten? It seems awkward and imprecise.

- For consistency within this section, we suggest revising the subheading (b) (4) to “Use in patients with depression.” This change will also avoid the implication that the section is discussing the use of Ambien CR to treat depression.

- We suggest the subsection title on pediatric patients be revised to “Use in pediatric patients” for consistency within the section.

(b) (4)

- (b) (4) The second section about drug-lab test interactions belongs under “7 Drug Interactions.” As such, this section can be deleted from Warnings and Precautions entirely.

6 Adverse Reactions

- For ease of reading, we suggest that the list of most serious adverse reactions that appears at the beginning of this section be presented as a bulleted list, with cross-references at the end of each to the particular subsection of Warnings and Precautions where the topic is discussed in detail.

6.1 Incidence in controlled clinical trials

- The preferred (although not required) title for this section is “Clinical Trials Experience.”

- Where appropriate, please change (b) (4) to “adverse reactions” in this section. The Adverse Reactions guidance states that, whenever possible, this section should include

plausibly-related "reactions," and not all "events" seen in the trials. When we are talking about "reactions," we should call them "reactions" and if we need to talk about "events," call them "events."

- (b) (4)

  Please revise this sentence to correct the repetitive language.

- *"one patient treated with placebo (n =97) was discontinued after an attempted suicide."*

  Can this sentence be reworded to avoid saying that the patient "was discontinued"?

- We note that the text under the subheading "Most commonly observed adverse events in controlled trials" is inadvertently centered on the page. Please correct the justification.

- We note that Tables 1 and 2 are very long. Please consider if using a higher cut-off rate (e.g., 2% instead of 1%) for inclusion in the tables would be appropriate.

- With the implementation of the PLR and the new labeling guidances, there is an effort to eliminate "laundry lists" of rare events that are not plausibly related to the drug. Please consider if the lists of adverse events by body system that appear at the end of this section are appropriate to keep in the label.

(b) (4)

7 Drug Interactions

- In general, this section should present information on the clinically relevant drug interactions, and what to do about them (e.g, adjust the dose, stagger administration times). Detailed findings from pharmacokinetic drug interactions studies should be presented under "12.3 Pharmacokinetics" and cross-referenced from here to there.

7.1 CNS active drugs

- This section presents data on numerous drug interaction studies, some of which revealed important interactions and some that did not. In order to present the most relevant information to the reader, please consider reordering the information within this section to present the interactions that have clinical implications first (e.g., don't discuss the lack of an interaction with haloperidol first in the second paragraph).

7.2 Drugs that affect drug metabolism via cytochrome P450

- As recommended above, please consider revising these two paragraphs to broadly discuss the clinical implications of these interactions, while presenting the detailed pharmacokinetic findings under "12.3 Pharmacokinetics."

7.3 Other drugs

- As noted under the Warnings and Precaution section, vague section titles should be avoided in labeling. Instead, we suggest that each drug with clinically important interactions have its own subheading for ease of reading. If there is a group of drugs that were studied and revealed no interactions, they could be grouped together under a separate, appropriately titled, numbered subsection.

8.2 Labor and Delivery

- Because this section conveys no useful information for the reader, it may be deleted.

8.3 Nursing mothers

- The language in this section is not consistent with the regulations for the Nursing Mothers section. Please verify the required language that is applicable for this drug from section 201.57(c)(9)(iii) of the regulations and incorporate it here.

8.5 Geriatric Use

- This section does not include language required by the regulations [see 201.57(c)(9)(v)]. Please revise accordingly.

- Please consider adding a mention to this section of the need to use lower doses in elderly patients and a cross-reference to section 5.6 for additional information on use in elderly patients.

9.2 Abuse

- *"Studies of abuse potential in former drug abusers found that the effects of single doses of an* (b) (4) *of zolpidem tartrate* (b) (4) *40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo. "*

  Please delete (b) (4) from this sentence because it is unnecessary.

12.3 Pharmacokinetics

- The figure for plasma concentration vs. time should be numbered and titled.

- In the cross-reference at the end of the subsection on hepatic impairment, please reverse the order of the two referenced sections so they are presented in numerical order (i.e., Dosage and Administration first, followed by Warnings and Precautions).

14.1 Controlled trials supporting safety and efficacy

- Please consider revising this subsection title because this section contains no discussion of the drug's safety profile.

14.2 Studies Pertinent to Safety Concerns for Sedative/Hypnotic Drugs

- *"In five clinical studies; three controlled studies in adults (18-64 years of age) administered Ambien CR 12.5 mg and two controlled studies in the elderly (≥ 65 years of age) administered Ambien CR 6.25 mg or 12.5 mg, the effect of Ambien CR on vigilance, memory, or motor function were assessed using neurocognitive tests."*

  For ease of reading, please delete the semi-colon after "In five clinical studies" and use brackets around "three controlled studies in adults (18-64 years of age) administered Ambien CR 12.5 mg and two controlled studies in the elderly (≥ 65 years of age) administered Ambien CR 6.25 mg or 12.5 mg."

- *"In a 6-month placebo-controlled study in which Ambien CR was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first night off medication."*

  For consistency within the label, please consider changing "6-month" to "24-week."

  Please change "Total Sleep Time" to all lower case lettering.

17 [redacted] (b) (4)

- The title of this section must be "Patient Counseling Information" as required in the regulations.

- Because this product has a Medication Guide, the first line immediately after the main section title should read, "See Medication Guide (17.X)," entirely in italics.

- The text in this section should be revised to reflect the information that is important for the prescriber to convey to the patient. It should be written for the clinician, not for the patient.

- Please consider if all topics important for prescribers to convey to the patient are adequately covered here. Currently, this section discusses only the complex behaviors and some general instructions for use. Should other topics be added here (e.g., the risk of allergic reactions, risk of withdrawal effects)? Each topic can be presented as its own bullet or paragraph for ease of reading.

17.2 Medication Guide

- The paragraph that currently appears here can be deleted. The line that will be added immediately after “17 Patient Counseling Information” is meant to alert the prescriber to the existence of the medication guide, thus making this paragraph unnecessary.

Manufacturer Information

- The date that appears at the end of this label should be deleted. The date that appears at the end of Highlights is intended to replace the date that has traditionally appeared at the end of labels.

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

/s/

Iris Masucci
11/13/2007 09:57:44 AM
DDMAC REVIEWER

Laurie Burke
11/28/2007 02:06:28 PM
INTERDISCIPLINARY

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21774 Supplement # 003 Efficacy Supple Type SE-1

Proprietary Name: Ambien CR
Established Name: Zolpidem Tartrate CR
Strengths: 5 and 10 mg po capsules

Applicant: sanofi Aventis, U.S., Inc.
Agent for Applicant (if applicable):

Date of Application: 12/21/06
Date of Receipt: 12/21/06
Date clock started after UN: 12/21/06
Date of Filing Meeting: 2/16/07
Filing Date: 2/19/07
Action Goal Date (optional): 12/20/07 User Fee Goal Date: 12/20/07

Indication(s) requested: long term use (6 months); label update

Type of Original NDA: (b)(1) x (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) x (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S XX P X
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid XX Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain: on IR formulation only; no on this formulation

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication N/A ☐ NO ☐

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  N/A YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

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

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

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

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

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES X
   This application is: All electronic X Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? _____ 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 X 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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  Req for deferral YES X NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? N/A YES ☐ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

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

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

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: IND 25,361

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☐
  If yes, distribute minutes before filing meeting.

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

- Any SPA agreements? Date(s) _____ NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? N/A ☐ NO ☐ YES

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☐ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

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

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES x NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☐ NO X

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO X

ATTACHMENT

MEMO OF FILING MEETING

DATE: 4/3/07

NDA #: 21774/S-003

DRUG NAMES: Ambien CR (zolpidem tartrate)

APPLICANT: sanofi-aventis US, Inc.

BACKGROUND: This supplemental new drug application provides for an extended use (long term use – up to 6 months) for the use of Ambien CR (zolpidem tartrate) for the treatment of insomnia.

ATTENDEES: 5

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	D. Elizabeth McNeil, M.D.
Statistical:	Ohid Siddiqui, Ph.D.
Pharmacology:	Melissa Banks, Ph.D.
Biopharmaceutical:	Sally Yasuda, PharmD., M.S.
Regulatory Project Management:	Cathleen Michaloski, BSN, MPH
Other Consults:	

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

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? N/A ☐ NO ☐
  YES
  If no, explain:
- Advisory Committee Meeting needed? N/A 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 ☐

STATISTICS ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☐
  YES

PHARMACOLOGY/TOX X FILE X REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: no
REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

XX 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.☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3.☐ 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.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5.☐ Convey document filing issues/no filing issues to applicant by Day 74.

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager

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

/s/

Cathleen Michaloski
11/13/2007 01:31:54 PM
CSO

Cathleen Michaloski
11/13/2007 01:32:28 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21774Orig1s003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-774 SUPPL # 003 (004, 007, 008 inclusive) 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 ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

EFC4529
EFC4530

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 25,361	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 25,361	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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

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

/s/

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

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21774 Supplement Type (e.g. SE5): SE1 Supplement Number: 003

Stamp Date: Feb 20, 2007 PDUFA Goal Date: Dec 20, 2007

HFD 120 Trade and generic names/dosage form: Ambien CR (zolpidem tartrate) tablets, oral 12.5 mg and 6.25 (elderly)

Applicant: Sanofi Aventis Inc. Therapeutic Class:

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- ☐ Yes. Please proceed to the next question.
- XX No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): for use 7-10 days duration

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1 insomnia (only)

Indication #1: insomnia (sleep maintenance)

; this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- XX No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- XX Yes: Please proceed to Section A.
- ☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- XXX There are safety concerns
- ☐ Other: see attached memo

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:
Cathy Michaloski

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Memo from Dr. Mcneil
A bit of background that may help clarify matters:

The drug which is currently under review (PDUFA date 12/21) is Ambien CR- an extended release form of zolpidem tartrate.
Ambien CR was approved in 2005. At that time a partial waiver was granted for pediatric studies in preschoolers and a deferral was granted for school aged children.

In late 2006, the sponsor submitted a pediatric exclusivity study of Ambien (the immediate release form of zolpidem tartrate) in children with ADHD-associated insomnia. The study did not demonstrate efficacy. An unacceptably high rate of hallucinations was seen; 7.4% in the active group as compared to 0% in the placebo group. While there are post-marketing reports of hallucinations in adults using zolpidem, the incidence of hallucinations in adults during the controlled clinical trials was 1%.

The product did not receive a pediatric indication but language about the failed study with the high rate of psychiatric events was placed in the label. The exact language (reproduced below) to be included in both the Ambien and the Ambien CR labels. We arrived at the final language for the pediatric section after discussion with generics (Ruby Wang), OCC (Kim Dettlebach) and Pediatrics (Hari Sachs) in March of 2007.

The pediatric section for all zolpidem products (generic and branded) currently reads:
Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, (b) (4) (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse (b) (4) observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) (see (b) (4) Warnings and Precautions (b) (4).
Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

I have recommended a waiver of pediatric studies for Ambien CR since I do not see that the potential benefit outweighs the risk of psychiatric adverse events in this vulnerable population. The drug moiety being evaluated in a study of Ambien CR would be zolpidem tartrate, the same moiety evaluated in the study referred to above. The Division has not yet finalized all of the reviews so a final decision on waiver versus deferral has not yet been made.

If PeRC needs further information, please feel free to contact us.

Elizabeth

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

omplete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Pediatric Research and Equity Act Waivers

Product name and active ingredient/ dosage form: Ambien CR (zolpidem tartrate) 12.5 mg in adults; 6.25 mg in elderly

IND/NDA/BLA #: NDA 21774/003 Supplement Type: SE1 long term (6 mo) efficacy
Supplement Number: 003

HFD-120

Sponsor:sanofi-aventis, Inc.

Indications(s): treatment of sleep maintenance insomnia
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. All children aged 16 years and under

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

   As demonstrated in the studies done to acquire pediatric exclusivity for zolpidem, this product would be ineffective or unsafe in the pediatric group(s) for which a waiver is being requested.

   This information will be included in the pediatric use section of labeling.

   Background:

The drug which is currently under review (PDUFA date 12/21) is Ambien CR- an extended release form of zolpidem tartrate.
Ambien CR was approved in 2005. At that time a partial waiver was granted for pediatric studies in preschoolers and a deferral was granted for school aged children.

In late 2006, the sponsor submitted a pediatric exclusivity study of Ambien (the immediate release form of zolpidem tartrate) in children with ADHD-associated insomnia. The study did not demonstrate efficacy. An unacceptably high rate of hallucinations was seen; 7.4% in the active group as compared to 0% in the placebo group. While there are post-marketing reports of hallucinations in adults using zolpidem, the incidence of hallucinations in adults during the controlled clinical trials was 1%.

The product did not receive a pediatric indication but language about the failed study with the high rate of psychiatric events was placed in the label. The exact language (reproduced below) to be included in both the Ambien and the Ambien CR labels. We arrived at the final language for the pediatric section after discussion with generics (Ruby Wang), OCC (Kim Dettlebach) and Pediatrics (Hari Sachs) in March of 2007.

The pediatric section for all zolpidem products (generic and branded) currently reads:
Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using

psychoanaleptics), were treated with an oral solution of zolpidem, [redacted] (b) (4) [redacted] (b) (4) (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse [redacted] (b) (4) observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) [redacted] (b) (4) Warnings and Precautions: [redacted] (b) (4) Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse [redacted] (b) (4)

We will add a sentence which states:

FDA has not required pediatric studies of Ambien CR in the pediatric population based on these efficacy and safety findings.

Sent by email to Sponsor 5/16/07; NDA 21774/003

Dear Dr Ji:
Please provide SASCODES (without any SAS MACRO statements) so that we may reproduce the following tables from Study LTE5407. Please send by the SASCODES by Monday (05/21).

Table (8.1.1.1) 1 - Patient's global impression - item-1 - aid to sleep at Week-12 – ITT population
Table (8.1.1.2) 1 - Patient's global impression - item-1 - aid to sleep (favorable/unfavorable responses) at Week-12 - ITT population
Table (8.1.2.1) 1 - CGI - improvement scale at Week 12 - ITT population
Table (8.1.2.1) 2 - PGI items 2, 3, and 4 at Week-12 - ITT population
Table (8.1.2.1) 3 - Patient's morning questionnaire - mean change from baseline within month 3 - ITT population
Table (8.1.2.2) 1 - Patient's global impression - item 1 - aid to sleep per visit - ITT population
Table (8.1.2.2) 2 - Patient's global impression - item 2 - time to fall asleep per visit - ITT population
Table (8.1.2.2) 3 - Patient's global impression - item 3 - total sleep time per visit - ITT population
Table (8.1.2.2) 4 - Patient's global impression - item 4 - medication strength per visit - ITT population
Table (8.1.2.2) 5 - CGI - Improvement scale per visit - ITT population
Table (8.1.2.2) 6 - Total sleep time (min) - change from baseline per actual month - ITT population
Table (8.1.2.2) 7 - Wake time after sleep onset (min) - change from baseline per actual month - ITT population
Table (8.1.2.2) 8 - Sleep onset latency (min) - change from baseline per actual month - ITT population
Table (8.1.2.2) 9 - Quality of sleep - change from baseline per actual month - ITT population
Table (8.1.2.2) 10 - Number of nocturnal awakenings - change from baseline per actual month - ITT population
Table (8.1.2.2) 11 - Patient's global impression - Items 1, 2, 3, and 4 at endpoint - ITT population
Table (8.1.2.2) 12 – CGI – improvement scale at endpoint – ITT population

Any questions please call me.
Cathleen

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
FDA/CDER/ODE 1
cathleen.michaloski@fda.hhs.gov
P 301-796-1123

F 301-796-9842

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

/s/

Cathleen Michaloski
8/22/2007 10:36:27 AM
CSO

Cathleen Michaloski
8/22/2007 10:44:09 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-774/S-003

Sanofi Aventis U.S., LLC
300 Somerset Corporate Blvd.
Bridgewater, NJ 08807

Attention: Qinghua (Sarah) Ji, M.D.
Assistant Director, Regulatory Development

Dear Dr. Ji:

Please refer to your February 20, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ambien CR, 12.5 mg and 6.25 mg 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 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 Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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

/s/

Russell Katz

5/2/2007 01:02:34 PM

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

RECORD OF TELECON

Date:	February 15, 2007
NDA # /Supplement #	21774 / 003
Sponsor:	sanofi-aventis, Inc. Submitted 12/21/06; Received 12/21/06
Sponsor Representative:	Qinghua (Sara) Ji, M.D. Daryl DeKarske, MPH, Mark Moyer MS, Richard Gural, Ph.D.
FDA Representatives:	Russell Katz, M.D, D. Elizabeth McNeil, M.D., Jacqueline Ware, PharmD, Cathleen Michaloski, MPH Division of Neurology HFD-120
Subject:	Status of Ambien CR Efficacy Supplement

The sponsor submitted this 6 month efficacy supplement on 12/21/06. On 1/3/07 the sponsor was notified by fax through CDER EDR that there was a problem with the crt folder and that a replacement crt folder was needed. The sponsor claimed that they did not receive the fax requesting this information and therefore were unaware that any problems existed up until the date of this t-con (2/15/07). The Division did not identify the crt folder problem until a few days ago. The Division reminded the sponsor that even though the fax cannot be confirmed as received, the sponsor still has an obligation to submit a full reviewable application on Day 1. The Division further noted that 2 months of review time have been lost and this imposes a heavy burden on the review staff.

Since the 60 day filing date is Monday 1/19/07 a regulatory decision has to be made as to the adequacy of filing of the supplement by Friday 2/16/07. Ordinarily the Agency would refuse to file the application in this case. The Division explained to the sponsor that there were 2 options available to the Agency. The first option would be to **Refuse to File (RTF**) the application since a significant amount and content of clinical and statistical data are missing to allow for a substantive review. Under this scenario the sponsor would need to forfeit 25 % of their User Fee. The second option would be to re-code the current submission as a **pre-submission** which would re-start the PDUFA clock on the date the Agency receives the replacement crt folder. This option would not affect the User Fee.

The sponsor expressed agreement to the second option. The sponsor stated that they agree to consider the current information as a presubmission and stated they understood that the clock would be re-started once the full and correct information was determined to have submitted. They intend to send the new information on Tuesday 2/20/07. Further, the sponsor stated they understood that a new 60 day filing period would be re-imposed and that they were in agreement to this consequence.

_____

Cathleen Michaloski, BSN, MPH

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

/s/

Cathleen Michaloski
3/8/2007 11:28:51 AM
CSO

Cathleen Michaloski
3/8/2007 11:33:37 AM
CSO