

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-774

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-774
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:	NDA Response to Approvable Letter
Sponsor:	Sanofi-Synthelabo, Inc.
Submission Date:	July 6, 2005
OCPB Division:	DPE-I
OND Division:	Division of Neurology Drug Products HFD-120
OCPB Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCPB Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

This review evaluates a change in labeling that the Sponsor has submitted in the Response to Approvable Letter submission. OCPB was requested by the Clinical Division to review labeling in the Clinical Pharmacology section of the proposed Ambien CR product that was not in the original proposed labeling (June 2004). The sections in question were the 1) Clinical Pharmacology/Pharmacodynamics section regarding nomenclature of chemical structures and 2) the Clinical Pharmacology/Pharmacokinetics section regarding a comparison of the Ambien CR and IR products. The present review is based on the original OCPB review of the June 2004 submission that was performed in DPE2, HFD-170 by Drs. David Lee and Suresh Doddapaneni.

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has the following recommendations.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) is not aware of data to support

In fact, available data (individual curves) do not support this. OCPB recommends the following changes in the proposed labeling of the Pharmacokinetics section:

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

NDA 21-774
Ambien CR

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).

Please forward these comments to the Sponsor. In addition, the paragraph regarding chemical structures should be referred to the Office of New Drug Chemistry.

Sally Usdin Yasuda, MS, PharmD
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3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

This review evaluates a change in labeling that the Sponsor has submitted in the Response to Approvable Letter submission. OCPB was requested by the Clinical Division to review a section of the labeling regarding a comparison of the Ambien CR and IR products that was not in the original proposed labeling (June 2004). The present review is based on the original OCPB review of the June 2004 submission that was performed in DPE2, HFD-170 by Drs. David Lee and Suresh Doddapaneni.

3.2 Current Submission

The following sections were sent by Dr. Elizabeth McNeil with a request for review of the highlighted areas.

CLINICAL PHARMACOLOGY

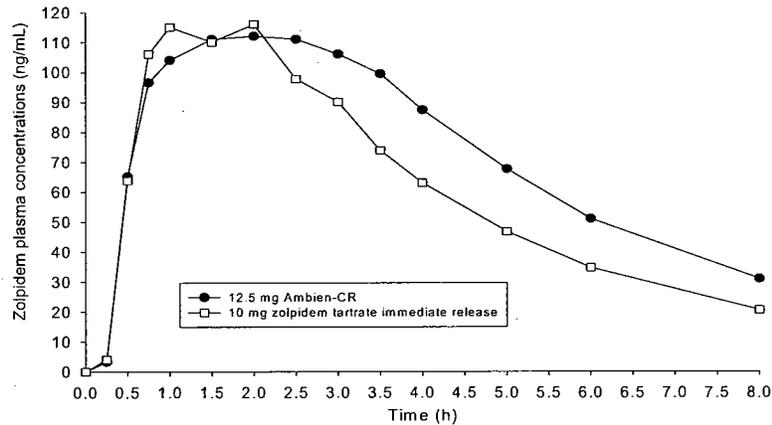
Pharmacodynamics:

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines [new language, which may be acceptable but need to confirm this with PK folks-Elizabeth], 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 BZ₁ receptor preferentially with a high affinity ratio of the alpha₁/alpha₅ subunits. The BZ₁ 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 BZ₁ 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.

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 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 section in Clinical Pharmacology/Pharmacodynamics regarding the chemical structure should be referred to Office of New Drug Chemistry.

The following refers to the proposed changes in the pharmacokinetics labeling. The comparison of Ambien CR and the immediate release form of zolpidem was not proposed in the original labeling. The OCPB review of the original submission considered the clinical pharmacology study that compared these formulations (Study GAR4624). This was a study comparing two zolpidem-MR formulations (10 mg and 12.5 mg) to the 10 mg IR marketed product in 24 young healthy male subjects. The sponsor refers to figure 2.7.1.2.3 in the original submission from that study to support the new statements in the proposed labeling. That figure, shown below, also reflects the PK of the 10 mg modified release product but otherwise agrees with the figure presented above in the proposed labeling.

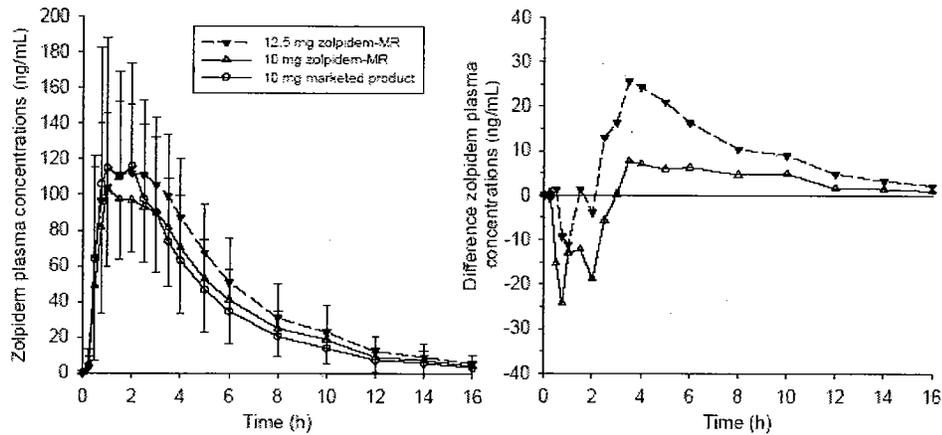


Figure (2.7.1.2.3) 1 - Mean (SD) zolpidem plasma concentration-time profiles obtained after single oral administration of zolpidem-MR 10 mg and 12.5 mg and of the 10 mg-marketed tablet (left), and mean of the difference between zolpidem-MR 10 mg and 12.5 mg and the 10 mg-marketed tablet (right) – (n = 24, study GAR4624)

The mean pharmacokinetic parameters from that study are shown below, taken from the original OCPB review.

Mean pharmacokinetic parameters of zolpidem:

Formulation		C _{max} (ng/mL) ^b	t _{max} (h) ^c	AUC (ng.h/mL)	t _{1/2α} (h)	F(abi) (%)	MRT (h)
8 mg intravenous infusion	Mean (SD)	245 (44.3)	-	707 (275)	2.56 (0.61)	-	-
	PE ₁	0.71	NS	1.06	NS	-	-
10 mg marketed product (reference)	Mean (SD)	167 (57.2)	0.83	589 (306)	2.59 (0.54)	65.8 (20.3)	4.24 (0.85)
	PE ₁	0.71	NS	1.06	NS	-	1.14
	90% CI	0.65-0.79	NS	0.95-1.19	NS	-	1.08-1.21
10 mg zolpidem-MR	Mean (SD)	118 (55.2)	1.0	611 (307)	2.77 (0.52)	68.4 (16.7)	4.85 (0.77)
	PE ₁	0.71	NS	1.06	NS	-	1.14
	90% CI	0.65-0.79	NS	0.95-1.19	NS	-	1.08-1.21
12.5 mg zolpidem-MR	Mean (SD)	134 (55.7)	1.5	740 (296)	2.83 (0.68)	68.3 (21.2)	5.02 (0.97)
	PE ₁	0.82	NS	1.04	NS	-	1.18
	90% CI	0.74-0.91	NS	0.93-1.17	NS	-	1.12-1.25

It can be seen that the elimination half-life observed with Ambien CR 12.5 mg is similar to that obtained with IR zolpidem tartrate (10 mg) and that is stated in the OCPB review.

the individual curves shown below do not support that.

1 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

3.3 Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) is not aware of data to support _____

In fact, available data (individual curves) do not support this. OCPB recommends the following changes in the proposed labeling of the Pharmacokinetics section:

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 mean plasma concentration time profiles for Ambien CR (12.5 mg) and for zolpidem tartrate (10 mg) are shown below.
The terminal elimination half-life observed with Ambien CR (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg).

Please forward these comments to the Sponsor. In addition, the paragraph regarding chemical structures should be referred to the Office of New Chemistry.

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/s/

Sally Yasuda
8/23/2005 02:49:39 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
8/24/2005 01:19:08 PM
BIOPHARMACEUTICS

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1 Executive Summary

Sanofi-Synthelabo, Inc. has submitted the Ambien® CR NDA for approval for — treatment of insomnia. In this current Ambien® CR NDA, the Applicant wishes to add the —

— The Applicant has submitted 11 studies under the Clinical Pharmacology section of the NDA. Additionally, there were 2 Phase III studies submitted in this NDA.

The main concept of this modified-release (MR) formulation (consists of a two-layer tablet that provides biphasic release of zolpidem: immediate followed by extended release) is to achieve comparable initial plasma concentrations to zolpidem 10 mg and to maintain plasma concentrations of the drug during the middle of the night while keeping the same half-life, and a low potential for next-day residual effects.

The “sleep maintenance” claim has been studied in two efficacy studies. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 have not been established.

The Clinical Pharmacology and Biopharmaceutics studies assessed dose selection, absolute bioavailability, bioavailability relative to Ambien tablets, effect of food, bioequivalence of the commercial and clinical trial formulations. The submitted Clinical Pharmacology and Biopharmaceutics information in this NDA package is adequate; however, a modification to the Ambien CR Package Insert is suggested.

1.1 Recommendations

From Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) point of view, the information contained in the NDA is acceptable provided that a mutually satisfactory agreement can be reached between the Agency and Sponsor regarding the text in the package insert (See Section 3: Detailed Labeling Recommendations).

The entire 'Pharmacokinetics' section of the 'Clinical Pharmacology' label has been re-formatted to follow the ADME format; additionally, it is noted that some changes are made to what is proposed by the Applicant, e.g., in the 'Dosage and Administration' section, for hepatic impairment subjects, the dosing revision is proposed.

1.2 Phase IV Commitments – None

1.3 Summary of CPB Findings

Currently, Ambien 5 mg and 10 mg tablets are marketed for the short term treatment of insomnia. Ambien tablets were shown to decrease sleep latency and to increase duration of sleep for up to 35 days in controlled studies. In this NDA, approval is sought for Ambien CR 6.25 mg and 12.5 mg tablets for — sleep maintenance. In support, data from eleven clinical pharmacology and two phase III studies were submitted.

The Clinical Pharmacology and Biopharmaceutics studies assessed dose selection, absolute bioavailability, bioavailability relative to Ambien tablets, effect of food, bioequivalence of the commercial and clinical trial formulations, IVIVC, pharmacokinetics in the elderly, and gender differences in pharmacokinetics. With respect to all other aspects (such as metabolism, drug-drug interactions, hepatic and renal impairment, etc.), data acquired previously with Ambien tablets is being relied upon. The two Phase III clinical trials were adequate, randomized, placebo controlled and assessed Ambien CR 12.5 mg dose in young adults in study EFC 4529 and Ambien CR 6.25 mg dose in the elderly in study EFC4530.

To decrease the sleep latency, — and maintain the sleep, several formulations with differing ratios of immediate release and extended release fractions were developed. The 12.5 mg formulation designed to release *in vitro*, 60% of the dose immediately and 40% released up to four hours was selected for further development. This formulation was felt to have produced the best sleep qualities with least residual effects out of the several different tested formulations. For Ambien tablets, significant pharmacokinetics differences were seen for the elderly compared to young adults (means for C_{max}, T_{1/2}, and AUC were higher in the elderly by 50%, 32%, and 64%, respectively). As such, recommended dose for the elderly is half of that for young adults (5 mg versus 10 mg). For these reasons, 6.25 mg dose was tested in the elderly phase III trial while 12.5 mg dose was assessed in the young adult trial. In both studies, Ambien CR had a statistically significant treatment effect compared to placebo

The absolute bioavailability of Ambien CR tablets is about 70%. Ambien CR bioavailability relative to Ambien tablet is about 100%. The 12.5 mg and 6.25 mg doses were approximately

dose-linear. Minimal accumulation after repeated once daily dosing of Ambien CR is expected because of zolpidem's relatively short elimination half-life of 2 to 3 hours.

With food, mean AUC and Cmax of Ambien CR were decreased by 23% and 30%, respectively, while median Tmax was increased from 2 hours to 4 hours. As such, Ambien CR should be administered two hours after a meal.

With respect to dosage adjustment in hepatic impairment patients, an initial 5-mg dose is recommended in these patients. However, for Ambien CR tablets, sponsor is proposing a downward dosage adjustment without providing a rationale. Similar to Ambien tablets, patients with hepatic impairment should be recommended an initial 6.25 mg dose.

There is no significant gender effect with Ambien CR tablets. In the elderly, plasma levels were elevated similar to those seen previously with Ambien tablets. Commercial and clinical trial formulations were bioequivalent. An acceptable IVIVC correlation was demonstrated for Ambien CR tablets.

Overall, adequate data characterizing the Clinical Pharmacology and Biopharmaceutics aspects of Ambien CR tablets was provided.

2 QBR

2.1 General Attributes of the Drug and Drug Product

Zolpidem tartrate (10 and/or 5 mg tablets) has been approved in 105 countries including the United States, Europe, Australia and Japan. In the United States, zolpidem tartrate is marketed as Ambien® since 1993 (NDA 19-908) for the short term treatment of insomnia. Ambien was shown to decrease sleep latency and to increase duration of sleep for up to 35 days in controlled studies. The current NDA seeks approval of a modified release formulation of zolpidem of sleep maintenance.

The Clinical Pharmacology and Biopharmaceutics studies assessed dose selection, absolute bioavailability, bioavailability relative to Ambien tablets, effect of food, bioequivalence of the commercial and clinical trial formulations, IVIVC, pharmacokinetics in the elderly, and gender differences in pharmacokinetics. With respect to all other aspects (such as metabolism, drug-drug interactions, hepatic and renal impairment, etc.), data acquired previously with Ambien tablets is being relied upon. The two phase III clinical trials were adequate, randomized, placebo controlled and assessed Ambien CR 12.5 mg dose in young adults in study EFC 4529 and Ambien CR 6.25 mg dose in the elderly in study EFC4530.

2.1.1 What is the mechanism of action of Zolpidem?

Zolpidem is a non-benzodiazepine hypnotic that acts at the GABA-A receptor complex.

Zolpidem is a hypnotic and belongs to non-benzodiazepine agents. It is a non-benzodiazepine hypnotic of the imidazopyridine class. The pharmacological effects of zolpidem are produced by an agonist action at an allosteric binding site associated with the GABA-A receptor complex. Unlike most other drugs which act at similar binding sites (i.e., benzodiazepines), zolpidem shows selective binding to receptors containing alpha1 subunits. Recent evidence has shown that this subtype of receptor is specifically involved in mediating hypnotic actions.

2.1.2 What is the product rationale?

Zolpidem release characteristics were modified to target initial concentrations comparable to those of Ambien tablets and to maintain concentrations during the middle of the night to decrease sleep latency, —, and maintain the sleep for the Ambien CR product relative to Ambien tablets.

Zolpidem tartrate modified release tablets (Zolpidem-MR tablets) are coated bi-convex two layer-tablets (two-layers provide biphasic release of zolpidem: 60% of the dose as immediate release within about 30 minutes and the remaining 40% of the dose as prolonged release up to 4 hours). Zolpidem-MR tablets are to achieve comparable initial plasma concentrations to currently marketed zolpidem-IR tablets and to maintain plasma concentrations of the drug during the middle of the night while keeping the same half-life, and a low potential for next-day residual effects.

The Applicant stated that since the active substance remains unchanged, no major changes were expected in the safety profile of zolpidem-MR at doses of 6.25 and 12.5 mg compared to zolpidem at doses of 5, 10 and 15 mg. The increase in dose, or higher residual plasma concentrations of zolpidem-MR 12.5 mg compared with the 10 mg-marketed product were not expected to substantially modify the safety profile. The long-term safety profile of zolpidem was established in the NDA 19-908 and confirmed through the large post-marketing experience obtained after more than 10 years of marketing.

2.1.3 What is the composition of Ambien CR tablets?

Ambien CR 6.25 mg and 12.5 mg tablets are coated two layer tablets. Layer's 1 and 2 have immediate release and extended release properties, respectively. The tablet coating dissolves rapidly on coming into contact with an aqueous medium. Layer 1 dissolves immediately, while layer 2 forms a gel and then erodes slowly, which provides for the prolonged release of zolpidem tartrate.

The release profile of zolpidem tartrate from the modified release tablets is equivalent for both strengths. It is bi-modal, with an immediate release of part of the zolpidem tartrate content of the tablet, followed by a prolonged release of the remaining drug substance over a period of 4 hours. This bi-modal release profile is ensured by the presence of two layers in the tablet. The tablet coating dissolves rapidly on coming into contact with an aqueous medium. One layer of the tablet (layer 1) dissolves immediately, while the other layer (layer 2) forms a gel and then erodes slowly, which provides for the prolonged release of zolpidem tartrate.

Composition of 6.25 mg MR tablet:

Components	Function	Compendial Reference	Unit (mg)	Unit (%) ^a
Zolpidem tartrate	Active	In-house		
Lactose monohydrate ^b		NF		
Microcrystalline cellulose		NF		
Sodium starch glycolate		NF		
Hypromellose		USP		
Magnesium stearate		NF		
Colloidal silicon dioxide		NF		
Ferric oxide, red		NF		
Potassium bitartrate		USP		
Titanium dioxide		USP		
Polyethylene glycol				
Total tablet weight (mg)			260.000	-

Composition of the 12.5 mg MR tablet:

Components	Function	Compendial Reference	Unit (mg)	Unit (%) ^a
Zolpidem tartrate	Active	In-house		
Lactose monohydrate ^b		NF		
Microcrystalline cellulose		NF		
Sodium starch glycolate		NF		
Hypromellose		USP		
Magnesium stearate		NF		
Colloidal silicon dioxide		NF		
Ferric oxide, yellow		NF		
Potassium bitartrate		USP		
Titanium dioxide		USP		
Polyethylene glycol		NF		
Total tablet weight (mg)			260.000	-

2.2 General Clinical Pharmacology

2.2.1 What is the available Clinical Pharmacology information on zolpidem?

Absolute bioavailability is about 70%. Mean C_{max} is 121 ng/mL (range: 58 to 272) occurring at a mean time (t_{max}) of 1.6 hours after administration of the 10 mg-marketed IR product. Mean zolpidem t_{1/2} is 2.5 hours. Zolpidem demonstrates linear kinetics in the dose range of 2.5 to 40 mg immediate-release formulations, with respect to C_{max} and AUC. Zolpidem does not accumulate in young adults following nightly dosing for 15 days with the 20 mg IR formulation.

In vitro studies using human liver microsomes and heterologously expressed individual human cytochromes P450 (CYPs) have demonstrated that zolpidem is biotransformed to three pharmacologically inactive hydroxylated metabolites by a series of CYP enzymes including CYP3A4, CYP2C9, CYP1A2, CYP2D6 and CYP2C19, in decreasing order of importance. CYP3A4 is the principal enzyme responsible for zolpidem metabolism, accounting for approximately 60% of net CYP-mediated hepatic clearance. Zolpidem itself is not a significant inhibitor of human CYP isoforms.

In chronic hepatic insufficiency patients, 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. The pharmacokinetics were not altered in patients with end-stage renal failure undergoing hemodialysis.

2.2.2 Exposure-response

2.2.2.1 Are there an Exposure/Response (E/R) relationship for efficacy and/or safety for Ambien CR?

There is no data assessing concentration-response relationship for Ambien CR with respect to efficacy and safety. Fixed doses of 12.5 mg for young adults and 6.25 mg for the elderly are proposed based on the findings from (1) previous efficacy, safety, and pharmacokinetics information acquired for Ambien tablets and (2) the formulation selection study for different formulations of Ambien CR (formulations with differing ratios of immediate release and extended release portions). To decrease the sleep latency, increase sleep duration and maintain the sleep, several formulations with differing ratios of immediate release and extended release fractions were developed. The 12.5 mg formulation designed to release in vitro, 60% of the dose immediately and 40% released up to four hours was selected for further development. This formulation was felt to have produced the best sleep qualities with least residual effects out of the several different tested formulations. For Ambien tablets, significant pharmacokinetics differences were seen for the elderly compared to young adults (means for C_{max}, T_{1/2}, and AUC were higher in the elderly by 50%, 32%, and 64%, respectively). As such, recommended dose for the elderly is half of that for young adults (5 mg versus 10 mg). For these reasons, 6.25 mg dose was tested in the elderly phase III trial while 12.5 mg dose was assessed in the young adult trial. According to the sponsor, in both studies, Ambien CR had a statistically significant treatment effect compared to placebo.

Study PDY4054 assessed pharmacodynamic properties of several different formulations of Ambien CR. Study PDY4054 was designed to evaluate the pharmacodynamic properties of several zolpidem-MR formulations using polysomnography (PSG) in a model of sleep disturbance. Eight formulations of potential interest were selected for investigation based on their total dosage compared with the 10 mg-marketed product and their drug release profiles.

Zolpidem-MR formulations by immediate and prolonged release doses in study PDY4054

Formulations	A	B	C	D	E ^a	F	G	H
Total dose (mg)			12.5	-	12.5	-	12.5	
Drug content of layer 1								
Drug content of layer 2								
Dose released in vitro within 30 minutes (mg)					7.5			
Dose released in vitro between 30 minutes and 4 hours (mg)					5.0			

Formulation E is identical to zolpidem-MR 12.5 mg.

Thirty-six healthy young adult male and female subjects (18 to 40 years of age) randomly received all 10 treatment conditions. Each subject received a single dose during a treatment period; each treatment period was separated by a washout period of at least seven days.

Polysomnography assessments, psychometric tests (of vigilance, memory, and motor functions), subjective assessments (of QOS and awakening), and plasma concentrations at awakening were evaluated. Polysomnography recordings were scored manually according to the standard criteria of Rechtschaffen and Kales by a trained electroencephalogram (EEG) technician, who was blinded to the study drugs.

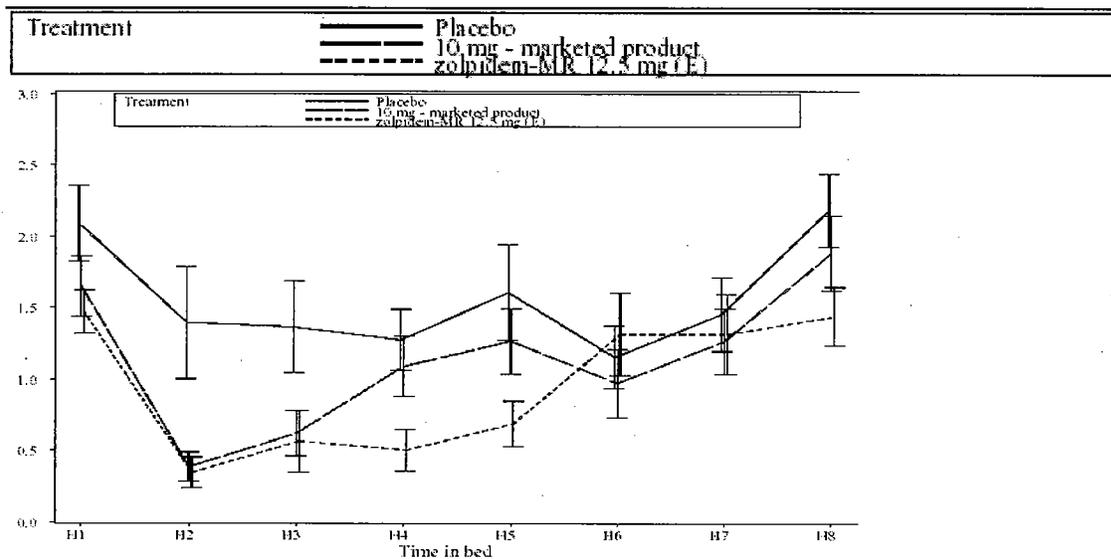
Variables from PSG recordings were segmented into hourly information, and the variables from the psychomotor tests were recorded 8 and 9 hours postdose. All variables were analyzed at each timepoint using a linear mixed-effects model with fixed term for sequence, period and treatment, and random term for subject within sequence, using SAS PROC MIXED procedure. Exploratory treatment comparisons between zolpidem-MR formulation E and the 10 mg-marketed product were performed.

- Most formulations did not fulfill expected criteria in terms of increase in duration of activity without residual effect that would have supported a clinical interest in further development;
- formulations F, G, and H induced residual effects;
- formulations A, B, and C did not increase the duration of the activity in the middle of the night, and formulation D demonstrated this activity but to a lesser extent than did formulation E;
- As a consequence, formulation E was selected and tested in the Phase 3 studies.

Polysomnography

Formulation E had a sustained effect on the number of awakenings up to 5 hours post dose, whereas the 10 mg-marketed product significantly reduced the number of awakenings only up to 3 hours post dosing when compared with placebo. The difference between formulation E and the 10 mg-marketed product was statistically significant at 4 hours post dosing and close to statistical significance ($p = 0.0542$) at 5 hours post dose, showing a more prolonged duration of activity:

Number of awakenings per hour of time in bed [mean (\pm SEM)]:



Psychometric assessment of residual effects

Formulation E did not differ from placebo on any of the psychometric tests at 8 or 9 hours postdosing.

Sleep evaluation questionnaire

At 9 hours postdosing, formulation E showed a statistically significant improvement in the item "Ease of getting to sleep" ($p = 0.0004$) and in the item "Quality of sleep" ($p = 0.0007$) compared with placebo. The two other items, "Awakening" and "Behavior after awakening", remained unchanged and were not different from placebo. In conclusion, formulation E appeared to be the optimal selection, with increase of duration of activity (especially in the middle of the night) and lack of residual effects 8 and 9 hours postdosing.

2.2.2.2 Does zolpidem prolong the QT or QTc interval?

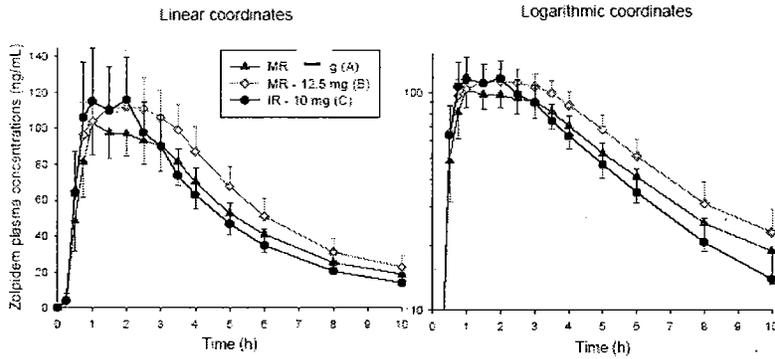
The Applicant did not submit any QT information. It is unknown if zolpidem can cause QT prolongation. However, post-marketing reports do not appear to show that zolpidem causes Torsade de pointes.

2.2.3 Are the pharmacokinetics of zolpidem-MR tablets adequately characterized?

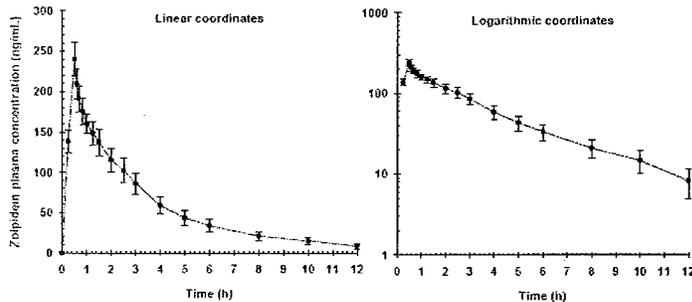
The absolute bioavailability of the 12.5 mg zolpidem-MR tablet is about 68% and is similar to the absolute bioavailability of 66% for the 10 mg IR tablet. zolpidem-MR 6.25 mg and 12.5 mg tablets appear to exhibit approximate dose-linearity. The terminal half-life of zolpidem for Ambien and Ambien CR is similar, about 2-3 hours. Minimal accumulation after repeated once daily dosing is expected because of zolpidem's relatively short elimination half-life of 2 to 3 hours.

Absolute Bioavailability and single dose pharmacokinetics of Ambien CR

Study GAR4624 compared two zolpidem-MR formulations [7 mg formulation (α) and 12.5 mg formulation (β)] to both the 10 mg IR marketed product and to an IV formulation of zolpidem tartrate (8 mg) in 24 young healthy male subjects. Intravenous administration over a 30-minute infusion was administered during a non-randomized fourth period.



Mean plasma concentration-time profiles of zolpidem obtained in 24 healthy young male subjects after a single oral administration of the biphasic 10 and 12.5 mg formulations (treatments A and B) and of the IR 10 mg tablet (treatment C)



Mean plasma concentration-time profile of zolpidem obtained in 24 healthy young male subjects after an intravenous infusion (30 minutes) of 8 mg dose.

**APPEARS THIS WAY
ON ORIGINAL**

Mean pharmacokinetic parameters of zolpidem:

Formulation		C _{max} (b) (ng/mL)	t _{max} (h) ^c	AUC (ng.h/mL)	t _{1/2z} (h)	F(abs) (%)	MRT (h)
8 mg intravenous infusion	Mean (SD)	245 (44.3)	-	707 (275)	2.56 (0.61)	-	-
	PE _{0.5}	0.71	NS	1.06	NS	1.14	
10 mg marketed product (reference)	Mean (SD)	167 (57.2)	0.88	589 (306)	2.59 (0.54)	65.8 (20.3)	4.24 (0.85)
	90% CI	0.65-0.79	NS	0.95-1.19	NS	1.08-1.21	
7.5 mg zolpidem-MR	Mean (SD)	118 (35.2)	1.0	611 (307)	2.77 (0.52)	68.4 (16.7)	4.85 (0.77)
	90% CI	0.74-0.91	NS	0.93-1.17	NS	1.12-1.25	
12.5 mg zolpidem-MR	Mean (SD)	134 (35.7)	1.5	740 (296)	2.83 (0.68)	68.3 (21.2)	5.02 (0.97)
	90% CI	0.74-0.91	NS	0.93-1.17	NS	1.12-1.25	

The F (abs) values were 65.8, 68.4 and 68.3% for treatment IR 10 mg, MR 7.5 mg, and MR 12.5 mg, respectively.

Pharmacokinetics of zolpidem-MR after multiple doses

No formal multiple dose study was conducted; however, accumulation after repeated dosing is not expected with zolpidem-MR due to its short elimination half-life (2 to 3 hours) and the once daily dosing. This has been further confirmed by residual plasma concentrations measured in efficacy studies. Single plasma concentrations were measured after day 1 and day 15 dosing in the two efficacy studies (EFC 4529 and EFC4530) conducted in adult and elderly insomnia patients with the 12.5 mg and 6.25 mg doses, respectively. The sampling time was approximately 9 hours after administration.

There was no statistically significant difference between zolpidem C_{9h} values obtained on D1 and on D15 in both adult and elderly patients.

Dose linearity

A study was not conducted to assess dose-proportionality of Ambien CR 6.25 mg and 7.5 mg strengths. However, across study comparisons of data (from studies assessing bioequivalence of the commercial and clinical trial formulations of 6.25 mg and 12.5 mg strengths), it appears that zolpidem-MR formulation exhibits approximate dose-linearity.

2.3 Intrinsic Factors

2.3.1 Do age, gender, drug-drug interactions, hepatic impairment, and renal impairment affect the pharmacokinetics of Ambien CR?

Effect of age and gender on the pharmacokinetics of Ambien CR was investigated. However, with respect to all other aspects such as drug-drug interactions, hepatic impairment, and renal impairment, data acquired previously with Ambien tablets is being relied upon.

Age and Gender

The pharmacokinetic data of a total of 237 subjects from five single dose Phase 1 studies (ALI5057, BDR5477, BDR5478, GAR4624 and POP4055) were combined and the gender, body weight and age group effects were evaluated in Study POH0047:

Main pharmacokinetic parameters obtained after a single oral dose of zolpidem-MR in young and elderly subjects by dose (6.25 mg and 12.5 mg) and gender

Parameter	Descriptive statistics	YOUNG				ELDERLY	
		Zolpidem-MR 6.25 mg		Zolpidem-MR 12.5 mg		Zolpidem-MR 6.25 mg	
		Male	Female	Male	Female	Male	Female
Number of subjects		24	12	83	58	32	28
C_{max} (ng/mL)	Mean (CV%)	43.7 (59.6)	79.4 (45.6)	125 (37.3)	175 (41.5)	66.8 (44.0)	74.2 (35.9)
	Geometric mean	36.2	69.7	115	158	61.2	70.0
t_{max}(h)	Median	2.5	3.0	1.5	2.5	2.5	2.5
AUC (ng.h/mL)	Mean (CV%)	267 (84.9)	551 (48.6)	654 (46.5)	1093 (56.4)	456 (61.6)	466 (60.0)
	Geometric mean	191	449	572	905	385	408
t_{1/2z} (h)	Mean (CV%)	2.29 (33.7)	3.31 (29.1)	2.54 (23.3)	2.95 (32.3)	3.20 (29.5)	2.87 (32.4)
	Geometric mean	2.17	3.12	2.47	2.80	3.07	2.75

C_{max} = maximum plasma concentration; t_{max} = time to reach C_{max}; AUC = area under the plasma concentration-time curve extrapolated to infinity; t_{1/2z} = terminal half-life; CV% = coefficient of variation

Young subjects,

The following C_{max} and AUC ratios have been calculated.

Gender ratio (female/male) estimates with 90% CIs for C_{max} and AUC (with and without normalization for body weight) in young healthy subjects

Parameter	Female/Male Ratios Estimate With Confidence Interval		
	Estimate	90% CI ^a	Pr > t
C _{max}	1.49	[1.33, 1.67]	<0.0001
Weight normalized C _{max}	1.24	[1.10, 1.40]	0.0030
AUC	1.74	[1.49, 2.04]	<0.0001
Weight normalized AUC	1.45	[1.23, 1.71]	0.0002

CI = confidence interval; C_{max} = maximum plasma concentration; AUC = area under the plasma concentration-time curve extrapolated to infinity.

^a CIs for the ratios were computed using the anti-log transformation.

- Zolpidem C_{max} and AUC were statistically significantly higher (p<0.0001) in females compared with males.
- Gender ratio (female/male) estimates were 1.49 and 1.74 for C_{max} and AUC, respectively.
- Normalization to body weight decreased the gender ratio to 1.24 and 1.45 for C_{max} and AUC, respectively. However, the difference remained statistically significant (p = 0.0030 for C_{max} and p = 0.0002 for AUC).

- Overall, a slight increase in $t_{1/2z}$ for females (2.95 hours) compared with males (2.54 hours) was observed following a zolpidem-MR 12.5 mg single dose, but was not considered to be of clinical relevance.
- No significant gender effect was shown on t_{max} .

Elderly Subjects:

The following C_{max} and AUC ratios have been calculated.

Main pharmacokinetic parameters obtained after single oral dose of zolpidem-MR 6.25 mg in elderly subjects and gender ratio estimates with 90% CIs

Parameter	Elderly Female/Male Ratios Estimate With Confidence Interval	
	Estimate	90% CI ^a
C_{max} (ng/mL)	1.13	[0.93, 1.37] ^b
AUC (ng.h/mL)	1.02	[0.78, 1.33] ^b

^a CIs for the ratios were computed using the anti-log transformation,

^b No statistically significant difference between male and female subjects.

- No statistically significant gender effect could be shown for C_{max} or AUC values with or without normalization of body weight).
- Gender ratio (female/male) estimates were 1.13 and 1.02 for C_{max} and AUC, respectively.

Short Summary: The results of this inter-study analysis indicated that a high variability in the pharmacokinetics of zolpidem-MR was observed:

- a gender effect in young subjects with C_{max} and AUC values 49% and 74% higher, respectively, in females than in males; this could partly be explained by a difference in body weight.
- no significant gender effect in elderly subjects; Additionally,
 - in elderly male subjects, a significant increase in C_{max} and AUC of 56% and 82%, respectively, compared to young male subjects after zolpidem-MR 6.25 mg administration;
 - in females, the age effect was not significant with increases of 18% in C_{max} and 7% in AUC.

All these characteristics are consistent with those known for zolpidem-marketed product (NDA 19-908).

2.3.2 What is the status of pediatric studies and/or any pediatric plan for study?

Studies were not conducted in pediatric subjects with zolpidem. A deferral from conducting studies is sought in pediatrics.

2.4 Extrinsic Factors – Not applicable

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation bioequivalent to the pivotal clinical trial formulation?

The commercial and clinical trial formulations are bioequivalent.

The bioequivalence of the proposed commercial zolpidem-MR 6.25 mg and 12.5 mg formulations (2C3) versus the clinical zolpidem-MR formulations (1A1) of the corresponding strength, after single oral administration was evaluated. The two studies were single-center, open-label, single nighttime dose, randomized, two-treatment, two-period, two-sequence crossover studies in fasting conditions. Each of the two treatment periods was separated by a washout period of seven days.

The zolpidem-MR 6.25 mg and 12.5 mg strengths of commercial formulation (2C3) were bioequivalent to the clinical trial formulation (1A1).

Mean (SD) pharmacokinetic parameters of zolpidem, treatment ratio estimates and 90% CIs for zolpidem-MR 6.25 mg (2C3) formulation versus zolpidem-MR 6.25 mg (1A1) formulation:

Zolpidem Parameters	Zolpidem-MR 6.25 mg (2C3) Formulation (test)	Zolpidem-MR 6.25 mg (1A1) Formulation (ref)	Ratio Estimate [90% CIs] ^c
C _{max} (ng/mL)	61.4 (28.4)	64.5 (35.3)	0.99 [0.92; 1.06]
t _{max} (h) ^a	2.50 [0.50-10.00]	2.50 [0.50-8.00]	0.00 [-0.25; 0.25] ^b - NS
AUC _{last} (ng.h/mL)	378 (222)	408 (268)	0.96 [0.90; 1.01]
AUC (ng.h/mL)	405 (253)	435 (304)	0.95 [0.89; 1.01]
t _{1/2z} (h)	2.84 (0.94)	2.88 (1.00)	NS

^a median (range).

^b median difference and 90% CIs (Hodges-Lehman approach), NS – not significant

^c ratio of test versus reference.

Mean (SD) pharmacokinetic parameters of zolpidem, treatment ratio estimates and 90% CIs for zolpidem-MR 12.5 mg (2C3) formulation versus zolpidem-MR 12.5 mg (1A1) formulation:

Zolpidem Parameters	Zolpidem-MR 12.5 mg (2C3) Formulation (test)	Zolpidem-MR 12.5 mg (1A1) Formulation (ref)	Ratio Estimate [90% CIs] ^c
C _{max} (ng/mL)	136 (58.6)	136 (63.3)	1.02 [0.95; 1.09]
t _{max} (h) ^a	2.00 [0.50-5.00]	2.29 [0.50-8.00]	0.25 [0.00; 0.50] ^b - NS
AUC _{last} (ng.h/mL)	721 (403)	749 (445)	0.99 [0.92; 1.06]
AUC (ng.h/mL)	748 (434)	787 (501)	0.98 [0.92; 1.06]
t _{1/2z} (h)	2.67 (0.76)	2.70 (0.86)	NS

^a median (range).

^b median difference and 90% CIs (Hodges-Lehman approach), NS – not significant

^c ratio of test versus reference.

2.5.2 What is the effect of food on the bioavailability of zolpidem from Ambien CR? What dosing recommendation should be made, if any, regarding administration of Ambien CR in relation to meals?

Under fed conditions relative to fasting state, mean AUC and C_{max} values decreased by 23% and 30%, respectively while median t_{max} was prolonged from 2 to 4 hours. As such, Ambien CR should be administered two hours after a meal.

Study ALI5057 compared the pharmacokinetics of zolpidem-MR 12.5 mg when administered as a single dose while fasting or 30 minutes after a standardized high-fat “breakfast” (dinner) in 23 healthy male and 22 healthy young female subjects.

With food, mean AUC and C_{max} values were decreased by 23% and 30%, respectively; median t_{max} was prolonged from 2 to 4 hours.

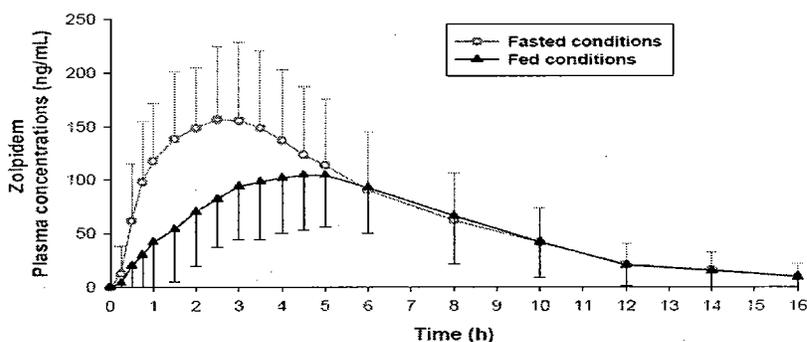
Mean (SD) pharmacokinetic parameters of zolpidem, treatment ratio estimates and 90% CIs for zolpidem-MR 12.5 mg administered fed or fasted:

Zolpidem Parameters	Zolpidem-MR 12.5 mg Fed (test)	Zolpidem-MR 12.5 mg Fasted (ref)	Ratio Estimate [90% CIs] ^c
C _{max} (ng/mL)	132 (50.4)	188 (71.7)	0.70 [0.65; 0.76]
t _{max} (h) ^a	4.00 [1.00-8.00]	2.00 [0.75-4.00]	1.75 [1.25; 2.25] ^b
AUC (ng.h/mL)	894 (516)	1155 (629)	0.77 [0.72 ; 0.83]

^a median (range),

^b median difference and 90% CIs (Hodges-Lehman approach),

^c ratio fed versus fasted.



Mean (SD) zolpidem plasma concentrations vs. time profile after a single dose of zolpidem-MR 12.5 mg in fasted and fed states.

2.5.3 Is there any IVIVC information for Ambien?

In the current submission, the Applicant did not submit the IVIVC information. However, the Applicant has previously submitted a request to the Division of Neuropharmacological Drug Products to concur on a Level A IVIVC establishment, and that a biowaiver can be granted for the proposed to-be-marketed Ambien CR tablets (I 25,361 Serials #239 and 246). The submitted information was reviewed (11/21/03 and 4/21/04, respectively) and found acceptable.

Additionally, in the current submission, the Applicant conducted a bioequivalence study to compare the Phase 3 and to-be-marketed Ambien CR tablets.

2.5.4 Are the dissolution conditions and specifications adequate to ensure in vivo performance and quality of the product?

The proposed dissolution method and specifications appear to be adequate.

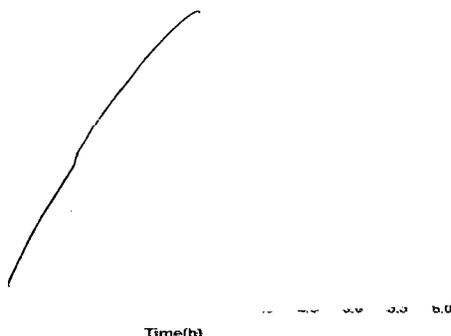
The proposed dissolution method is as follows ; USP apparatus I (basket) at _____ rotation per minute (rpm) with _____ at 37°C during 6 hours. Dissolution profiles of zolpidem-MR tablets are not affected by the basket rotation speed between _____ rpm, the dissolution medium _____ and the dissolution medium _____. The proposed specifications are: _____ at 30 min, _____ at 90 min, _____ at 240 min.

Dissolution profiles for all zolpidem-MR 12.5 mg batches manufactured are summarized below:

Summary of in vitro dissolution studies:

Study Ref. No.	Product ID/ Batch No.	Dosage Form	Conditions	No. of Dosage Units	Sampling Times Mean % Dissolved (Range)			
					0.5	1.5	4 (h)	
GAR4624	CL-03281 CL-03283 (IA1)	12.5 mg tablet	Dissolution: Apparatus I, + grid Speed of rotation: _____ rpm Medium/Temperatur 37°C	6	58	75	91	
				6	60	80	102	
PDY4054	CL-03483 CL-03501 CL-03512 CL-03535 CL-03536 CL-03547 CL-03549 CL-03711 (IA1)	12.5 mg tablet (A) 12.5 mg tablet (B) 12.5 mg tablet (C) 12.5 mg tablet (D) 12.5 mg tablet (E) 12.5 mg tablet (F) 12.5 mg tablet (G) 12.5 mg tablet (H)	Dissolution: Apparatus I (USP) Speed of rotation: _____ rpm Medium/Temperatur 37°C	6	66	48	83	101
				12	72	70	96	98
				6	40	85	100	
				6	81	66	99	
				6	50	91	96	
				6	74			
				6	65	81	98	
				6	60	79	98	
EFC4529 PDY5035 PDY5036 BDR5478	CL-04700 (IA1)	12.5 mg tablet	Dissolution: Apparatus I (USP) Speed of rotation: _____ rpm Medium/Temperatur 37°C	6	60	77	98	
ALI5057	CL-05614 (2B2)	12.5 mg tablet		6	59	76	97	
BDR5478	CL-06562 (2C3)	12.5 mg tablet		6	62	80	98	
POP4055	CL-04774 (IA1)	6.25 mg tablet		6	64	83	103	
EFC4530 PDY5035 BDR5477	CL-05037 (IA1)	6.25 mg tablet		6	61	79	98	
BDR5477	CL-06561 (2C3)	6.25 mg tablet		6	60	76	95	

Release profile for 12.5-mg tablet formulation



Dissolution profiles of zolpidem-MR 12.5 mg tablets (1A1), (2B2), and (2C3)

2.6 Analytical Section

2.6.1 Is the analytical assay method adequately validated?

Analytical assay method used to quantify zolpidem in plasma was sensitive and specific. Limit of quantification, storage stability, within- and between-run precision and accuracy parameters were acceptable.

An electrospray ionization liquid chromatography tandem mass spectrometry (LC-MS/MS) method was developed and fully validated for the quantification of zolpidem in human plasma, following extraction using _____ as the internal standard. Chromatographic separation was accomplished using an _____ column (C18, 2.1 mm x 50 mm, 5 μ m) at 50°C with a mobile phase of 20 mM ammonium formate (pH 3)/methanol at 0.5 mL/min. The assay was validated from 0.5 ng/mL [limit of quantification (LOQ)] to 100 ng/mL in human plasma.

Stability of zolpidem in plasma (1 and 100 ng/mL) was investigated under various storage conditions. Zolpidem was stable when stored in plasma at room temperature for at least 48 hours, after at least three freeze-thaw cycles, and after processing for at least 168 hours at room temperature. Dilution studies demonstrated that plasma concentrations up to 1000 ng/mL for zolpidem could be reliably analyzed when diluted (1:10, v:v) into the assay calibration range. Samples could be processed on the robot and injected on the autosampler with no evidence of carryover. Accuracy and precision were assessed on six separate occasions at 0.50, 1.00, 10.0, and 100 ng/mL for zolpidem (see table below). The ranges of accuracy and precision appear appropriate.

Conc. (ng/mL)		Percent Accuracy (95% CI)	Within-run Percent Precision (95% CI)	Between-run Percent Precision (95% CI)	Total Percent Precision (95% CI)
Nominal	Mean				
0.5	0.46	-7.49 [-13.1, -1.90]	2.02 [1.43, 3.43]	5.65 [3.30, 13.8]	6.00 [3.88, 14.0]
1	0.99	-0.62 [-3.02, 1.78]	2.37 [1.68, 4.03]	1.83 [0.00, 5.47]	2.99 [2.28, 6.05]
10	10.33	3.30 [2.52, 4.08]	3.16 [2.27, 5.22]	0.00 [NC, NC]	3.16 [2.27, 5.22]
100	100.03	0.03 [-1.71, 1.78]	2.47 [1.77, 4.08]	0.85 [0.00, 3.80]	2.61 [2.06, 4.73]

3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. The entire section has been reformatted by this reviewer to follow the ADME format and to have Ambien CR information follow Ambien information under each of the subsections. Otherwise, no major changes are made to what is proposed by the sponsor. However, in the Dosage and Administration section for hepatic impairment subjects, this reviewer is proposing revisions. See Appendix 4.1 for the Applicant's package insert proposal.

CLINICAL PHARMACOLOGY

Pharmacodynamics: 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 ((alpha)) subunit and is referred to as the benzodiazepine (BZ) receptor.

is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties,

In contrast to the benzodiazepines, which nonselectively bind to and activate all receptor subtypes, zolpidem in vitro binds the receptor preferentially with a high affinity ratio of the alpha 1 /alpha 5 subunits. The receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (parsreticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. This selective binding of zolpidem on the 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.

Pharmacokinetics:**Absorption:**

For Ambien CR, administered as a single 12.5-mg dose in healthy male adult subjects, the mean peak concentration (C_{max}) 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 was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy volunteers 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 be administered two hours after a meal.

Distribution:

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

Metabolism:

Ambien is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination:

For Ambien CR, 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:

For Ambien CR, administered as a single 6.25-mg dose in 24 elderly (=65 years) healthy subjects, the mean peak concentration (C_{max}) 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

Following a single 20-mg oral zolpidem 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 normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency (see Precautions and Dosage and Administration).

Renal

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 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. Ambien (zolpidem tartrate) pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Dosage and Administration

Ambien CR

Patients with hepatic insufficiency do not clear the drug as rapidly as healthy adults.

**APPEARS THIS WAY
ON ORIGINAL**

18 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(4) Draft Labeling

Distributed by:
 Sanofi-Synthelabo Inc.
 New York, NY 10016

Ambien® [Ⓢ]
 (zolpidem tartrate)

Ambien CR™ [Ⓢ]
 (zolpidem tartrate controlled release tablets)

Printed in USA

Revised March 2004

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4.2 Consult Review (including Pharmacometric Reviews) – Not applicable.

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
<i>General Information About the Submission</i>				
	Information		Information	
NDA Number	21-774		Brand Name	Ambien CR
OCPB Division (I, II, III)	II		Generic Name	Zolpidem tartrate
Medical Division	HFD-170		Drug Class	Hypnotic
OCPB Reviewer	David Lee		Indication(s)	Insomnia
OCPB Team Leader	Suresh Doddapaneni		Dosage Form	Controlled release tablet
			Dosing Regimen	Single dose
Date of Submission	6/08/04		Route of Administration	Oral
Estimated Due Date of OCPB Review	-		Sponsor	Sanofi-Synthelabo, Inc
Medical Division Due Date	4/8/05		Priority Classification	
PDUFA Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				

<i>Healthy Volunteers-</i>				
single dose:	X	4	4	
multiple dose:				
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:	X			
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	3	3	
Phase 2/3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X			
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		11	11	
Filability and QBR comments				

	"X" if yes	Comments
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

**This is a representation of an electronic record that was signed electronically and
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/s/

David Lee
3/31/05 03:27:25 PM
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Suresh Doddapaneni
3/31/05 03:30:05 PM
BIOPHARMACEUTICS