CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-412
Brand Name:	TM FLASHDOSE
Generic Name:	Zolpidem Tartrate
Sponsor:	Biovail Laboratories, Inc.
Type of Dosage Form:	Orally Disintegrating Tablet (ODT)
Strengths:	5 mg, 10 mg
Indications:	Short-Term Treatment of Insomnia
OCPB Reviewer:	Ta-Chen Wu, Ph.D.
OCPB Team Leader:	Ramana S. Uppoor, Ph.D.
OCPB Division:	DPE-I HFD-860
OND Division:	Division of Neuropharmacological Drug Products HFD-120
Submission Date:	November 24, 2004
Type of Submission:	Response to Approvable Letter

Table of Contents

1. Executive Summary

The current submission is an NDA amendment to provide a complete response to the Approvable Letter dated February 21, 2003 for NDA 21-412 and to the subsequent communications with the Agency related to proposals to reformulate the 5 and 10 mg Zolpidem Tartrate Orally Disintegrating Tablets (ODT) from the original — formulation. Biovail is seeking approval for TM FLASHDOSE (Zolpidem Tartrate — —)DT), developed to match the reference Ambien® (NDA 19-908), for short-term treatment of insomnia. b(4)

In support of this application the Sponsor has submitted 2 biostudies using the proposed to-be-marketed (TBM) formulation with the supportive in vitro dissolution data. The 2 biostudies included in the Clinical Pharmacology program are:

- Study 2840: BE study comparing 10 mg ODT and RLD Ambien® of the same strength
- Study 2841: Dosage strength equivalence study between 1 x 10 mg ODT and 2 x 5 mg ODT.

An *in vivo* bioequivalence study was conducted to evaluate the bioequivalence between the highest strength (10 mg) of the proposed zolpidem tartrate —— ODT administered with or without water and the commercially available Ambien® immediate release tablets of the same strength. Results indicated that the 10 mg ODT of highest strength is bioequivalent to the reference Ambien® 10 mg tablet. Dosage strength equivalency was evaluated between the highest 10 mg ODT strength and the lowest 5 mg ODT strength. The bioequivalence was demonstrated between these two dosage strengths of zolpidem tartrate —— ODT. b(4)

OCPB has previously recommended in the Approvable Letter dated October 31, 2002, that the sponsor change the dissolution specification to Q= —% in 30 minutes (using USP paddle apparatus, 50 rpm, pH 5.8 buffer). At the telecon of January 31, 2003, OCPB agreed to potentially allow an interim specification of Q= — in 60 minutes, while maintaining the pH 5.8 media at 50 rpm. The sponsor has agreed to generate additional dissolution data for next 3 production batches and submit the data to see if a specification at 30 minutes or 60 minutes time point is more appropriate for this product. In the current submission, the sponsor proposed a different dissolution method and specification (0.1N HCl at 75 rpm paddle speed, Q=(—in 30 minutes) for the reformulated dosage strengths. Dissolution of both strengths is essentially complete within 5 minutes and is not discriminatory using the currently proposed method. Due to the inadequate data generated in dissolution medium pH 5.8, we will allow an interim specification of 0.1N HCl, Q= —% in 30 minutes, especially given that a disintegration specification is also available. However, it is critical to generate adequate dissolution data with a more optimal dissolution method. Therefore, a Phase IV commitment is necessary. b(4)

1.1. Recommendations

Office of Clinical Pharmacology and Biopharmaceutics has reviewed the submission and found that this submission is acceptable from an OCPB perspective, provided that the Sponsor agrees with the interim dissolution specifications recommended by the Agency, along with the Phase IV commitment.

Based on the dissolution data of the biobatches, OCPB does not believe that the Sponsor's current proposal for dissolution method (75 rpm) and the choice of dissolution medium (0.1N HCl) are optimal for this product since the dissolution is very rapid (< 5 minutes) and the method does not appear to be discriminatory. Please note that the similar recommendation in previous OCPB review, including the better choice of pH 5.8 phosphate buffer at 50 rpm, had been conveyed to the Sponsor and the sponsor had agreed to OCPB's recommendation (dated 1/31/03) at that time. We believe that the currently proposed method (dissolution medium 0.1N HCl and agitation speed) and the dissolution specifications can at best be allowed only as interim specifications. Following are the interim dissolution method and specifications recommended by the Agency:

Method: USP apparatus II (Paddle)
Speed: 75 rpm
Medium: 0.1N HCl
Temperature: 37 ± 0.5°C
Specification: Q = [redacted] in 30 minutes b(4)

The above Recommendations and the labeling changes (starts on page 21) pertinent to the Clinical Pharmacology and Biopharmaceutics should be conveyed to the Sponsor.

1.2. Phase IV Commitments

The Sponsor should commit to the following:

1. Optimize the dissolution method and specifications using 50 rpm paddle speed and a different dissolution medium (e.g., pH 5.8 buffer).
2. Generate data on biobatches and next 3 production batches for both 5 and 10 mg strengths using the selected more optimized dissolution method. The Sponsor should submit these data to the Agency within one year from the date of approval for the final selection of the dissolution specification.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence between Zolpidem Tartrate [redacted] ODT and the RLD Ambien®: b(4)

Relative bioavailability of the highest strength zolpidem tartrate 10 mg ODT was compared to the equivalent strength of reference Ambien® tablets. A three-way crossover study (as part of the pivotal Study 2840) was conducted in 36 healthy subjects under fasting conditions. Similar pharmacokinetic profiles from ODT formulation and Ambien® tablet were observed for zolpidem. The zolpidem 10 mg ODT is shown to be

bioequivalent to reference Ambien® 10 mg tablet based on acceptance criteria for BE (i.e., 80-125% CI) of AUC_{0-t}, AUC_{0-inf}, and C_{max}.

Effects of administration with water:

A randomized, single-dose, open-label, three-way crossover study (as part of the Study 2840) was conducted in 36 normal, healthy subjects to evaluate the effect of administration with or without water when zolpidem tartrate 10 mg ODT formulation was given under fasting conditions. The 10-mg ODT was allowed to dissolve on tongue and then swallowed with or without water. No significant effect of water on bioavailability was observed.

Dosage strength equivalency:

The relative bioavailability of zolpidem was evaluated in one pivotal BE study (Study 2841) comparing single dose of 2 x 5 mg ODT vs. 1 x 10 mg ODT administered under fasting conditions. Both strengths of ODT were allowed to dissolve on tongue and then swallowed without water. This study demonstrated bioequivalence between two dosage strengths with respect to the rate and extent of absorption. Therefore, the dosage strength equivalency has been established between 5 mg and 10 mg zolpidem tartrate ——— ODTs. b(4)

Dissolution Specifications:

OCPB does not accept the choice of dissolution medium (0.1N HCl) and the paddle speed at 75 rpm proposed by the Sponsor as the most optimal method for this product. Based on the dissolution data of the biobatches provided in the current submission, we believe that the method (dissolution medium and agitation speed) and the dissolution specifications need to be modified for the new formulation. Following are the interim dissolution method and specifications recommended by the Agency:

Method: USP apparatus II (Paddle)
Speed: 75 rpm
Medium: 0.1N HCl
Temperature: 37 ± 0.5°C
Specification: Q = —— n 30 minutes b(4)

The sponsor needs to commit to optimize the dissolution method for this product.

Ta-Chen Wu, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Ramana S. Uppoor, Ph.D.
Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: Mehul U. Mehta, Ph.D.
Director, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21-412
CSO/R. Gujral
/Biopharm/T.C. Wu
/TL Biopharm/R. Uppoor
HFD-860 /DD DPEI/M. Mehta, A. Rahman

2. *Question-Based Review (QBR)*

2.1. *General Attributes of the Drug*

What pertinent regulatory background or history contributes to the current assessments of this drug?

The current submission is a complete response to the approvable letter dated February 21, 2003 for NDA 21-412 and to the subsequent communications with the Agency related to proposals to reformulate the 5 and 10 mg Zolpidem Tartrate Orally Disintegrating Tablets (ODT) from the original —— formulation. Biovail is seeking approval for Zolpidem Tartrate ODTs, developed to match the RLD Ambien® (NDA 19-908), for short-term treatment of insomnia. b(4)

Two labeling issues were raised in the approvable letter, which included safety and stability issue for —— and the unavailability of a 5 mg strength for patients with hepatic impairment and elderly. To address those issues, Biovail has obtained the agreement from the Agency on August 29 and September 10, 2003, to reformulate the tablets as —— 5 and 10 mg ODTs. b(4)

This NDA 21-412 was then transferred from the Division of Neuropharmacological Drug Products (DNDP) to the Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP) in December 2003. Subsequently, Biovail obtained the Agency's agreement on the conduct of two additional biostudies to support the approval of the new 5 mg and 10 mg strengths of Zolpidem Tartrate —— ODT formulations and requested a biowaiver for food-effect study since the original —— and reformulated —— formulations contain the same taste masked microspheres (TMMS). Both requests were granted by the Division on January 30, 2004. b(4)

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Zolpidem tartrate is an orally administered non-benzodiazepine hypnotic of the imidazopyridine class. The commercially available RLD Ambien® is available in 5-mg and 10-mg strength tablets for oral administration. Zolpidem tartrate is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88, with a pKa value at 6.2.

TM FLASHDOSE (zolpidem tartrate) is formulated as orally disintegrating tablets, resulting in two separate release mechanisms: disintegration of the tablet matrix occurs in the mouth, followed by dissolution of the taste-masked microspheres in the stomach where the active ingredient is released. The new —— ODT formulations have appearance as follows: b(4)

- 5 mg tablets are round white speckled tablets with a dimple on both sides and debossed with 'ZT' on one side and '5' on the other

- 10 mg tablets are round blue speckled tablets with a dimple on both sides and debossed with 'ZT' on one side and '10' on the other

2.1.2. What are the proposed mechanism of action and therapeutic indication?

Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class. In reference to the innovator product, Ambien®, the proposed TM FLASHDOSE ODT formulation is indicated for the short-term treatment of insomnia, for the same therapeutic use. Details can be seen in the approved label for Ambien® and the original NDA 21-412 review by Dr. Maria Sunzel.

2.1.3. What are the proposed dosages and route of administration?

The proposed dosing regimen is similar to the RLD Ambien®. As indicated in the label, the dose of TM FLASHDOSE should be individualized. The recommended dose for adults is 10 mg immediately before bedtime. An initial 5 mg dose is recommended in patients with hepatic insufficiency and elderly patients and patients should be closely monitored. The total dose should not exceed 10 mg.

TM FLASHDOSE is intended to be administered by being placed on the tongue and subsequently swallowed with or without water. The TM FLASHDOSE should not be administered with food or immediately after a meal.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The proposed to-be-marketed formulation was used in definitive biostudies. The clinical pharmacology program was designed to demonstrate:

1. The bioequivalence between the highest strength (10 mg) of the proposed zolpidem tartrate —— ODT administered with or without water and the commercially available Ambien® tablets of the same strength
2. The bioequivalence between the highest strength of 10-mg and the lowest strength of 5-mg zolpidem tartrate —— ODT

b(4)

As shown in Table 1 below, two pivotal bioavailability studies were performed in a total of 72 healthy volunteers to support this application. No clinical efficacy trials were conducted for this NDA.

Protocol Number (Study No.)	Study Title	Study Design	Related IND or NDA Numbers

2840 (B04-668PK-N04F1)	A Three-Way Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Comparative Bioavailability Study of Zolpidem Tartrate 10 mg ODT Administered with and without Water versus Ambien® 10 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects	Randomized 3-treatment, 3-period, 3-sequence crossover design under single dose fasting conditions, with and without water	NDA 21-412
2841 (B04-669PK-N04F1)	A Two-Way Crossover, Randomized, Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Dosage Strength Proportionality Study of Two Strengths of Zolpidem Tartrate ODT (2 x 5 mg and 1 x 10 mg) in Normal Healthy Non-Smoking, Male and Female Subjects	Randomized 2-treatment, 2-period, 2-sequence crossover design under single dose fasting conditions (without water)	NDA 21-412

2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters?

Zolpidem tartrate is converted to inactive metabolites that are eliminated primarily by renal excretion. Therefore, metabolite levels were not measured in the present submission.

2.2.3. What are the pharmacokinetic characteristics of the drug and its major metabolite?

Zolpidem demonstrates linear kinetics in the dose range of 5-20 mg after single or multiple dosing. The elimination half-life (T1/2) is short in healthy subjects. Zolpidem tartrate is converted to inactive metabolites that are eliminated primarily by renal excretion. Details of the basic pharmacokinetics and metabolism of zolpidem can be seen in the approved label for Ambien® and the original NDA 21-412 review.

Following a single oral dose of 10-mg TM FLASHDOSE to healthy subjects under fasting conditions, T_{max} of zolpidem occurred at approximately 1.75 hours when administered without water and at average 1.25 hours with water. The T_{max} of the reference Ambien® in the same study occurred at 1.5 hours. The terminal $T_{1/2}$ obtained from the studies for zolpidem from TM FLASHDOSE and reference Ambien® ranged from approximately 3.23 to 3.49 hours. Overall, the pharmacokinetic characteristics of zolpidem were similar between the reformulated —— ODT and the Ambien® tablet. b(4)

2.3. Intrinsic Factors

The influence of gender on the pharmacokinetics of zolpidem tartrate ODT were evaluated based on the data obtained in 2 definitive BE studies. No pharmacokinetic studies were conducted in special populations.

2.3.1. What is the effect of Gender?

No major gender effect was seen on C_{max} and AUC in Study 2840 (see Tables 14 and 15) and Study 2841 (see Table 22).

2.4. Extrinsic Factors

No study for effects of extrinsic factors was conducted.

2.5. General Biopharmaceutics

The Biopharmaceutic program was designed to develop a formulation of TM FLASHDOSE that would deliver an equivalent amount of drug to the systemic circulation as the approved tablet. That is, only the performance of the proposed ODT formulation comparing to the approved reference product will be addressed.

The specific objectives of the development plan for Zolpidem Tartrate ODT were to achieve the following:

1. Simple and convenient dosing with a tablet that can be taken without water;
2. Delivery of the same total amount of drug to the systemic circulation as delivered by Ambien® tablets;
3. Similar or lower maximum (peak) concentration during dosing with the ODT as compared with Ambien® tablets.

The Sponsor indicates that the proposed ODT dosage form will be more suitable for patients having difficulty in swallowing intact tablets or having no immediate assess to water.

2.5.1. What is the proposed formulation of the drug product?

The original formulation is ——— The Sponsor proposed the reformulation to facilitate the development of 5 mg strength, and the change in formulation was exclusively related to ——— b(4)

The ODT formulation consists of drug-containing taste-masked microspheres (TMMS) based on Biovail's proprietary CEFORM® technology to produce 5 mg and 10 mg dosage strengths. The composition of TMMS on a % w/w basis is the same for these two strengths. In addition, the 5mg and 10mg Zolpidem ODT tablets contain the same TMMS used for the original formulation ———

b(4)

Table 2. Quantitative composition of the original and the reformulated zolpidem tartrate ODT formulations

Component per Tablet, Grade	ORIGINAL	REFORMULATED (Current Submission)			
	10 mg Tablet	10 mg Tablet		5 mg Tablet	
	Quantity per unit (mg)	Quantity per unit (mg)	%	Quantity per unit (mg)	%

b(4)

Comment:

1. The total changes of excipients in the reformulated 10 mg zolpidem tartrate ODTs, compared to the original 10 mg formulation, have exceeded 10% (i.e., Level 3 changes). According to the Guidance for Industry on SUPAC-IR: "Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation" (http://www.fda.gov/cder/guidance/cmc5.pdf), for Level 3 changes a full *in vivo* BE study and the multiple-point dissolution profile with adequate sampling points should be performed to document the bioequivalence between different dosage strengths. The Sponsor has conducted an *in vivo* BE study (2840) to document the bioequivalence between 10 mg zolpidem tartrate ODT to the reference Ambien® tablets of same strength. b(4)
2. The 5 and 10 mg zolpidem tartrate ODTs of the new formulation are not quantitatively proportional. The total changes of excipients in the reformulated zolpidem tartrate ODTs in the lowest strength of 5 mg, compared to the highest 10 mg strength, of TBM product have exceeded 10% (i.e., Level 3 changes). The Sponsor has conducted an *in vivo* dosage strength BE study (2841) to bridge these two dosage strengths and carried out the supportive *in vitro* dissolution studies to document the bioequivalence.

2.5.2. Is the to-be-marketed ODT formulation bioequivalent to the RLD formulation of same strength?

To establish bioequivalence between the TBM zolpidem tartrate —— ODT and the reference Ambien® tablets of same strength, one biostudy was conducted by the Sponsor to evaluate the relative bioavailability of the highest strength 10 mg zolpidem tartrate ODT: b(4)

- Study 2840 was a 3-way crossover study in 36 healthy non-smoking male and female subjects. The 10-mg zolpidem tartrate —— ODT from a TBM batch (0403023) was administered without (Treatment A) or with water (Treatment B), compared to the reference 10-mg Ambien® tablets (Treatment C), under fasting conditions. Pharmacokinetic parameters and statistics are summarized in Tables 3 and 4. b(4)

Table 3. Pharmacokinetic parameters for zolpidem

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Zolpidem Tartrate 10 mg ODT – without water (A) (n = 36)	Zolpidem Tartrate 10 mg ODT – with water (B) (n = 36)	Ambien® 10 mg Tablets (C) (n = 36)
AUC_{0-t} (ng·hr/mL)	530.54 (45.11%) 576.99 ± 260.30	525.32 (51.80%) 587.51 ± 304.31	517.29 (47.16%) 574.44 ± 270.88
AUC_{0-inf} (ng·hr/mL)	542.51 (47.58%) 592.84 ± 282.09	535.93 (53.70%) 602.41 ± 323.49	529.96 (49.84%) 592.48 ± 295.27
C_{max} (ng/mL)	96.91 (32.14%) 101.68 ± 32.68	108.20 (33.33%) 113.23 ± 37.74	109.37 (32.78%) 115.03 ± 37.70
T_{max} (hr)*	1.75 (0.50 – 4.00)	1.25 (0.50 – 3.00)	1.50 (0.50-4.02)
$t_{1/2}$ (hr)†	3.49 ± 1.23	3.35 ± 1.21	3.45 ± 1.45

Table 4. Relative bioavailability analysis of zolpidem after single oral dose of 10 mg zolpidem tartrate —— ODT and 10 mg Ambien® Tablets b(4)

Parameter	A vs. C		B vs. C	
	90% CI	Ratio of Means	90% CI	Ratio of Means
AUC_{0-t}	95.43% - 111.19%	103.01%	94.23% - 109.80%	101.72%
AUC_{0-inf}	95.17% - 111.08%	102.82%	93.76% - 109.44%	101.30%
C_{max}	81.98% - 96.57%	88.97%	91.26% - 107.50%	99.05%

Similar pharmacokinetic profiles were observed following oral administration of zolpidem tartrate —— 10 mg ODT with or without water, and the reference Ambien® 10 mg tablet. Bioavailability of zolpidem tartrate —— 10 mg ODT was similar to the reference Ambien® tablet of same strength. Statistical analysis of exposure measurements (AUC_{0-t}, AUC_{0-inf}, and C_{max}), based on acceptance criteria for BE, i.e., 80-125% CI, revealed that the zolpidem tartrate —— 10 mg ODT (highest strength) administered with or without water is bioequivalent to 10 mg Ambien® tablet under single-dose fasting conditions. b(4)

2.5.3. What is the effect of administration with water?

Study 2840 was conducted in part to evaluate the effect of administration with or without water when zolpidem tartrate 10 mg ODT formulation was given under fasting conditions.

- Treatment A: No water was ingested after the single 10-mg ODT was completely dissolved on the tongue and swallowed and until 1 hour post-dose
- Treatment B: 240 mL of ambient temperature water was ingested within 1 minute after the single 10-mg ODT was completely dissolved on the tongue

Pharmacokinetic parameters and statistics are summarized in Table 5.

b(4)

Table 5. Relative bioavailability analysis of zolpidem after a single oral dose of zolpidem tartrate —— 10 mg ODT

Parameter	B vs. A	
	90% CI	Ratio of Means
AUC_{0-t}	91.48% - 106.59%	98.75%
AUC_{0-inf}	91.19% - 106.44%	98.52%
C_{max}	102.57% - 120.82%	111.32%

As shown in the above results, ingesting 240 mL water immediately after the ODT disintegrated on the tongue produced similar pharmacokinetic profiles and appeared not to affect the bioavailability of zolpidem. Statistical analysis of exposures measurements (AUC_{0-t}, AUC_{0-inf}, and C_{max}), based on acceptance criteria for BE, i.e., 80-125% CI, indicates that water has no effect on absorption of zolpidem following oral administration of the zolpidem tartrate 10 mg ODT.

Comments:

1. There was a slight increase in mean T_{max} when zolpidem ODT was taken without water (1.91 hours) compared to reference Ambien® tablet (1.59 hours) and to zolpidem ODT taken with water (1.34 hours; p= 0.0048). However, such slight delay in time to reach C_{max} is not likely to have clinical significance.
2. Study 2840 for the effect of administration with water is not very valuable to evaluate the effect of swallowing vs. allowing to disintegrate, since in both treatment groups the 10 mg zolpidem ODT was allowed to dissolve in oral cavity prior to swallowing. It would be a more optimal study design to detect the effect of swallowing water by instructing the subjects in Treatment group B (with water) to swallow the ODT directly with 240 mL water without intentionally letting the ODT disintegrate on the tongue and sucking on the tablet prior to the swallowing. However, since bioequivalence has been demonstrated in this study between reference tablet and ODT when let to disintegrate/dissolve and swallowed without water, label claim with and without water can be allowed.

2.5.4. Was the dosage form equivalence established for the to-be-marketed formulations?

The Sponsor has conducted one definitive study (Study 2841) to demonstrate the dosage strength equivalency for the TBM zolpidem tartrate ——— ODT formulation.

Study 2841 was a 2-way crossover design to evaluate the dosage strength proportionality between 2 x 5-mg and 1 x 10-mg zolpidem tartrate ——— ODT from commercial-scale batches in 36 healthy non-smoking male and female subjects under fasting conditions. No water was ingested after the single doses of 2 x 5-mg vs. 1 x 10-mg ODT were completely disintegrated on the tongue and swallowed and until 1 hour post-dose. Mean pharmacokinetic parameters and statistics are summarized in Tables 6 and 7. b(4)

Table 6. Pharmacokinetic parameters for zolpidem

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Zolpidem Tartrate 2 x 5 mg ODT (A) (n=36)	Zolpidem Tartrate 1 x 10 mg ODT (B) (n=36)
AUC_{0-t} (ng·hr/mL)	506.18 (53.17) 577.69 ± 307.17	515.64 (46.83) 580.60 ± 271.90
AUC_{0-inf} (ng·hr/mL)	515.69 (54.28) 590.14 ± 320.35	525.47 (46.83) 591.49 ± 276.98
C_{max} (ng/mL)	103.47 (36.03) 110.10 ± 39.67	99.68 (34.77) 105.89 ± 36.82
T_{max} (hr)*	1.75 (0.25 – 4.00)	1.75 (0.75 - 4.10)
$t_{1/2}$ (hr)	3.23 ± 1.16	3.29 ± 1.08

Table 7. Relative bioavailability analysis of zolpidem after single dosing with 2 x 5-mg and 1 x 10 mg zolpidem tartrate ——— b(4)

Parameter	90% CI	Ratio of Means
AUC_{0-t}	91.11% - 105.77%	98.17%
AUC_{0-inf}	91.06% - 105.77%	98.14%
C_{max}	96.16% - 112.05%	103.80%

Based on the results of statistical analysis of exposure measurements of zolpidem, it is concluded that the dosage strength equivalency is established between two strengths (2 x 5 mg vs. 1 x 10 mg) of zolpidem tartrate ODT formulations.

2.5.5. Does food affect the bioavailability of zolpidem tartrate ——— formulation? b(4)

No study was conducted to evaluate the effects of high-fat food on bioavailability of zolpidem tartrate ——— ODT formulations. The Sponsor expected the same effect on both the original and the new formulations by a high-fat meal since both formulations contain the same taste masked microspheres (as seen in Table 3). The original ODT formulations have been shown to be bioequivalent to the reference Ambien® tablets. The Sponsor's justification was accepted by the Agency (NDA 21-412 review by Dr. David

Lee) and a biowaiver for food-effect study was granted for the reformulated —— formulations.

b(4)

2.5.6. Is the dissolution method appropriate for zolpidem tartrate —— ODT formulation?

The Sponsor has proposed the following dissolution test method and specifications, with justification, for zolpidem tartrate —— ODT formulation:

b(4)

Apparatus: USP apparatus II (paddles)
Stirring Speed: 75 rpm
Dissolution Medium: 0.1N HCl
Volume of Medium: 500 mL for 5 mg ODT; 900 mL for 10 mg ODT
Temperature: 37.0 ± 0.5°C
Specification: Q = —% in 30 minutes
(Complies with USP <711> Unit Sample Acceptance Criteria)
Dissolution Analytical Method:
Withdraw an aliquot of the dissolution medium at each sampling point and analyze by —————— HPLC.

b(4)

Since the new zolpidem tartrate —— ODTs were intended to release the active moiety in the stomach after being swallowed within the intact taste-masked microspheres, the Sponsor has proposed the 0.1 N HCl as dissolution medium for its physiological similarity to the gastric fluid. The Sponsor states that the proposed specification is in accordance with the OCPB's request in the Approvable Letter dated October 31, 2002.

b(4)

The Sponsor also indicates that the assessments for effects of dissolution media and the choice of paddle speed were evaluated. The *in vitro* dissolution testing was performed for both strengths of biobatches in 3 different media (0.1 N HCl, pH 4.5 acetate buffer, and pH 5.8 phosphate buffer) using USP II apparatus (paddle). Biovail reports that all strengths of the new formulation in all media met the release specification of NLT —% (Q) at 30 minutes.

Comparative dissolution data in multiple media and paddle speeds for zolpidem tartrate ODTs used in biostudies are shown in the following Tables:

Table 8. Dissolution data of zolpidem tartrate ODTs in 0.1N HCl

Strength	Lot Number	Paddle speed	Numbers of Tablets	Time (Minutes)	% Label Claim		
					Mean	Minimum	Maximum
5 mg	0403026	75 rpm	6	5	100		
			6	15	101		
			6	30	101		
			6	60	101		

b(4)

10 mg	0403023	75 rpm	6	5	101
			6	15	101
			6	30	101
			6	60	101

b(4)

Table 9. Dissolution data of zolpidem tartrate ODTs in pH 4.5 and pH 5.8 buffer

Strength	Lot Number	Paddle speed	Numbers of Tablets	Time (Minutes)	% Label Claim		
					Mean	Minimum	Maximum
pH 4.5 acetate buffer at 37°C							
5 mg	0403026	50 rpm	12	5	82		
			12	30	94		
			12	60	96		
10 mg	0403023	50 rpm	12	5	93		
			12	30	99		
			12	60	100		
pH 5.8 phosphate buffer at 37°C							
5 mg	0403026	50 rpm	12	5	75		
			12	30	94		
			12	60	94		
10 mg	0403023	50 rpm	12	5	87		
			12	30	100		
			12	60	101		

b(4)

Table 10. Dissolution testing summary for zolpidem tartrate ODTs

Strength	Lot Number	Paddle speed	Numbers of Tablets	Time (Minutes)	% Label Claim		
					Mean	Minimum	Maximum
pH 4.5 acetate buffer at 37°C							
5 mg	0403026	50 rpm	12	5	78		
			12	10	91		
			12	15	94		
			12	20	96		
			12	30	96		
			12	60	99		
10 mg	0403023	50 rpm	12	5	91		
			12	10	100		
			12	15	101		
			12	20	100		
			12	30	100		
			12	60	100		
0.1N HCl at 37°C							

b(4)

5 mg	0403026	50 rpm	12	5	88
			12	10	92
			12	15	94
			12	20	95
			12	30	96
			12	60	97
10 mg	0403023	50 rpm	12	5	98
			12	10	99
			12	15	100
			12	20	100
			12	30	99
			12	60	99

b(4)

The mean dissolution profiles of both strengths were similar in various media of different pH values, and the profiles indicated rapid dissolution for both. The dissolution for both strengths was essentially complete by 5 minutes in 0.1N HCl medium, and ≥ 90% by 20 minutes in either pH 4.5 acetate buffer or pH 5.8 phosphate buffer.

Comment:

The Sponsor has not provided sufficient data and clear justifications for the selections of dissolution method (peddle speed and dissolution medium) and specifications.

- Based on the above dissolution data, as provided by the Sponsor, under different conditions, the choice of 0.1N HCl as dissolution medium is not acceptable due to the lack of discriminatory ability under the study conditions. In the original NDA review by Dr. Maria Sunzel, OCPB found the proposed *in vitro* dissolution method (pH 5.8 phosphate buffer, apparatus II at 50 rpm) acceptable, but also recommended the specification being changed to Q = —— in 30 minutes. This was conveyed to Biovail in the Approvable Letter dated October 31, 2002. According to the OCPB review by Dr. Veneeta Tandon, OCPB did not agree with Sponsor's proposal of changing the medium to 0.1N HCl. Instead, OCPB recommended an interim specification of Q = —— in 60 minutes and that the sponsor evaluate dissolution at 30 minutes using pH 5.8 buffer for at least 3 production batches and on the existing biobatches on stability, if possible. Comments were conveyed to the Sponsor via a telecon on 1/31/2003 and Biovail had agreed to this commitment at the telecon on 1/31/2003.

b(4)

- According to the FDA Guidance, the mild agitation conditions should be maintained during dissolution testing to allow maximum discriminating ability. The Sponsor should provide comparative dissolution data for both strengths in multiple media and at both 50 and 75 rpm paddle speed to justify the selection of 75 rpm.
- At this time, the sponsor's proposed dissolution method/specification can only be allowed as interim specification.

2.5.7. Is there *in vivo-in vitro* Correlation?

No *in vitro-in vivo* correlation studies have been conducted with zolpidem tartrate ODT. The specifications for *in vitro* disintegration of the ODT formulation is less than 30

seconds. The mean *in vivo* disintegration time ranged from 10 seconds for the 5-mg tablet to 12-15 seconds for the 10-mg tablet.

In Vivo Disintegration Time

The *in vivo* disintegration time for zolpidem tartrate —— ODT formulation was defined by the Sponsor as "The time interval between placing the tablet on the tongue to the onset of disintegration", and was measured in both Study 2840 and Study 2841. During each treatment, subjects were given a timer to note the time taken for disintegration of the tablet(s) in the mouth. Data from each subject are shown in the Individual Study Reviews; mean values and ranges of the data are shown in the following Table: b(4)

Table 11. Mean *in vivo* disintegration times for zolpidem tartrate 5 and 10 mg ODTs

Study #	Treatment	Mean Disintegration Time* (Seconds)	Range* (Min. – Max.) (Seconds)
2840 (n = 35)	A: 10mg Zolpidem Tartrate ODT (No Water)	15	
	B: 10mg Zolpidem Tartrate ODT (Water)	15	
2841 (n = 36)	A: 2x5mg (10 mg) Zolpidem Tartrate ODT	10	
	B: 1x 10mg (10 mg) Zolpidem Tartrate ODT	12	

b(4)

Study 2840: Based on 35 completed subjects, the mean *in vivo* disintegration times of zolpidem were 15 seconds for both Treatments A (3-32 seconds) and B (4-60 seconds), respectively.
Study 2841: Based on 36 completed subjects, the mean *in vivo* disintegration times of zolpidem were 10 and 12 seconds for Treatments A (3-24 seconds) and Treatment B (4-33 seconds), respectively.

As shown, *in vivo* disintegration was rapid for the 2 tablet strengths (5 and 10 mg) and occurred in less than 60 seconds, mostly within 30 seconds, with the exception of one subject at the observed maximal 60 seconds.

The Sponsor has revised the specifications for *in vitro* disintegration testing from NMT —seconds to NMT — seconds (Release) and NMT —seconds (Shelf Life), which will be reviewed by the Chemist. b(4)

2.6. Analytical Section

OCPB finds the bioanalytical methods for zolpidem adequate and justified.

2.6.1. What bioanalytical methods are used to assess concentrations of zolpidem?

Plasma concentrations of zolpidem were analyzed with ——— as the internal standard using solid state extraction and a validated HPLC ——— method. The same method was used in all biostudies and was performed by Bioanalytical Laboratory, Biovail Contract Research. b(4)

An eight-point calibration curve, excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ (1.000 ng/mL) and ULOQ (511.797 ng/mL) of zolpidem. A weighted ($1/conc^2$) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Duplicate QC samples for zolpidem at three concentration levels, along with two calibration curves, were analyzed with each batch of the samples.

2.6.2. Which metabolites have been selected for analysis and why?

None

2.6.3. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

An eight-point calibration curve, excluding the blank sample, was constructed in human plasma. Plasma samples were properly diluted for the analyte concentrations to fall within the range of standard curves. A weighed ($1/conc^2$) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Linearity was evaluated by analysis of 5 standard curves for zolpidem and was indicated by a mean correlation coefficient of 0.9981. The standard curves for zolpidem ranged from 1.000 to 511.797 ng/mL.

2.6.4. What are the limits of quantification (LOQ)?

The lower limit of quantitation (LLOQ) with respect to analysis of zolpidem was 1.000 ng/mL.

2.6.5. What are the accuracy, precision, and selectivity at these limits?

Samples were found to be free of significant interfering peaks.

Intra-day reproducibility:
Accuracy and precision were determined with 6 replicates of QC samples for zolpidem at five concentration levels.

Precision: ———
Accuracy: ——— b(4)

Inter-day reproducibility:

The overall accuracy and precision were determined with 6 replicates of QC samples for 5 runs for zolpidem at five concentration levels.

Precision: [redacted]
Accuracy: [redacted]

b(4)

These assays were validated with the intra-assay and inter-assay precision and accuracy within ±15% and are found acceptable.

2.6.6. What is the sample stability under the conditions used in the study?

Sample stability was tested under various conditions with quality control samples at QC Low [redacted] and QC High [redacted] levels. Aged QC Low and QC High samples were assayed and analyzed along with freshly prepared QC Low and QC High samples.

b(4)

Freeze-thaw stability for zolpidem in human plasma was tested at -70°C±10°C and -25°C±10°C controlled at QC Low and QC High levels and samples were found to be stable for 3 freeze-thaw cycles.

Long-term stability of zolpidem was tested and was found to be stable in human plasma at -25°C ± 10 °C for 292 days and at -70°C±10°C for 29 days. In-process stability test showed that plasma sample was stable for 4 hours at room temperature.

Autosampler stability was tested on QC samples/extracted samples and the samples were found to be stable for up to 73 hours at room temperature.

2.6.7. What is the recovery under the conditions used in the study?

Percent recovery for zolpidem and the internal standard was evaluated at two QC levels (QC Low 2 and QC HIGH). The overall recoveries (%CV) for zolpidem and the internal standard were [redacted] respectively. The Sponsor stated that some evaporation of the reconstituted solution gave rise to the slightly higher recovery.

b(4)

2.6.8. What is the QC sample plan?

Six replicates of QC samples for zolpidem at five concentration levels, along with five calibration curves, were analyzed with each batch of the samples for intra-day reproducibility. Six replicates of QC samples for 5 runs for zolpidem at five concentration levels, along with five calibration curves, were analyzed with each batch of the samples for inter-day reproducibility. Five QC samples for zolpidem consisted of [redacted] For testing the sample stability, two QC levels employed consisted of [redacted].

b(4)

3. Detailed Labeling Recommendations

The Sponsor has proposed changes for the "Clinical Pharmacology" section of the label. Office of Clinical Pharmacology and Biopharmaceutics has reviewed the proposed labeling for zolpidem tartrate ———— ODT and finds it acceptable provided that revision is made to the labeling language. b(4)

Labeling recommendation to be sent to the Sponsor:
The following describes the proposed changes (in red): the underlined text is the proposed change to the label language; the ~~strikethrough~~ is recommendation for deletion from the perspective of OCPB.

4. Appendices

4.1. Package insert (Sponsor proposed and annotated with agency recommendation)

APPEARS THIS WAY
ON ORIGINAL

19 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

Study 2840 (Protocol #: B04-668PK-N04F1)

A Three-Way Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Comparative Bioavailability Study of Zolpidem Tartrate 10 mg ODT Administered with and without Water versus Ambien® 10 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects

Principal Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Center: Biovail Contract Research
- 460 Comstock Road, Toronto, ON, M1L 4S4 Canada
- 689 Warden Avenue, Units 1 & 2,
Toronto, ON, M1L 4R6 Canada
Study Period: May 16, 2004 – June 1, 2004

Objectives:

- To compare the bioavailability of Zolpidem Tartrate ———; ODT formulation administered with and without water to the reference Ambien® tablets under single-dose fasting conditions

b(4)

Test formulation: Zolpidem Tartrate 10 mg ODT, Lot #: 0403023 (Biovail Technologies Ltd., Ireland), Batch size: —— Expiry: 06-01-2004

b(4)

Reference formulation: Ambien® 10 mg Tablets, Lot #: TC41C (Sanofi-Synthelabo, Inc.), Batch size: N/A, Expiry: 11-01-2005

Study Design:

This study was a randomized, open-label, single-dose, three-way crossover design in 36 normal, healthy, non-smoking male and female subjects under fasting conditions. Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 18.5 and 29.9 kg/m^2, who met the inclusion and exclusion criteria, were enrolled in the study.

In all Treatments, the Test and Reference products were administered at 22:00 PM following a fast of ≥4 hours. All subjects remained fasted for at least 4 hours post-dose. Subjects received one of the following 3 treatments (total dose = 10 mg each) on three 3-days periods separated by a one-week washout period:

Treatment A (Test product, without water): One 10-mg Zolpidem Tartrate ——— ODT was placed directly on each subject's tongue, and the actual dosing time was

b(4)

recorded upon placing the tablet on the tongue. Subjects were instructed to suck on the ODT for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. A mouth-check was performed to confirm that the drug had been ingested. No water was provided until 1 hour post-dose.

Treatment B (Test product, with water): One 10-mg Zolpidem Tartrate ——— ODT was placed directly on each subject's tongue, and the actual dosing time was recorded upon placing the tablet on the tongue. Subjects were instructed to suck on the ODT for one minute or longer until it completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. The subjects were then given 240 mL of ambient temperature water that was ingested within 1 minute. A mouth-check was performed to confirm that the drug had been ingested. b(4)

Treatment C (Reference product, with water): One 10-mg Ambien® Tablet was administered with 240 mL of ambient temperature water.

For Treatments A and B, the subjects were given a timer for recording the time taken for disintegration of the tablets in the mouth. The timers were started the moment the tablets were placed on the tongue and stopped when the tablets had begun to break.

Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects were institutionalized the day of dosing and remained in the clinic until the morning of Day 2.

Safety Assessments:

Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and routine laboratory measurements (hepatitis C and B, HIV, biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine testing). In addition, pregnancy tests (urine hCG and serum β-CG) were performed on all female subjects. Screen for urine drugs of abuse, urine nicotine and saliva alcohol, pregnancy tests, will be performed upon check-in for each study period. Physical examination and urinalysis testing will be performed prior to discharge at the completion of the study. Adverse events were monitored throughout the study.

Pharmacokinetics Assessments:
A total of 19 blood samples (7 mL each) were collected from each subject for determination of zolpidem at pre-dose, 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 hours post-dose. Plasma samples were stored frozen at - 25°C ± 10°C until assayed.

Plasma concentrations of zolpidem were analyzed with ——— as the internal standard using a validated HPLC ——— method. An eight-point calibration curve (1.000, 1.999, 3.998, 15.994, 63.975, 127.950, 255.899, and 511.797 ng/mL), excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ b(4)

(1.000 ng/mL) and ULOQ (511.797 ng/mL) of zolpidem. A weighted ($1/conc^2$) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Two calibration curves and duplicated QC samples for zolpidem at three concentration levels were analyzed with each batch of the samples.

Table 12. Assay validation for Study 2840

		Zolpidem
Method:		HPLC-[redacted]
Standard curve		
	Range:	[redacted]
	Precision:	
	Accuracy:	
	Linearity:	
LOQ		
	LLOQ:	
	ULOQ:	
QC		
	Low:	
	Precision:	
	Accuracy:	
	Med:	
	Precision:	
	Accuracy:	
	High:	
	Precision:	
	Accuracy:	

b(4)

Pharmacokinetic Analysis:
The pharmacokinetic analysis was performed on all subjects who completed the 3 study periods. The following pharmacokinetic parameters for zolpidem from all Treatment groups were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and MRT. The pharmacokinetic comparisons will be conducted as (1) Treatment A (zolpidem tartrate 10 mg ODT -without water) vs. Treatment C (Ambien® 10 mg Tablet), Treatment B (zolpidem tartrate 10 mg ODT -with water) vs. Treatment A (zolpidem tartrate 10mg ODT -without water), and Treatment B (zolpidem tartrate 10 mg ODT -with water) vs. Treatment C (Ambien® 10 mg tablet).

Statistical Analysis:
Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of zolpidem.

Using GLM procedures in SAS, analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed Tmax, Kel, t1/2, and MRT at the significance level of 0.05. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the ln-transformed AUC_{0-t}, AUC_{0-}

$_{inf}$ and C_{max} between the test and reference formulations. Data from subjects who experience emesis during the study may be removed from the statistical analysis.

RESULTS

Demographics of Subjects:

Thirty-six subjects (18 males, 18 females) with a mean age of 35 years (range = 19-48 years of age) were enrolled in the study. The subjects' mean height was 1.69 m (ranged 1.49-1.92 m) and their mean weight was 74 kg (ranged 55-99 kg). The subjects' mean BMI was 25.78 kg/m^2 (ranged 18.81-29.76 kg/m^2). The subjects consisted of 22 Caucasians, 3 Asians, 9 Blacks and 2 Hispanics. One subject discontinued from the study due to the administrative reasons. Thirty-five subjects (17 males, 18 females) completed the study, and final pharmacokinetic and statistical analyses were performed on 35 evaluable subjects who completed the study.

Pharmacokinetic Summary:

Mean zolpidem plasma concentration-time profiles following single oral doses of 10 mg test (Treatment A and B) and reference (Treatment C) formulations under fasting condition are shown in Figure 1. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 13-15.

Figure 1. Mean zolpidem plasma concentration-time profiles following single oral doses of 10 mg Test without water (Treatment A), 10 mg Test with water (Treatment B), and Reference (Treatment C) formulations (N = 35)

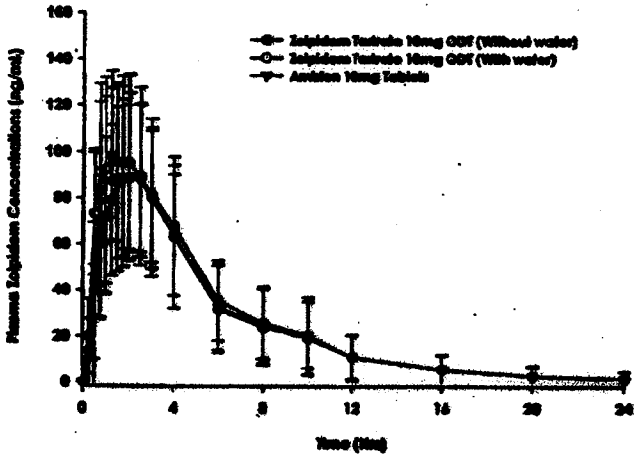


Table 13. Mean pharmacokinetic parameters for zolpidem following single-dose zolpidem 10 mg —— ODT (without water) and Ambien® tablets 10 mg in 35 healthy male and female volunteers

b(4)

Pharmacokinetic Parameters	Geometric Mean (%CV) Arithmetic Mean ± SD		
	Zolpidem Tartrate 10 mg ODT – without water (A) (n = 39)	Zolpidem Tartrate 10 mg ODT – with water (B) (n = 39)	Ambien® 10 mg Tablets (C) (n = 39)
AUC_{0-t} (ng·hr/mL)	530.54 (45.11%) 576.09 ± 260.39	525.32 (51.80%) 587.51 ± 304.31	517.25 (47.10%) 574.44 ± 270.88
AUC_{0-inf} (ng·hr/mL)	542.51 (47.58%) 592.84 ± 282.09	535.93 (53.70%) 602.41 ± 323.49	529.96 (49.84%) 592.48 ± 295.27
C_{max} (ng/mL)	96.91 (32.14%) 101.68 ± 32.68	108.20 (33.33%) 113.28 ± 37.74	105.37 (32.78%) 115.03 ± 37.70
T_{max} (hr)*	1.75 (0.50 – 4.00)	1.25 (0.50 – 3.00)	1.50 (0.50-4.02)
$t_{1/2}$ (hr)†	3.49 ± 1.23	3.35 ± 1.21	3.45 ± 1.45

* median (min – max); † arithmetic mean ± SD

Table 14. Mean pharmacokinetic parameters for zolpidem in male subjects

Pharmacokinetic Parameters	Arithmetic Mean ± SD		
	Zolpidem Tartrate 10 mg ODT – without water (A) (n = 17)	Zolpidem Tartrate 10 mg ODT – with water (B) (n = 17)	Ambien® 10 mg Tablets (C) (n = 17)
AUC_{0-t} (ng·hr/mL)	536.10 ± 184.92	496.92 ± 203.88	464.69 ± 188.96
AUC_{0-inf} (ng·hr/mL)	545.10 ± 187.19	506.01 ± 209.00	472.75 ± 191.89
C_{max} (ng/mL)	104.35 ± 29.98	107.12 ± 28.20	110.10 ± 40.60
T_{max} (hr)*	1.75 (0.50 - 4.00)	1.00 (0.50 - 2.00)	1.00 (0.50 - 4.00)
$t_{1/2}$ (hr)	3.17 ± 0.94	2.98 ± 1.04	2.88 ± 1.01

* median (min – max)

Table 15. Mean pharmacokinetic parameters for zolpidem in female subjects

Pharmacokinetic Parameters	Arithmetic Mean ± SD		
	Zolpidem Tartrate 10 mg ODT – without water (A) (n = 18)	Zolpidem Tartrate 10 mg ODT – with water (B) (n = 18)	Ambien® 10 mg Tablets (C) (n = 18)
AUC_{0-t} (ng·hr/mL)	615.60 ± 316.35	673.06 ± 360.74	678.08 ± 299.54
AUC_{0-inf} (ng·hr/mL)	637.92 ± 348.90	693.46 ± 387.45	708.56 ± 334.43
C_{max} (ng/mL)	99.16 ± 38.72	119.00 ± 45.04	119.69 ± 35.91
T_{max} (hr)*	2.25 (0.75 - 4.00)	1.75 (0.50 - 3.00)	1.75 (0.50 - 4.03)
$t_{1/2}$ (hr)	3.79 ± 1.40	3.71 ± 1.28	4.00 ± 1.62

* median (min – max)

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 16-18.

Table 16. Relative bioavailability analysis of zolpidem tartrate 10 mg ODT-without water (Treatment A) and Ambien® tablets 10 mg (Treatment C) for zolpidem

Parameter	90% CI	Ratio of Means
AUC_{0-t}	95.43% - 111.19%	103.01%
AUC_{0-inf}	95.17% - 111.08%	102.82%
C_{max}	81.98% - 96.57%	88.97%

Table 17. Relative bioavailability analysis of zolpidem tartrate 10 mg ODT-with water (Treatment B) and Ambien® tablets 10 mg (Treatment C) for zolpidem

Parameter	90% CI	Ratio of Means
AUC_{0-t}	94.23% - 109.80%	101.72%
AUC_{0-inf}	93.76% - 109.44%	101.30%
C_{max}	91.26% - 107.50%	99.05%

Table 18. Relative bioavailability analysis of zolpidem tartrate 10 mg ODT-with water (Treatment B) vs. ODT-without water (Treatment A) for zolpidem

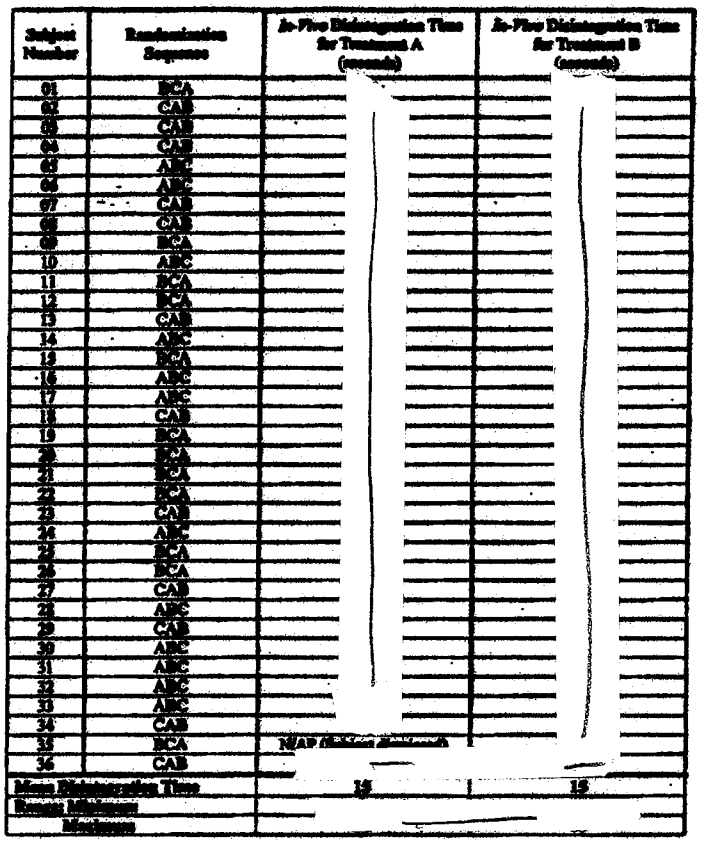
Parameter	90% CI	Ratio of Means
AUC_{0-t}	91.48% - 106.59%	98.75%
AUC_{0-inf}	91.19% - 106.44%	98.52%
C_{max}	102.57% - 120.82%	111.32%

***In Vivo* Disintegrating Time:**

Based on 35 completed subjects, the mean *in vivo* disintegration times of zolpidem were 15 seconds for both Treatments A (— s) and B (— econds), respectively. *In vivo* disintegration was rapid for both strengths (5 and 10 mg) and occurred mostly within 30 seconds, with the exception of one subject at the observed maximal — seconds. b(4)

Table 19. Individual *in vivo* disintegrating time

APPEARS THIS WAY
ON ORIGINAL



b(4)

CONCLUSION:

- Zolpidem exhibited similar pharmacokinetic profiles following oral administration of zolpidem tartrate — 10 mg ODT without water (Treatment A) and with water (Treatment B), and following oral administration of Ambien® 10 mg tablet under fasting condition. The rate and extent of absorption of zolpidem from these treatments were similar. b(4)

- The zolpidem tartrate — 10 mg ODT administered without water is bioequivalent to Ambien® 10 mg tablet (based on acceptance criteria for BE, i.e., 80-125% CI, for AUC_{0-t}, AUC_{0-inf}, and C_{max}) under single-dose fasting conditions. The ratios of geometric mean of AUC_{0-t}, AUC_{0-inf}, and C_{max} for zolpidem were 103.01%, 102.82%, and 88.97%, respectively. b(4)

- The zolpidem tartrate — 10 mg ODT administered with water is bioequivalent to Ambien® 10 mg tablet (based on acceptance criteria for BE, i.e., 80-125% CI, for AUC_{0-t}, AUC_{0-inf}, and C_{max}) under single-dose fasting conditions. The ratios of geometric mean of AUC_{0-t}, AUC_{0-inf}, and C_{max} for zolpidem were 101.72%, 101.30%, and 99.05%, respectively. b(4)

- The zolpidem tartrate ____ 10 mg ODT administered without water is bioequivalent to that administered with water under single-dose fasting conditions. The 90% CI of the geometric mean ratios of AUC_{0-t}, AUC_{0-inf}, and C_{max} for zolpidem were 98.75%, 98.52%, and 111.32%, respectively, and were within the range of 80-125%, the acceptance criteria for BE. It was concluded that water had no effect on the rate and extent of absorption of zolpidem following oral administration of the zolpidem tartrate ——— 10 mg ODT.

b(4)

Comment:

1. There was a slight increase in mean T_{max} when zolpidem ODT was taken without water (1.91 hours) compared to reference Ambien® tablet (1.59 hours) and to zolpidem ODT taken with water (1.34 hours; p= 0.0048). However, this slight delay in time to reach C_{max} is not likely to have clinical significance.
2. Study 2840 for the effect of administration with water is not very valuable to evaluate the effect of swallowing vs. allowing to disintegrate, since in both treatment groups the 10 mg zolpidem ODT was allowed to dissolve in oral cavity prior to swallowing. It would be a more optimal study design to detect the effect of swallowing water by instructing the subjects in Treatment group B (with water) to swallow the ODT directly with 240 mL water without intentionally letting the ODT disintegrate on the tongue and sucking on the tablet prior to the swallowing. However, since bioequivalence has been demonstrated in this study between reference tablet and ODT when let to dissolve without water or followed by swallowing with water, and between two modes of administration for ODT, label claim with and without water can be allowed.

Study 2841 (Protocol #: B04-669PK-N04F1)

A Two-Way Crossover, Randomized, Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Dosage Strength Proportionality Study of Two Strengths of Zolpidem Tartrate ODT (2 x 5 mg and 1 x 10 mg) in Normal Healthy Non-Smoking, Male and Female Subjects

Principal Investigator: Paul Y. Tam, M.D., F.R.C.P., F.A.C.P.
Study Center: Biovail Contract Research
- 460 Comstock Road, Toronto, ON, M1L 4S4 Canada
- 689 Warden Avenue, Units 1 & 2,
Toronto, ON, M1L 4R6 Canada
Study Period: May 19, 2004 – May 28, 2004

Objectives:

- To assess the dosage strength proportionality of zolpidem from a 5 mg and 10 mg Zolpidem Tartrate —— ODT administered as 2 x 5 mg QD and 1 x 10 mg QD under fasting conditions

b(4)

Test formulation: Zolpidem Tartrate 5 mg ODT, Lot #: 0403026 (Biovail Technologies Ltd., Ireland), Batch size: —— Expiry: 06-01-2004

Reference formulation: Zolpidem Tartrate 10 mg ODT, Lot #: 0403023 (Biovail Technologies Ltd., Ireland), Batch size: —— Expiry: 06-01-2004

b(4)

Study Design:

This study was a randomized, open-label, single-dose, two-way crossover design in 36 normal, healthy, male and female subjects under fasting conditions. Subjects within an age range of 18 to 65 years and a Body Mass Index (BMI) between 18.5 and 29.9 kg/m^2, who met the inclusion and exclusion criteria, were enrolled in the study.

In all Treatments, the Test and Reference products were administered at 22:00 PM following a fast of ≥4 hours. All subjects remained fasted for at least 4 hours post-dose. Subjects received one of the following 2 treatments (total dose = 10 mg each) on two 3-days periods separated by a one-week washout period:

Treatment A (2 x 5 mg): Two 5-mg Zolpidem Tartrate —— ODT were placed directly on each subject's tongue, and the actual dosing time was recorded upon placing the tablet on the tongue. Subjects were instructed to suck on the ODT for one minute or longer until they completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. A mouth-check was performed to confirm that the drug had been ingested. No water was provided until 1 hour post-dose.

b(4)

Treatment B (1 x 10 mg): One 10-mg Zolpidem Tartrate ——— ODT was placed directly on each subject's tongue, and the actual dosing time was recorded upon placing the tablet on the tongue. Subjects were instructed to suck on the ODT for one minute or longer until they completely dissolved in the mouth, and not to swallow or chew any portion of the tablet. A mouth-check was performed to confirm that the drug had been ingested. No water was provided until 1 hour post-dose. b(4)

For Treatments A and B, the subjects were given a timer for recording the time taken for disintegration of the tablets in the mouth. The timers were started the moment the tablets were placed on the tongue and stopped when the tablets had begun to break.

Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. Subjects were institutionalized the day of dosing and remained in the clinic until the morning of Day 2.

Safety Assessments:
Safety assessments were conducted at screening and during the study, including physical examination and vital signs (blood pressure, heart rate, and temperature), 12-lead electrocardiograms (ECG), and routine laboratory measurements (hepatitis C and B, HIV, biochemistry, hematology, urinalysis, urine drugs of abuse, urine nicotine testing). In addition, pregnancy tests (urine hCG and serum β-CG) were performed on all female subjects. Screen for urine drugs of abuse, urine nicotine and saliva alcohol, pregnancy tests, will be performed upon check-in for each study period. Physical examination and urinalysis testing will be performed prior to discharge at the completion of the study. Adverse events were monitored throughout the study.

Pharmacokinetics Assessments:
A total of 19 blood samples (7 mL each) were collected from each subject for determination of zolpidem at pre-dose, 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0 and 24.0 hours post-dose. Plasma samples were stored frozen at - 25°C ± 10°C until assayed.

Plasma concentrations of zolpidem were analyzed with ——— as the internal standard using a validated HPLC ——— method. An eight-point calibration curve (1.000, 1.999, 3.998, 15.994, 63.975, 127.950, 255.899, and 511.797 ng/mL), excluding the blank sample, was constructed in human plasma to cover the ranges between LLOQ (1.000 ng/mL) and ULOQ (511.797 ng/mL) of zolpidem. A weighed ($1/conc^2$) linear regression analysis was employed to determine the slope and intercept of the calibration curves. Two calibration curves and duplicated QC samples for zolpidem at three concentration levels were analyzed with each batch of the samples. b(4)

Table 20. Assay validation for Study 2841

	Zolpidem
Method:	HPLC ———
Standard curve	

b(4)

	Range:	
	Precision:	
	Accuracy:	
	Linearity:	
LOQ		
	LLOQ:	
	ULOQ:	
QC		
	Low:	
	Precision:	
	Accuracy:	
	Med:	
	Precision:	
	Accuracy:	
	High:	
	Precision:	
	Accuracy:	

b(4)

Pharmacokinetic Analysis:
The pharmacokinetic analysis was performed on all subjects who completed the two study periods. The following pharmacokinetic parameters for zolpidem from all Treatment groups were calculated by standard non-compartmental methods: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$, and MRT.

Statistical Analysis:
Descriptive statistics, including arithmetic mean, standard deviation (SD), and inter-subject coefficient of variation (CV), were performed on the plasma concentrations and all pharmacokinetic parameters of zolpidem.

Using GLM procedures in SAS, analysis of variance (ANOVA) was performed on log-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} and on untransformed Tmax, Kel, t1/2, and MRT at the significance level of 0.05. The intra-subject coefficient of variation (CV) was calculated using the Mean Square Error (MSE) from the ANOVA table. The ratio of geometric means and the 90% geometric confidence interval (90% C.I.) were calculated based on the difference in the Least Squares Means of the log-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} between the test and reference formulations. Data from subjects who experience emesis during the study may be removed from the statistical analysis.

RESULTS

Demographics of Subjects:
Thirty-six subjects (18 males, 18 females) with a mean age of 39 years (range = 20-61 years of age) were enrolled in the study. The subjects' mean height was 1.69 m (ranged 1.48-1.93 m) and their mean weight was 73 kg (ranged 49-100 kg). The subjects' mean BMI was 25.2 kg/m^2 (ranged 19.6-29.7 kg/m^2). The subjects consisted of 26 Caucasians, 3 Blacks and 7 Hispanics. All 36 subjects completed the study, and final pharmacokinetic and statistical analyses were performed on all subjects who completed the study.

Pharmacokinetic Summary:

Mean zolpidem plasma concentration-time profiles following single oral doses of zolpidem tartrate 2 x 5 mg ODT formulation (Treatment A) and 1 x 10 mg ODT formulation (Treatment B) are shown in Figure 2. The summary of pharmacokinetic parameters and statistical analysis of each pharmacokinetic parameter are shown in Tables 21-22.

Figure 2. **Mean zolpidem plasma concentration-time profiles following single oral doses of zolpidem tartrate 2 x 5 mg ODT formulation (Treatment A) and 1 x 10 mg zolpidem tartrate ODT formulation (Treatment B) (N = 36)**

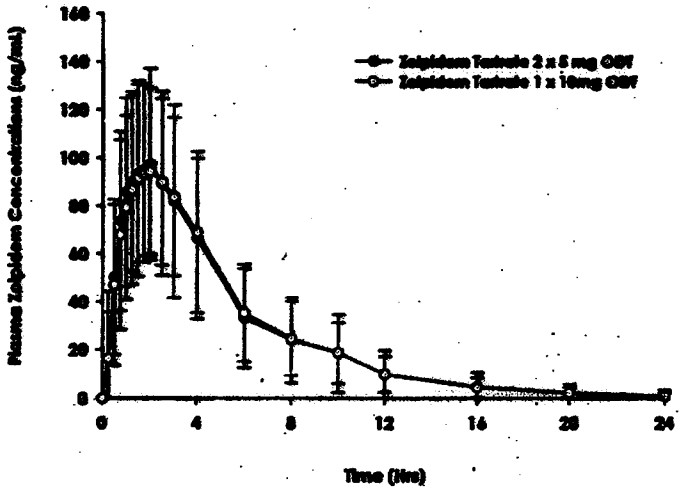


Table 21. **Mean pharmacokinetic parameters for zolpidem following single oral doses of zolpidem tartrate 2 x 5 mg ODT formulation (Treatment A) and 1 x 10 mg ODT formulation (Treatment B) (N = 36)**

Pharmacokinetic Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD	
	Zolpidem Tartrate 2 x 5 mg ODT (A) (n=36)	Zolpidem Tartrate 1 x 10 mg ODT (B) (n=36)
AUC_{0-t} (ng·hr/mL)	506.18 (53.17) 577.68 ± 307.17	515.66 (46.83) 580.69 ± 271.99
$AUC_{0-\infty}$ (ng·hr/mL)	515.89 (54.28) 590.14 ± 328.35	523.47 (46.83) 591.48 ± 276.98
C_{max} (ng/mL)	103.47 (34.80) 119.10 ± 39.67	99.88 (30.79) 109.89 ± 36.82
T_{max} (hr)*	1.75 (0.75 – 4.00)	1.75 (0.75 - 4.10)
$t_{1/2}$ (hr)	3.23 ± 1.16	3.29 ± 1.08

* median (min – max)

Table 22. **Mean pharmacokinetic parameters for zolpidem in male and female subgroups**

Pharmacokinetic Parameter	Arithmetic Mean ± SD			
	Zolpidem Tartrate 2 x 5 mg ODT (A) (n=16)		Zolpidem Tartrate 1 x 10 mg ODT (B) (n=16)	
	MALE	FEMALE	MALE	FEMALE
AUC_{0-t} (ng·hr/mL)	523.92 ± 241.08	632.47 ± 369.31	536.01 ± 206.63	625.20 ± 324.50
AUC_{0-inf} (ng·hr/mL)	533.75 ± 248.40	646.53 ± 377.96	546.93 ± 212.96	636.05 ± 329.28
C_{max} (ng/mL)	101.32 ± 32.63	118.88 ± 44.95	96.61 ± 38.41	113.37 ± 48.94
T_{max} (hr)*	1.50 (0.25 – 4.00)	1.75 (0.75 – 2.50)	1.75 (1.00 – 3.00)	1.75 (0.75 – 4.10)
$t_{1/2}$ (hr)	3.20 ± 1.09	3.25 ± 1.26	3.41 ± 1.14	3.17 ± 1.04

* median (min – max)

Results of relative bioavailability and statistical analyses for natural logarithm transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 23.

Table 23. Relative bioavailability analysis of zolpidem tartrate 2 x 5 mg ODT formulation (Treatment A) and 1 x 10 mg ODT formulation (Treatment B) for zolpidem

Parameter	90% CI	Ratio of Means
AUC_{0-t}	91.11% - 105.77%	98.17%
AUC_{0-inf}	91.06% - 105.77%	98.14%
C_{max}	96.16% - 112.05%	103.80%

In Vivo Disintegrating Time:

The mean *in vivo* disintegration times of zolpidem were 10 and 12 seconds for Treatments A (——— is) and Treatment B (——— onds), respectively. *In vivo* disintegration was rapid for the both strengths and occurred mostly within 30 seconds, with the exception of one subject at the observed maximal 33 seconds. b(4)

Table 24. Individual *in vivo* disintegrating time

APPEARS THIS WAY
ON ORIGINAL

Subject Number	Treatment Received in Period I	*In-Vivo* Disintegration Time (seconds)	Treatment Received in Period II	*In-Vivo* Disintegration Time (seconds)
01	B		A	
02	A		B	
03	A		B	
04	A		B	
05	A		B	
06	B		A	
07	A		B	
08	B		A	
09	B		A	
10	B		A	
11	A		B	
12	A		B	
13	B		A	
14	B		A	
15	B		A	
16	B		A	
17	A		B	
18	A		B	
19	B		A	
20	B		A	
21	A		B	
22	B		A	
23	B		A	
24	A		B	
25	A		B	
26	A		B	
27	A		B	
28	A		B	
29	B		A	
30	B		A	
31	A		B	

b(4)

Subject Number	Treatment Received in Period I	*In-Vivo* Disintegration Time (seconds)	Treatment Received in Period II	*In-Vivo* Disintegration Time (seconds)
32	B		A	
33	A		B	
34	B		A	
35	A		B	
36	B		A	

b(4)

	Treatment A	Treatment B
Mean (all subjects)	10	12
Range: Minimum		
Maximum		

CONCLUSION:

- **Zolpidem exhibited similar pharmacokinetic profiles following oral administration of 10 mg test (2 x 5 mg) or reference (1 x 10 mg) ODT formulation under fasting condition. The rate and extent of absorption of zolpidem from two treatments were similar. The ratios of geometric mean of AUC_{0-t}, AUC_{0-inf}, and C_{max} for zolpidem were 98.17%, 98.14%, and 103.80%, respectively. The 90% CI of the geometric mean ratios of AUC_{0-t} and AUC_{0-inf} for zolpidem were within the range of 80-125%.**

- **The dosage form equivalency with respect to the rate and extent of absorption of zolpidem was established between two strengths (2 x 5 mg vs. 1 x 10 mg) of zolpidem tartrate ODT under single-dose fasting conditions.**

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

/s/

Ta-Chen Wu
5/19/05 03:00:40 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
5/19/05 03:07:23 PM
BIOPHARMACEUTICS

Mehul Mehta
5/19/05 03:23:10 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Zolpidem Tartrate
PRODUCT (Brand Name):	Zolpidem Tartrate Orally Disintegrating Tablets
DOSAGE FORM:	Orally Disintegrating Tablets
DOSAGE STRENGTHS:	10 mg
NDA:	21-412
NDA TYPE:	Response to Approvable letter
SUBMISSION DATE:	1/15/03
SPONSOR:	Biovail Technologies Ltd.
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISON:	DPE I, HFD 860
OND DIVISION:	HFD 120

This submission is in response to the FDA approvable letter dated 31st October 2002.

RECOMMENDATION:

From the Office of Clinical Pharmacology and Biopharmaceutics perspective the sponsor has addressed the following two issues. The sponsor's response along with our comments on their response is given below. Please convey the FDA responses regarding dissolution and labeling on pages 2-4 to the sponsor. Also convey the comment to the Medical Officer on page 5 of this review. These comments have also been conveyed to the sponsor via a telecon on 31st January 2003.

1. **Dissolution:**

The Agency proposed a dissolution specification of Q = — % in 30 minutes instead of Q= — % in 60 minutes b(4)

Sponsor's Response:

Biovail acknowledges receipt of the agency's request to revise its current in-vitro dissolution method specification from "— % (Q) in 60minutes" to "—% (Q) in 30 minutes". Biovail's current buffered dissolution medium was originally adapted as it produces a relatively slow drug release capable of discriminating formulation changes during drug development compared to more traditional IR dosage form dissolution media such as 0.1N HCl (reference, Biovail original NDA, volume 4, page 227). Which would produce a very rapid dissolution rate. Consequently, a dissolution rate of —% (Q) in 30 minutes for Zolpidem Tartrate Orally Disintegrating tablets is not attainable while current buffered media and agitation speed parameters remain unchanged. Biovail has investigated the dissolution rate of its slowest tablets II in 0.1N HCl however, using a USP dissolution apparatus II rotating at 50 rpm with a 0.1N HCl media maintained at 37°C. The results are presented below. Biovail's Zolpidem Tartrate Orally Disintegrating Tablet 10mg achieves the FDA's 85% dissolution in 15 minutes in 0.1N HCl for drugs with a Biopharmaceutics Classification System 1 with ease. Biovail therefore requests that the agency consider (i) maintaining the current dissolution 60 minute specification, or (ii) in the event of the rejection of proposal i, Biovail be allowed to propose the alternative 0.1N HCl media, USP Apparatus II, 50 rpm dissolution method as the regulatory dissolution test for its immediate release formulation. b(4) b(4)

FDA Response:

We do not agree with the sponsor's proposal of changing the media to 0.1 N HCl which would not be discriminatory. However, if the sponsor feels that they do not have enough data on stability batches at the 30 minute time point, we can allow an INTERIM specification of Q= —% in 60 minutes till the sponsor gathers dissolution data from the stability batches at 30 minutes and 60 minutes. The sponsor should evaluate the dissolution at 30 minutes using pH 5.8 buffer for at least 3 production batches. Also provide the same on the existing biobatches (on stability), if possible. Once the dissolution data has been collected, the sponsor should change the dissolution specification to Q= —% in 30 minutes (if supported by the results) within a year. Please submit the final report including the results and revised dissolution specifications within a year of the date of approval. b(4)

The sponsor has agreed to this commitment at the telecon of 1/31/03. The interim dissolution specifications and methodology for Zolpidem orally disintegrating tablets are as follows:

Apparatus:	**USP apparatus 2 (paddle), 50 rpm**
Medium:	**Phosphate buffer, pH 5.8**
Volume:	**900 mL**

Temperature: 37±0.5°C
Specification: Q = —% in 60 minutes

b(4)

2. Labeling

FDA Response on labeling:

The sponsor proposes the following label for the "Pharmacokinetics" sub-section under "Clinical Pharmacology" section of the label. The reviewer has made additional changes as shown by strikeout and underlines. Sentences have been moved around to fit the appropriate sub-sections. The comments should be conveyed to the sponsor:

b(4)

1 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

COMMENT TO THE MEDICAL OFFICER:

Under the " Dosing and Administration" section of the label, the label states that

b(4)

Veneeta Tandon 1/31/03

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D. Uppoor 01/31/03

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-412	Submission Dates: December 29, 2001, March 27, June 28, 2002
Brand Name	Zolpidem Tartrate Rapidly Dissolving Tablets
Generic Name	Zolpidem tartrate
Reviewer	Maria Sunzel, Ph.D.
Team Leader	Ramana Uppoor, Ph.D.
OCPB Division	HFD-860
OND Division	HFD-120
Sponsor	Biovail Technologies Ltd., 3701 Concorde Parkway, Chantilly, VA 20151 (for Biovail Laboratories Inc.)
Relevant IND(s)	No IND number assigned
Submission Type; Code	Standard, 505(b)(2)
Formulation; Strength	Rapidly dissolving tablets; 10 mg (new dosage form)
Indication	Short-term treatment of insomnia

1 EXECUTIVE SUMMARY

This NDA review evaluates *in vivo* and *in vitro* data regarding rapidly dissolving zolpidem tartrate tablets (one strength: 10 mg, oral admin.), intended for short-term treatment of insomnia in adults. The rapidly dissolving tablets are _____ and disintegrate rapidly and disperse taste-masked drug-containing microspheres upon contact with e.g. saliva that are swallowed. b(4)

This new rapidly dissolving tablet formulation does not provide any additional clinical benefits compared to the approved tablets, but according to the sponsor 'will allow for better patient convenience and compliance, as it may be administered with or without water'.

The sponsor has submitted NDA 21-412 as a 505(b)(2) application. Three Phase I studies were submitted. It was shown that the rapidly dissolving tablets and the marketed Ambien tablets were bioequivalent during fed or fasting conditions, and that the rapidly dissolving tablets could be taken with or without water (90% CI's of C_{max} & AUC within 80-125%). No gender differences in the PK of zolpidem were observed. The sponsor refers to the approved product (Ambien tablets) for all other information regarding basic pharmacokinetics (PK), special populations, drug-drug interaction studies, as well as clinical efficacy and safety. No phase II/III studies in patients demonstrating efficacy or safety have been conducted with the new 10 mg tablet.

The proposed *in vitro* dissolution method is deemed acceptable. However, the proposed specification should be changed to Q= _ % in 30 min. b(4)

The sponsor's proposed label changes of the currently approved label relate to specific information to the rapidly dissolving zolpidem tartrate tablet. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends some revisions of the proposed text.

OCPB finds the submitted data in NDA 21-412 to be acceptable, and adequate to support an approvable action of the new formulation, pending the outcome of the DSI inspection report.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the submitted data in NDA 21-412 acceptable, and recommends an approvable action of the new formulation, the rapidly dissolving (10 mg zolpidem tartrate) tablet, pending the outcome of the DSI inspection report of one Phase I study (study #109297), and acceptance of dissolution specifications. The sponsor's proposed label changes of the currently approved label relate to specific information to the rapidly dissolving zolpidem tartrate tablet. The OCPB recommends some revisions of the proposed text (described in Section 5).

The proposed *in vitro* dissolution method is deemed acceptable (described in Section 4.4). However, the proposed specification should be changed to Q= —) in 30 minutes. b(4)

Please forward the comments above, and the labeling comments described in Section 5, to the sponsor. Please forward the labeling comments (Section 5) to the medical reviewer.

2 TABLE OF CONTENTS

3 SUMMARY OF CPB FINDINGS

3.1 Background

Zolpidem tartrate is a non-benzodiazepine hypnotic (an imidazopyridine), that interacts with the GABA-BZ (γ–butyric acid - benzodiazepine) receptor complex. In 1992 the Agency approved 5 & 10 mg zolpidem tartrate IR tablets, Ambien® by Lorex (joint venture between Pharmacia - formerly Searle, & Sanofi-Synthelabo). Ambien is indicated for the short-term treatment of insomnia (7-10 days) and the dosing recommendations are 10 mg immediately before bedtime. In elderly or debilitated patients, and patients with hepatic insufficiency a lower initial dose of 5 mg is recommended.

The following pharmacokinetic (PK) characteristics of zolpidem have been determined after oral doses of Ambien (IR) tablets:

- Rapid drug absorption (t_{max} 1.6 h after dose intake)
- Concomitant food intake reduces AUC (15%) & C_{max} (25%), and prolongs t_{max} by 60%
- Plasma protein binding: 92.5% (studied concentration range 40-790 ng/mL)
- Mainly metabolized (inactive metabolites) via cytochrome P450 (Literature data *in vitro*: CYP3A4, 2C9, & 1A2, with very minor involvement of CYP2D6 & 2C19)
- Total radioactivity (oral dose, n=3) excreted via urine (50-70%) and feces (30-40%)
- Terminal t½ of about 2.5 h (range 1.4 - 4.5 h), no accumulation after repeated QD PM doses
- Linear PK over the dose range of 5 mg – 20 mg/day
- Hepatic impairment: AUC increased 5-fold, C_{max} increased 2-fold, t½ prolonged 4.5-fold (dose reduction)
- Elderly (>70 yrs) *vs.* young adults: AUC increased 64% , C_{max} increased 50%, t½ prolonged 32% (dose reduction)
- Renal impairment (end stage renal disease): no effects on PK (no dose reduction)
- Race and gender – no information available in current label (PDR 2002)
- Drug-drug interactions (PDR 2002) with zolpidem &: alcohol: additive effect on psychomotor performance (general caution for other CNS active drugs); sertraline (34% increase in C_{max}, 53% decrease in t_{max} of zolpidem; sertraline unchanged); itraconazole (43% increase in AUC_{inf} of zolpidem), rifampin (58% decrease in C_{max}, 73% decrease in AUC, 53% decrease in t½ of zolpidem, reduced efficacy)
- No PK interaction (pharmacodynamic interaction in parentheses) reported after zolpidem and haloperidol, imipramine (20% decrease in C_{max} imipramine, increased sedation), chlorpromazine (increased sedation), fluoxetine, cimetidine, ranitidine digoxin, or warfarin (only prothrombin time measured)

3.2 Current Submission

This new NDA contains data regarding rapidly dissolving zolpidem tartrate tablets (one strength: 10 mg, oral admin.), intended for short-term treatment of insomnia in adults.

The sponsor (Biovail) has submitted NDA 21-412 as a 505(b)(2) application. The sponsor refers to the approved product for all other information regarding basic pharmacokinetics (PK), special populations, drug-drug interaction studies, as well as clinical efficacy and safety. No phase II/III studies in patients demonstrating efficacy or safety have been conducted with the new 10 mg tablet.

This new rapidly dissolving tablet formulation does not provide any additional clinical benefits compared to the approved tablets, but according to the sponsor 'will allow for better patient convenience and compliance, as it may be administered with or without water'. It should be

noted that no evidence of buccal absorption was observed, and time to peak zolpidem concentrations do not differ between the new dosage form and the approved product.

The sponsor has submitted reports from 3 single-dose Phase I studies, 95 (43F/52M) of 102 healthy subjects completed the studies. The sponsor states that 6 Phase I studies were performed, where 3 studies were of pilot character. The summary contains information about one pilot study in 18 additional subjects (no reports submitted for any pilot study).

PK information for zolpidem dosed as the to-be-marketed formulation from the submitted study reports covers the following items:

1. Relative bioavailability: Rapidly dissolving tablets *vs.* approved IR tablets after a single 10 mg dose during fasting conditions
2. Relative bioavailability: Rapidly dissolving tablets *vs.* approved IR tablets after a single 10 mg dose during fed conditions
3. Relative bioavailability: Rapidly dissolving tablets after a single 10 mg dose administered with or without water (fasting conditions)

It was shown that the rapidly dissolving tablets and the marketed Ambien tablets were bioequivalent during fed or fasting conditions, and that the rapidly dissolving tablets could be taken with or without water (bioequivalence acceptance criteria within 80-125% of C_{max} and AUC). In addition, no gender differences in the pharmacokinetics of zolpidem were observed in the three studies. The bioanalytical method used for zolpidem analysis of the plasma samples from the three *in vivo* studies in NDA 21-412 is considered adequately documented and validated.

The proposed *in vitro* dissolution method is deemed acceptable. However, the dissolution specifications should be changed to Q= —› at 30 min. b(4)

The sponsor's proposed label changes of the currently approved label relate to specific information to the rapidly dissolving zolpidem tartrate tablet. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends some revisions of the proposed text.

The Division of Scientific Investigations (DSI) inspected the clinical site (——— ——————— and bioanalytical facility (Biovail Contract Research, Toronto, Canada) of one relative bioavailability study (comparison of the new and approved zolpidem tartrate formulations during fasting conditions; study #109297; B01-549PK-ZOLN04). At this point in time, the DSI inspection report is still pending. b(4)

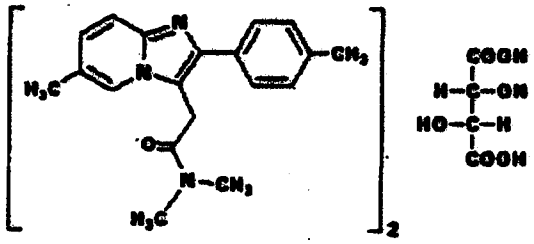
The OCPB finds that the submitted data in NDA 21-412 is acceptable and recommends an approvable action of the new formulation, the rapidly dissolving (10 mg zolpidem tartrate) tablet, pending the outcome of the DSI inspection report of the Phase I study.

APPEARS THIS WAY
ON ORIGINAL

4 QUESTION BASED REVIEW

4.1 General Attributes

What is the structural formula and what are the physicochemical properties of zolpidem tartrate?



Zolpidem is an imidazopyridine derivative. Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol and propylene glycol. Zolpidem tartrate's empirical formula is $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ and it has a molecular weight of 764.88.

What is zolpidem's mechanism of action?

Zolpidem is a sedative-hypnotic, and the compound is not structurally related to barbiturates or benzodiazepines (BZ). Zolpidem binds to the omega-1 subclass of BZ receptors in the brain (high affinity ratio of the $\alpha 1/\alpha 5$ subunits) without binding to peripheral BZ receptors (zolpidem has been shown to have minor or no muscle relaxant properties).

What are the indication and recommended doses of zolpidem tartrate (Ambien tablets)?

Zolpidem tartrate (Ambien) is indicated for the short-term treatment of insomnia. The drug has been shown to decrease sleep latency and increase the duration of sleep. As with other hypnotics, the use should generally be limited to 7 to 10 days (reevaluation of the patient is recommended if drug use exceeds 2 - 3 weeks).

The zolpidem doses should be individualized, but should not exceed 10 mg. The recommended dose for adult patients is 10 mg administered at bedtime. A lower dose of 5 mg is recommended in elderly or debilitated patients, and patients with hepatic impairment, due to an observed larger exposure (C_{max} & AUC) of zolpidem in these patient groups. No dose reduction is deemed necessary in patients with any degree of renal impairment. Lower doses than 10 mg may be warranted if zolpidem is co-administered with other drugs with CNS-depressant properties. The drug has not been evaluated in patients younger than 18 years of age.

4.2 Formulation

How is the 10 mg zolpidem tartrate rapidly dissolving tablet formulated?

The rapidly dissolving tablet disintegrates rapidly upon contact with e.g. saliva. When the tablet is exposed to a fluid, it disintegrates rapidly and disperses taste-masked drug-containing microspheres that are easily swallowed (without additional fluid intake).

The tablets are manufactured using both traditional manufacturing procedures (such as [redacted]) and Biovail's proprietary drug delivery technologies ([redacted] & Ceform®). The new formulation is [redacted] tablet formed by [redacted] taste-masked drug microspheres (Ceform® technology) and other excipients. The microspheres are manufactured using a process where [redacted]

b(4)

The blue specked, round, flat-faced tablets have a diameter of ~ mm, and a thickness of _ mm, and will be packed in blisters. The pharmaceutical composition of the 10 mg zolpidem tartrate rapidly dissolving tablet is shown in Section 7.2 of the Appendix. b(4)

What advantage does the new dosage form have compared to the approved IR tablet?

This new rapidly dissolving tablet formulation does not provide any additional clinical benefits compared to the approved tablets, but according to the sponsor 'will allow for better patient convenience and compliance, as it may be administered with or without water'.

4.3 In vivo relative bioavailability studies

What in vivo studies were performed?

The sponsor has conducted three relative bioavailability studies (open, randomized, crossover design), where single evening doses of zolpidem tartrate (10 mg) were given to healthy, adult, male, and female volunteers. In total, 102 subjects received at least one dose of zolpidem tartrate, and 95 (43F/52M) subjects completed the entire trials. *In vivo* data was collected from the following 3 relative bioavailability studies (see Appendix, Section 7.3 for details):

1. Rapidly dissolving tablets *vs.* approved IR tablets after a single 10 mg dose during fasting conditions (n=28, 15M/13F; 29.7 ± 8.0 years old)
2. Rapidly dissolving tablets *vs.* approved IR tablets after a single 10 mg dose during fed conditions (n=33, 19M/14F; 38.7 ± 10.6 years old)
3. Rapidly dissolving tablets after a single 10 mg dose administered with or without water (fasting conditions, n=32, 18M/14F; 43.5 ± 11.9 years old)

4.3.1 Bioequivalence of new formulation *vs.* approved product

Are C_{max} & AUC of zolpidem tartrate rapidly dissolving tablets similar to the Ambien IR tablet?

The C_{max} and AUC were similar between the 10 mg zolpidem tartrate rapidly dissolving tablet (test) and the 10 mg approved IR tablets (reference), and bioequivalence criteria (90% CI 80-125%) were met, both during fasting and fed conditions, as shown in Table 1.

TABLE 1. Ratios of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ [test tablet/reference tablet] and 90% confidence intervals (CIs) after a single oral dose of 10 mg zolpidem tartrate, during fasting (n=28) & fed conditions (n=33).

Parameter	Ratio (%)	90% Confidence Interval		Intra-subject CV (%)
		Lower	Upper	
Fasting				
C_{max}	94.4	85.0	104.8	22.3
AUC_{0-t}	96.5	88.3	105.5	19.5
$AUC_{0-\infty}$	96.7	88.0	106.3	20.3
Fed				
C_{max}	88.1	81.7	95.1	18.2
AUC_{0-t}	98.0	91.8	104.8	15.9
$AUC_{0-\infty}$	98.1	91.8	104.8	15.8

Can the zolpidem tartrate formulation be taken irrespective of concomitant food intake?

The potential effect of food on the zolpidem tartrate rapidly dissolving tablet compared to the fasted state was not evaluated in the same study. The influence of food on the pharmacokinetics (PK) of zolpidem is important, since the drug should have a rapid onset of hypnosis. In addition, the product label of the Ambien tablet clearly states that 'for faster sleep onset, Ambien should

not be administered with or immediately after a meal'. Indeed, food delayed the time to peak zolpidem concentrations, which were lower, after administration of either formulation (test or reference), as shown in Figure 1 and Table 2 (cross-study comparisons regarding fed & fasting states).

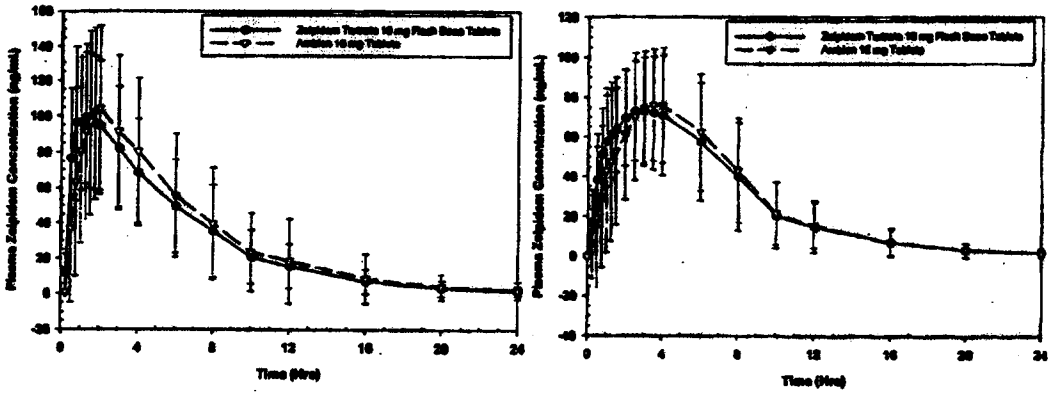


FIGURE 1. Mean (±SD) zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers. Solid circles: Rapidly dissolving tablets (test); Unfilled triangles: Ambien IR tablets (reference) Left panel: Fasted state (n=28); Right panel: Fed state (n=33)

TABLE 2. Mean ± SD pharmacokinetic parameters of zolpidem in the fed and fasted state after a 10 mg oral dose of the rapidly dissolving tablets (test) and Ambien (IR) tablets (reference). Cross-study-comparison (fed/fasting states)

Parameters	Test		Reference	
	Fasting	Fed	Fasting	Fed
C_{max} (ng/mL)	113 ± 38	82.4 ± 26.7	121 ± 47	94.1 ± 32.4
t_{max} (h)	1.6 ± 1.0	2.8 ± 1.3	1.8 ± 1.0	3.2 ± 1.7
$AUC_{(0-t)}$ (ng.h/mL)	688 ± 326	633 ± 326	742 ± 481	631 ± 294
$AUC_{(0-\infty)}$ (ng*hr/mL)	702 ± 342	645 ± 338	778 ± 513	644 ± 306
t½ (h)	3.3 ± 1.0	3.0 ± 1.0	3.3 ± 0.9	3.8 ± 0.72

Although the effect of food on the PK may be slightly less pronounced after intake of the new formulation than after dose intake of the approved tablet, the differences are minor. Therefore, the corresponding text regarding the potential food effects on the onset of sleep that is currently in the Ambien label should also be included in the label for the zolpidem tartrate rapidly dissolving tablets.

4.3.2 Relative bioavailability of the new formulation taken with or without water

Are PK of zolpidem tartrate rapidly dissolving tablets similar after intake with or without water?

The PK of zolpidem were similar after dose intake with water (test) and without water (reference) after a single evening dose of the 10 mg zolpidem tartrate rapidly dissolving tablet as shown in Table 3. Bioequivalence criteria (90% CI 80-125%) were met for C_{max} and AUC, as shown in Table 4.

TABLE 3. Mean ± SD pharmacokinetic parameters of zolpidem taken with (test) or without water (reference) after a single 10 mg evening dose of the rapidly dissolving tablets (n=32).

	Rapidly dissolving tablets	
Parameters	With water (test)	Without water (ref)
C_{max} (ng/mL)	91.9 ± 38.3	90.6 ± 37.4
t_{max} (h)	2.2 ± 1.5	2.4 ± 1.0
$AUC_{(0-t)}$ (ng.h/mL)	670 ± 430	659 ± 393
$AUC_{(0-\infty)}$ (ng*hr/mL)	693 ± 468	679 ± 422
t½ (h)	3.4 ± 1.2	3.4 ± 1.1

TABLE 4. Ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ [with water (test)/ without water (reference)] and 90% confidence intervals (CIs) after a single evening dose of 10 mg zolpidem tartrate rapidly dissolving tablet (n=32).

Parameter	Ratio (%)	90% Confidence Interval		Intra-subject
		Lower	Upper	CV (%)
C_{max}	100.6	92.6	109.3	19.5
AUC_{0-t}	98.3	90.2	107.2	20.3
$AUC_{0-\infty}$	98.5	90.5	107.3	20.1

4.3.3 Intrinsic factors (age and gender)

How old were the healthy volunteers, and did age influence the PK of zolpidem?

The 3 *in vivo* studies were conducted in healthy volunteers above 18 years of age, and restrictions regarding an upper age limit were not set. In the 3 studies the mean age was 30, 39, and 43 years, respectively. Since the studies were of crossover design, each subject served as his or her own control, therefore, the age related 50-60% increases in C_{max} and AUC (reported in the Ambien label) in elderly (>70 years old) compared to young volunteers does not influence the results. The C_{max} and AUC *vs.* age after a 10 mg dose of the rapidly dissolving tablet are shown in Figure 2 (the two studies performed in the fasting state). There are no obvious trends towards a higher exposure of zolpidem with age (oldest subject was 68 years of age) in these healthy volunteers.

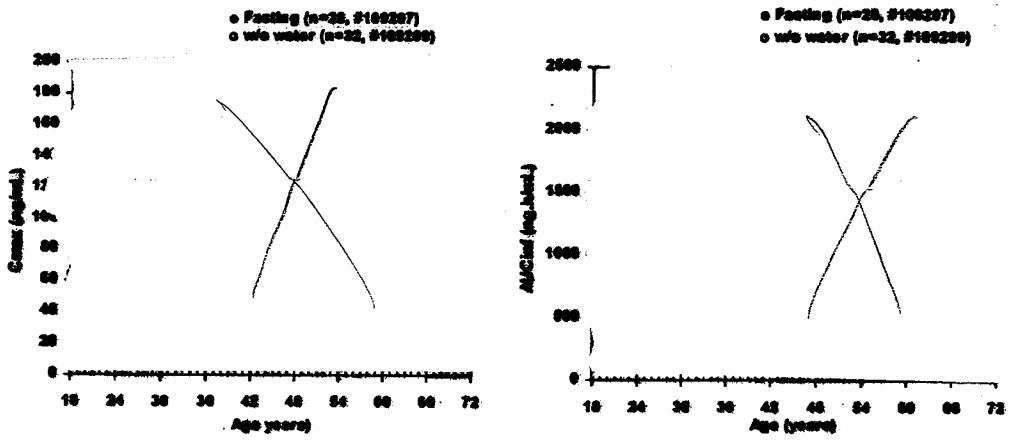
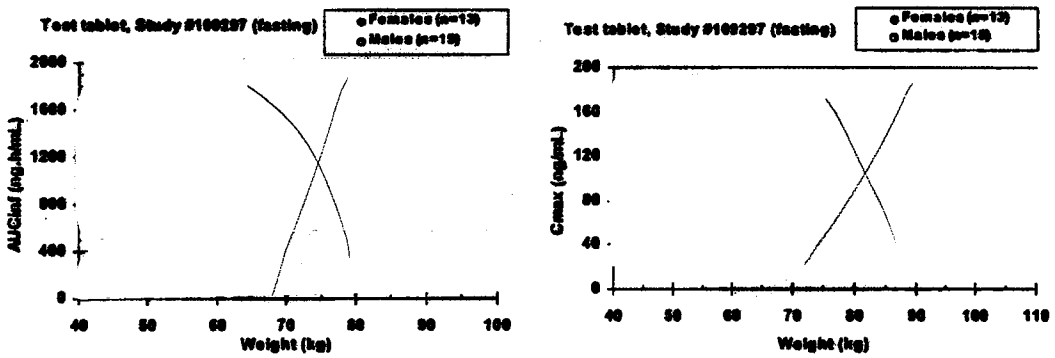


FIGURE 2. Individual C_{max} (left panel) and AUC (right panel) of zolpidem *vs.* age after single evening doses of 10 mg rapidly dissolving tablet to healthy male & female volunteers. Solid circles: Relative bioavailability study, fasting conditions (n=28); Unfilled circles: Relative bioavailability study, without water (n=32)

b(4)

Did gender influence the PK of zolpidem?

The sponsor performed a statistical analysis to evaluate potential gender effects on C_{max} and AUC in each of the 3 studies, and did not find any statistically significant differences between males and females. There was a trend toward lower C_{max} and AUC in the subjects with higher body weights, as shown in Figure 3.



b(4)

FIGURE 3. Individual AUC (left panel) and C_{max} (right panel) of zolpidem *vs.* body weight (kg) after single evening doses of 10 mg rapidly dissolving tablet to healthy male (n=15, unfilled circles) & female (n=13, unfilled circles) volunteers. Data from the relative bioavailability study, fasting conditions (#109297).

4.3.4 Comments on the *in vivo* studies

Were the in vivo studies appropriately conducted and were the statistical analyses acceptable? Was the new formulation well tolerated?

The studies are deemed to be adequately performed, and the statistical analyses were acceptable. This reviewer recalculated the ratios and 90% confidence intervals (bioequivalence analysis) for the 3 studies, the results were in agreement with the sponsor's calculations.

The Division of Scientific Investigations (DSI) inspected the clinical site and bioanalytical facility of one relative bioavailability study (comparison of the new and approved zolpidem tartrate formulations during fasting conditions; study #109297; B01-549PK-ZOLN04). At this point in time, the DSI inspection report is still pending.

There were very few adverse events (AEs) reported in the 3 studies (see individual study summaries in Appendix Section 7.3). This is expected, since the drug shortens time to onset of sleep and was administered in the evening, it is likely that most subjects fell asleep after dose intake. A total of 7 subjects did not complete the trials. Two subjects withdrew consent, 2 subjects were lost to follow-up (did not show up for the 2nd dose), 1 subject had a positive drug screen, and 2 subjects due to vomiting (new formulation: n=1, approved IR tablet: n=1). In addition, 2 female subjects were excluded from the bioequivalence analysis in the relative bioavailability study in the fasting state due to vomiting during one of the two periods (1 test tablet & 1 reference tablet). This is in accordance with the Agency's recommendations in the Guidance document regarding bioavailability/bioequivalence studies, and was found acceptable. For details including a reanalysis with the full data set, please refer to Appendix Section 7.3.1.

4.4 In vitro dissolution method and specification

Which in vitro dissolution method and specifications are proposed for the new formulation?

The sponsor has proposed the following *in vitro* dissolution method and specifications for the zolpidem tartrate rapidly dissolving tablet:

Apparatus:	USP Apparatus 2 (paddle), 50 rpm
Medium, volume:	pH 5.8 (±0.05) phosphate buffer, 900 mL
Temperature:	37±0.5°C
Specification:	Q= — % at 60 min

b(4)

A validated HPLC method with UV detection is used for the zolpidem tartrate analysis. The proposed method is deemed acceptable. However, the proposed specification should be changed to Q= — at 30 min. Justification of the proposed methodology is described in Section 4.5.

Which in vitro dissolution method and specifications are approved for the Ambien tablets?

The approved *in vitro* dissolution method for the Ambien tablets is similar (USP Apparatus 2, 50 rpm, 900 mL medium) but a different medium, 0.1 N HCl, was chosen, with a specification of NLT —% in 15 min.

b(4)

4.5 Justification of the proposed *in vitro* dissolution method

How does the sponsor justify the choice of in vitro dissolution medium and specification?

The sponsor has tested different paddle speeds (45, 50, & 55 rpm) and optimization tests of pH (phosphate buffer media of pH 5.7, 5.8, & 5.9), as well as different pH media (0.1 N HCl, & pH 4.5, pH 5.8 & pH 6.8 buffers).

The variation in paddle speeds resulted in a 1% difference between 50 rpm — released) and 55 rpm — released), and there was no difference in % released drug between 45 rpm and 50 rpm (medium: pH 5.8 phosphate buffer).

b(4)

The optimization tests of pH of the medium (phosphate buffer) resulted in a 1% difference between pH 5.7 — % released) and pH 5.8 (—) released), and there was no difference in % released drug between pH 5.8 and pH 5.9 phosphate buffers.

The mean dissolution-time profiles of the rapidly dissolving tablets in four different pH media are shown in Figure 2 on the next page (see Appendix, Section 7.5 for the tabulated data). The sponsor has chosen the pH 5.8 buffer as the medium for the proposed *in vitro* dissolution method.

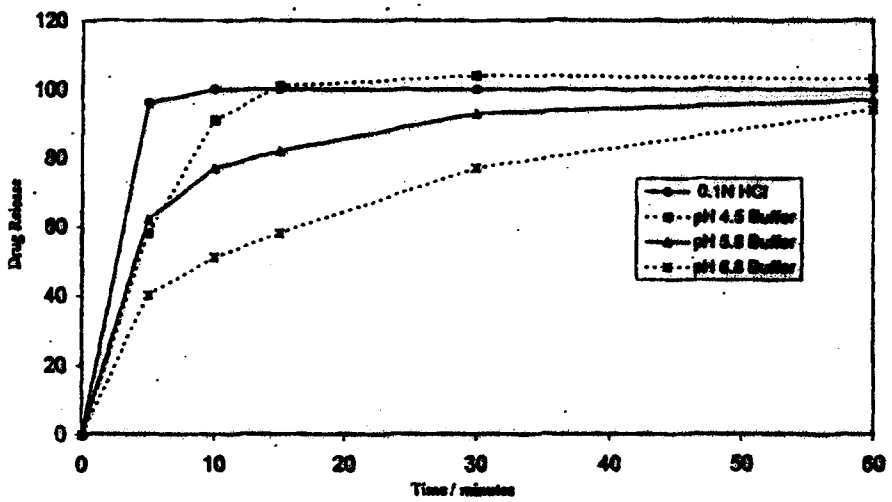


FIGURE 2. Mean (n=12) *in vitro* dissolution profiles (y-axis: % drug released, x-axis: min) of the rapidly disintegrating tablets in 4 different pH media. Lot #24870801 (biobatch)

Are the chosen in vitro dissolution method and specifications deemed acceptable?

The sponsor has chosen a different medium (pH 5.8 buffer) than the one approved for the innovator product (0.1N HCl), which is likely to be more discriminatory and makes this method more satisfactory as an *in vitro* quality control of the final product. However, as shown in Figure 2 above (& Appendix, Section 7.5, Table 1), there is a very minor difference in % drug released at 30 min (mean 93%, range min-max: — %) and 60 min (mean 97%, range min-max: —

b(4)

Therefore, we propose that the sponsor's specification of Q= — at 60 min should be changed to a specification of Q= — at 30 min.

b(4)

4.6 Bioanalytical method

Which analytical method was used in the plasma analyses? Is the method acceptable?

The sponsor used an HPLC (high performance liquid chromatography) method with ——— detection, for the plasma analyses of zolpidem. The same method was used for the 3 *in vivo* studies, and all analyses were performed at the same laboratory (Biovail Contract Research, Toronto, Canada). A more detailed description of the method is found in Appendix, Section 7.4.

b(4)

The method is linear over the zolpidem plasma concentration range of 1.000 ng/mL to 512.000 ng/mL (internal standard: ———). The HPLC method was also validated in regard to intra- and inter-assay precision & accuracy, extraction recovery, dilution integrity, and stability.

The bioanalytical method used for zolpidem analysis of the plasma samples from the three *in vivo* studies in NDA 21-412 is considered adequately documented and validated.

5 LABELING

What changes have been made to the approved label for Ambien IR tablets? Are these changes acceptable?

The sponsor has proposed revisions to the approved label. New information specific for the new tablet formulation is included in the section CLINICAL PHARMACOLOGY Pharmacokinetics. The entire, annotated label proposed by the sponsor is included in the Appendix, Section 7.7.

Labeling comments to the medical reviewer:

- [redacted]

- [redacted] b(4)

Labeling comments to the sponsor:

- [redacted]

b(4)

b(4)

6 SIGNATURES

Maria Sunzel, Ph.D. Maria Sunzel 07/25/02

RD/FT initialed by Ramana Uppoor, Ph.D. Uppoor 07/25/02

Division of Pharmaceutical Evaluation I,
Office of Clinical Pharmacology and Biopharmaceutics

OCPB Briefing Date: July 25, 2002; Attendees: Drs. T Laughren, P Andreason, G Mannheim, A Zajicek, A Jackson, P Marroum, M Sunzel, & R Uppoor

c.c.: NDA 21-412, HFD-120 (Homonnay, Klein, Andreason, Laughren, Shin), HFD-860 (Mehta, Marroum, Uppoor, Sunzel)

APPEARS THIS WAY
ON ORIGINAL

7 APPENDIX

7.1 Table of the *in vivo* pharmacokinetic studies

In vivo study summary Volume 1

Error in sponsor's table: Dosing in Study B01-550PK-ZOLN04 was performed under fed conditions (Pilot study not submitted, the sponsor also performed 3 studies to evaluate taste and texture of formulation, since no sampling was performed, the study reports were not submitted)

Table 1a (Attachment A): Biopharmaceutics Study Summary

Study Number	Basis	Study Design	Dosage Form(s)	Dose	Batch No. Finish/Date Manufactured	Batch Size	No. of Subjects Completed	Related IND or NDA Number	Applicant Conclusion	Previous Agency Response on Protocol with Date of Correspondence
PIVOTAL STUDIES										
B01-550PK-ZOLN01	Oral	Randomized, 2-treatment, 2-period, 2-sequence crossover design under single dose fasting conditions	Zolpidem Tartrate 10 mg Film-Coated Tablets Ambien® 10 mg Tablets	10 mg q.d. fasting 10 mg q.d. fasting	Lot 24870001 Manufactured: 08/2001 Lot 07131 Exp: May 2003		30 out of 34	N/A	The film-coat tablets were bioequivalent to Ambien Tablets under single-dose fasting conditions.	N/A
B01-550PK-ZOLN02	Oral	Randomized, 2-period, 2-sequence crossover design under single dose fed conditions	Zolpidem Tartrate 10 mg Film-Coated Tablets Ambien® 10 mg Tablets	10 mg q.d. fasting 10 mg q.d. fasting	Lot 24870001 Manufactured: 08/2001 Lot 07131 Exp: May 2003		33 out of 34	N/A	The film-coat tablets were bioequivalent to Ambien Tablets under single-dose fed conditions.	N/A
B01-550PK-ZOLN03	Oral	Randomized, 2-treatment, 2-period, 2-sequence crossover design under single dose fasting conditions, with and without water	Zolpidem Tartrate 10 mg Film-Coated Tablets Zolpidem Tartrate 10 mg Film-Coated Tablets	10 mg q.d. fasting 10 mg q.d. fasting	Lot 24870001 Manufactured: 08/2001 Lot 24870001 Manufactured: 08/2001		32 out of 34	N/A	Bioequivalence was established between the two modes of drug administration, i.e., with and without water.	N/A
PILOT STUDY										
B01-550PK-ZOLN04	Oral	Randomized, 2-treatment, 2-period, 2-sequence crossover design under single dose fasting conditions	Zolpidem Tartrate 10 mg Film-Coated Tablets Zolpidem Tartrate 10 mg Film-Coated Tablets Ambien® 10 mg Tablets	10 mg q.d. fasting 10 mg q.d. fasting 10 mg q.d. fasting	Lot GM7197 Manufactured: 04/2000 Lot GM7199 Manufactured: 04/2000 Lot 6C515 Exp: Mar 2003		16 out of 16	N/A	The film-coat tablets were bioequivalent to Ambien Tablets under single-dose fasting conditions.	N/A

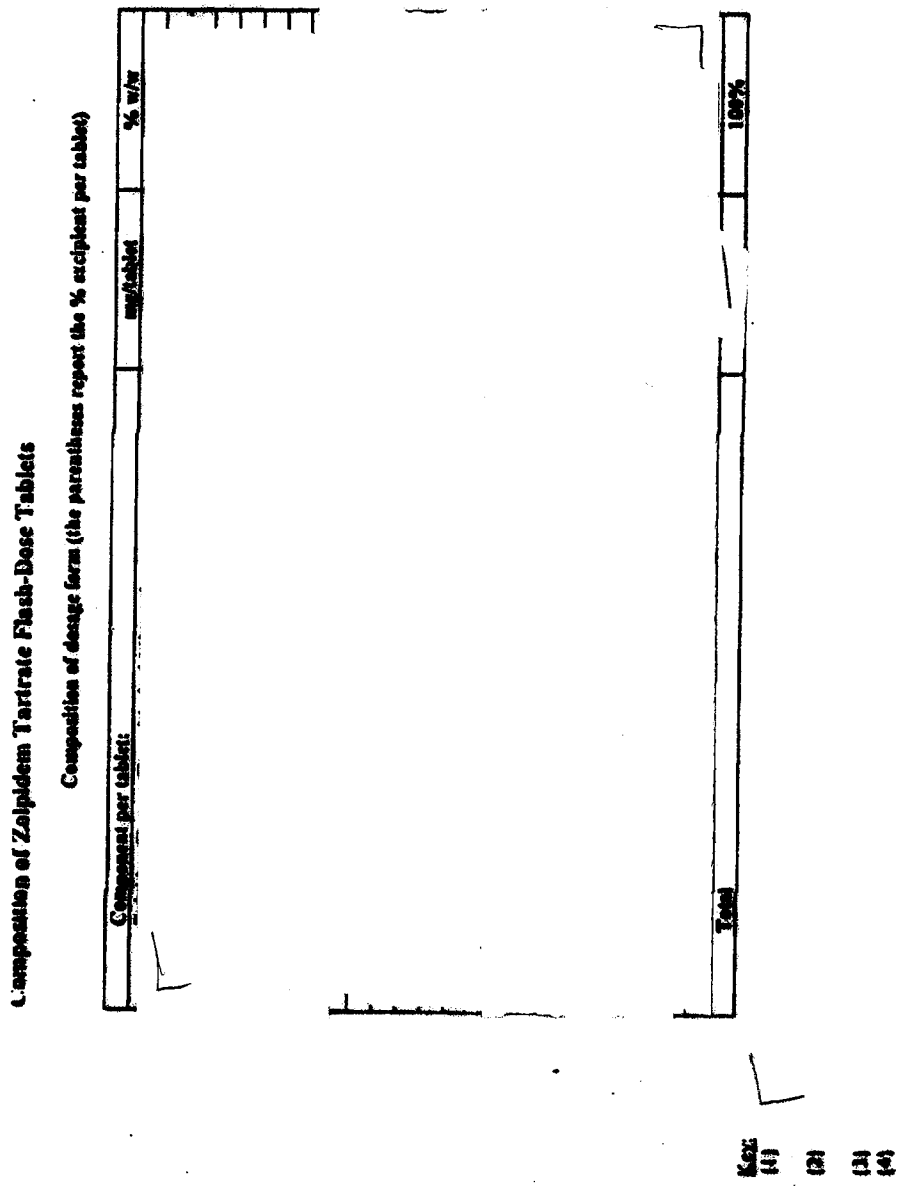
*Theoretical batch size at [illegible] units.
*Theoretical batch size at [illegible] units.

b(4)

b(4)

7.2 Composition of the tablet

Volume 1



b(4)

7.3 Individual *in vivo* study summaries

7.3.1 Bioequivalence evaluation of zolpidem tartrate rapidly dissolving tablets *vs.* Ambien tablets (fasting state)

Volume 7-11

Study title:
Study #109297 (Protocol B01-549PK-ZOLN04): A two-way, crossover, open-label, single-dose, fasting, evening administration, comparative bioavailability study of zolpidem tartrate flash dose 10 mg tablets vs. Ambien® 10 mg tablets in healthy non-smoking male and female subjects

Study Objective:
- To compare the rate and extent of absorption of 10 mg zolpidem rapidly dissolving ('flash dose') tablets to the marketed 10 mg Ambien IR tablets after a single evening dose in healthy volunteers during fasting conditions.

Study Design and Methods:
34 healthy male and female subjects (>18 years old) were to receive a single evening dose of 10 mg zolpidem tartrate, as the rapidly dissolving tablet (test) and the marketed Ambien IR tablet (reference) in this open-label, two-period, randomized, cross-over study. The subjects were admitted to the clinic, and were served dinner that was followed by a > 4-h 'fast', prior to and after the 10 PM evening dose intake. Water-intake was *ad lib*, but not allowed for ± 1 h of dose intake. The subjects received the following zolpidem tartrate treatments:

Treatment A (test): One 10 mg rapidly dissolving tablet was placed on the tongue and sucked for 1 min or longer, until completely dissolved (lot # 24870801; batch size: ——— tablets). Water (240 mL) was ingested within 1 min. b(4)

Treatment B (reference): One 10 mg Ambien IR tablet was given with water (240 mL)

The subjects remained in the clinic for approximately 24 h. No concomitant medications were allowed during the trial. The safety monitoring consisted of AE reporting throughout the trial, and pre- and post-study assessments that included vital signs, clinical laboratory & urinalyses, and physical examinations. There was a washout period of at least 7 days between treatments.

Blood samples for drug analyses were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 16, 20 & 24 h post-dose. Zolpidem plasma concentrations were determined by HPLC with ———— detection. The limit of quantitation of zolpidem was 1.0 ng/mL (see separate analytical section in Appendix). The analytical laboratory was blinded to the randomization code. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{½}$) of zolpidem were calculated by non-compartmental methods. Descriptive statistics for the parameters, analysis of variance, ratio of least squares mean, and 90% confidence intervals of the log transformed C_{max}, AUC_{0-t} and $AUC_{0-infinity}$ for the two treatments were calculated. b(4)

Results:
34 healthy male & female subjects (17M/17F, 18-44 years old) received one dose of zolpidem tartrate, and 30 subjects completed the study (2nd visit drop outs: 2 subj. did not return, 1 subj. had a positive drug screen, 1 subj. dropped out due to AE, Day 2 Visit 1). A total of 28 subjects (15M/13F; 29.7±8.0 years, range 18-43 years old) were included in the pharmacokinetic evaluation. Two female subjects were excluded from the analysis due vomiting during one of the two treatment periods (subj. 7: 1 h 2 min post-test dose, subj. 12: 52 min post-reference dose).

Pharmacokinetics:
The mean ± SD, and the individual zolpidem plasma concentration-time profiles after the two single doses are depicted in Figures 1 and 2, respectively.

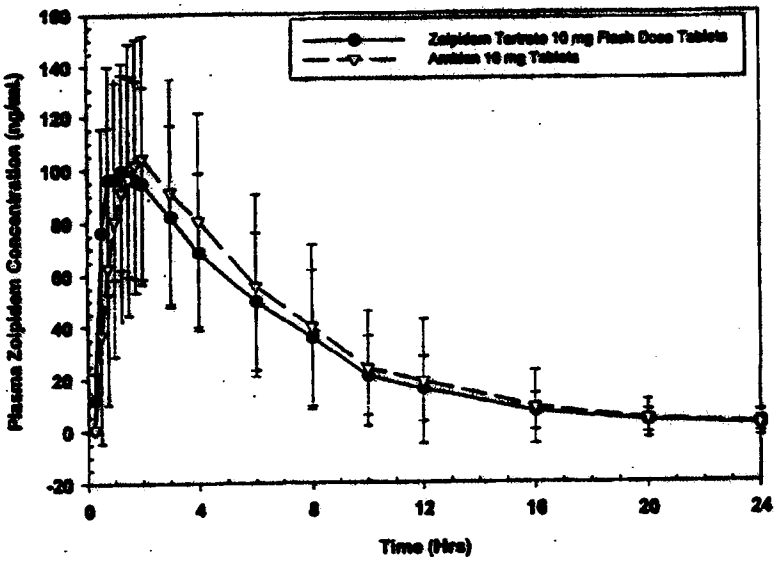
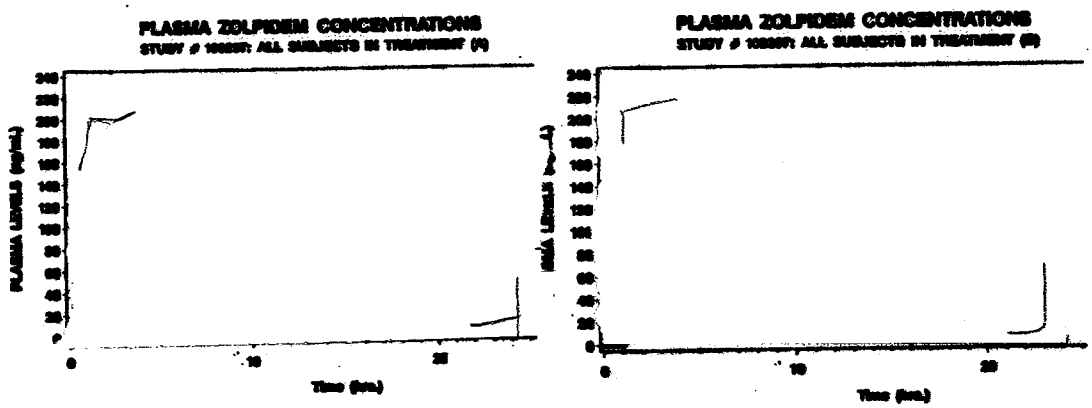


FIGURE 1. Mean (±SD) zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=28) in the fasted state. Solid circles: Rapidly dissolving tablets (test); Unfilled triangles: Ambien IR tablets (reference) [Study 549PK]



b(4)

FIGURE 2. Individual zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=28) in the fasted state. Left panel: Rapidly dissolving tablets (test); Right panel: Ambien IR tablets (reference) [Study 549PK]

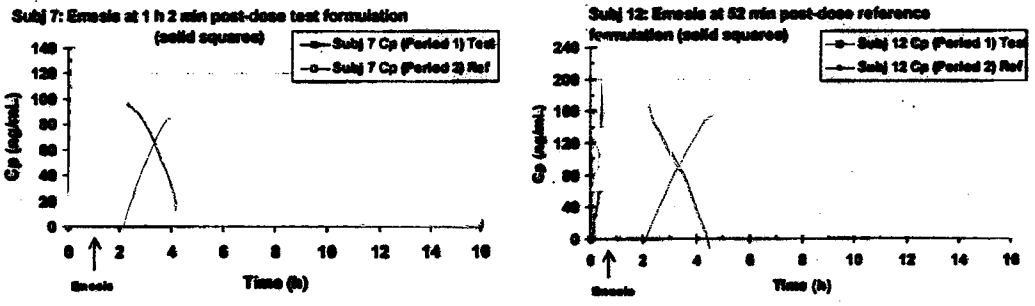
The pharmacokinetic (PK) parameters after the two single doses are depicted in Table 1. The median t_{max} for the rapidly dissolving tablets (test) and Ambien IR tablets (reference) was 1.5 h and 1.75 h, respectively.

TABLE 1. Mean (±SD) PK parameters after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=28) in the fasted state. Treatment A (test): Rapidly dissolving tablets; Treatment B (reference): Ambien IR tablets [Study 549PK]

Pharmacokinetic Parameters	Zolpidem (A) Mean ± SD	Ambien® (B) Mean ± SD
AUC_{0-t} (ng·hr/mL)	688.07 ± 326.20	741.77 ± 481.23
AUC_{0-Inf} (ng·hr/mL)	701.98 ± 342.17	778.06 ± 512.61
C_{max} (ng/mL)	112.66 ± 38.25	121.12 ± 46.56
T_{max} (hour)	1.55 ± 0.96	1.79 ± 0.96
$t_{½}$ (hour)	3.28 ± 1.01	3.29 ± 0.91
K_{el} (hour)	0.234 ± 0.089	0.227 ± 0.065

The two formulations were bioequivalent (acceptance criteria 80-125%) in the fasted state, both with regard to C_{max} and AUC, see main review for the tabulated results. An analysis of gender differences on the PK parameters was performed. No apparent differences in the PK (C_{max} &AUC) were observed between the male and female volunteers.

Subjects omitted from the analysis:
The zolpidem plasma concentration-profiles of the two subjects (no. 7 & 12) that were omitted from the analyses due to emesis are shown in Figure 3.



b(4)

FIGURE 3. Individual zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to Subject 7 (left panel) and Subject 12 (right panel). Both subjects were excluded from the bioequivalence analysis due to vomiting (Subj. 7 emesis 1 h 2 min post test dose; Subj. 12 emesis 52 min post reference dose) [Study 549PK]

Although deletion of data from subjects that vomits is recommended in the Agency's BA/BE Guidance (also see comments, next page), this reviewer recalculated the bioequivalence parameters on the full data set, since the vomiting did not have any marked effects on the zolpidem plasma profiles of these 2 subjects. The point estimates (90%CI) of C_{max}, AUC_{0-t} and $AUC_{0-infinity}$ were 89.11% (78.92-100.62%), 92.29% (82.58-103.15%), and 92.02% (81.93-103.34%), respectively.

Safety:
A total of 10 AEs were reported by 4 (11.8%) of the 34 subjects that received at least 1 dose of zolpidem tartrate. The reported AEs were vomiting (5 occurrences, n=3), nausea (n=3), headache (n=1), hypertension (n=1). One subject (female, subj. 8, approved IR tablet) terminated the study prematurely due to AEs (vomiting, nausea, headache & hypertension) according to the study report (subject reported as 'lost to follow-up' in CRF). There were a number of abnormal laboratory values that occurred at both screening and after the study (not reported as AEs).

Comments:
The exclusion of the data from the two subjects that vomited is in accordance with the procedures of data handling described in the Agency's Guidance 'Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations', Appendix 2 (October 2000). The Guidance recommends exclusion of data if vomiting occurs at or before 2 times median t_{max} for immediate release products. In this study the median t_{max} occurred at 1.5 h for the test product, at a median t_{max} of 1.75 h for the reference product. The inclusion of the data from the 2 subjects did not affect acceptability of the bioequivalence criteria (90% CI within 80-125%) of AUC, but the lower limit of the 90% CI of C_{max} was slightly outside the boundary (79%). However, since the data in this study indicates that zolpidem is mainly absorbed through the GI tract (not through buccal absorption), the influence of the vomiting episodes may have impacted drug absorption. Therefore, the exclusion of the data from the two subjects is deemed acceptable.

In conclusion, this study demonstrated bioequivalence between the 10 mg zolpidem tartrate rapidly dissolving tablets (test) and the currently marketed 10 mg Ambien tablets after single evening doses in the fasting state. The peak zolpidem concentrations also occurred at a similar time (t_{max}) for both products after the evening dose intake.

7.3.2 Bioequivalence evaluation of zolpidem tartrate rapidly dissolving tablets *vs.* Ambien tablets (fed state)

Volume 12-17

Study title:
Study #109298 (Protocol B01-550PK-ZOLN04): A two-way, crossover, open-label, single-dose, fed, evening administration, comparative bioavailability study of zolpidem tartrate flash dose 10 mg tablets vs. Ambien® 10 mg tablets in healthy non-smoking male and female subjects

Study Objective:
- To compare the rate and extent of absorption of 10 mg zolpidem rapidly dissolving ('flash dose') tablets to the marketed 10 mg Ambien IR tablets after a single evening dose in healthy volunteers during fed conditions.

Study Design and Methods:
34 healthy male and female subjects (>18 years old) were to receive a single evening dose of 10 mg zolpidem tartrate, as the rapidly dissolving tablet (test) and the marketed Ambien IR tablet (reference) in this open-label, two-period, randomized, cross-over study. The subjects were admitted to the clinic, and were served lunch (time of lunch not specified in protocol or report). A high-fat meal (36 g protein, 43 g fat, 66 g carbohydrates) was served and ingested within 30 min prior to the 10 PM evening dose intake. Water-intake was *ad lib*, but not allowed for ± 1 h of dose intake. A snack was served 4.5 h after dose intake (2.30 AM, Day 2, no information given on how many subjects actually had a snack). The subjects received the following zolpidem tartrate treatments within 5 min after ingestion of the meal:

Treatment A (test): One 10 mg rapidly dissolving tablet was placed on the tongue and sucked for 1 min or longer, until completely dissolved (lot # 24870801; batch size: —— tablets). Water (240 mL) was ingested within 1 min. b(4)

Treatment B (reference): One 10 mg Ambien IR tablet was given with water (240 mL)

The subjects remained in the clinic for approximately 24 h. No concomitant medications were allowed during the trial. The safety monitoring consisted of AE reporting throughout the trial, and pre- and post-study assessments that included vital signs, clinical laboratory & urinalyses, and physical examinations. There was a washout period of at least 7 days between treatments.

Blood samples for drug analyses were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 20 & 24 h post-dose. Zolpidem plasma concentrations were determined by HPLC with —————— etection. The limit of quantitation of zolpidem was 1.0 ng/mL (see separate analytical section in Appendix). The analytical laboratory was blinded to the randomization code. The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t½) of zolpidem were calculated by non-compartmental methods. Descriptive statistics for the parameters, analysis of variance, ratio of least squares mean, and 90% confidence intervals of the log transformed C_{max}, AUC_{0-t} and $AUC_{0-infinity}$ for the two treatments were calculated. b(4)

Results:
34 healthy male & female subjects (19M/15F, 21-75 years old) received one dose of zolpidem tartrate, and 33 subjects completed the study (1 female subj. dropped out due to AE, Day 2 Visit 1). The 33 subjects (19M/14F; 38.7±10.6 years, range 21-75 years old) who completed both treatments were included in the pharmacokinetic evaluation.

Pharmacokinetics:
The mean ± SD and the individual zolpidem plasma concentration-time profiles after the two single doses are depicted in Figures 1 and 2, respectively.

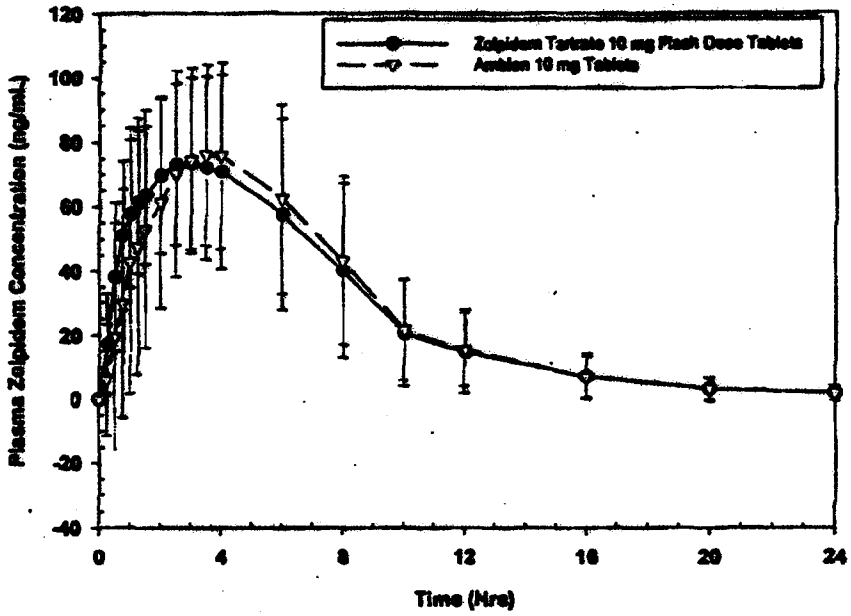
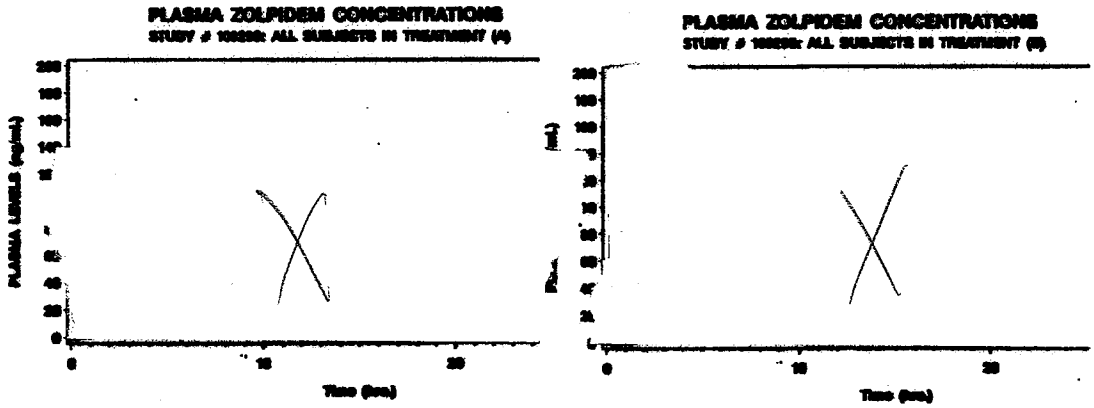


FIGURE 1. Mean (±SD) zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=33) in the fed state. Solid circles: Rapidly dissolving tablets (test); Unfilled triangles: Ambien IR tablets (reference) [Study 550PK]



b(4)

FIGURE 2. Individual zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=33) in the fed state. Left panel: Rapidly dissolving tablets (test); Right panel: Ambien IR tablets (reference) [Study 550PK]

The pharmacokinetic (PK) parameters after the two single doses are depicted in Table 1.

TABLE 1. Mean (±SD) PK parameters after a single evening dose of 10 mg zolpidem tartrate to healthy male & female volunteers (n=33) in the fed state. Treatment A (test): Rapidly dissolving tablets; Treatment B (reference): Ambien IR tablets [Study 550PK]

Pharmacokinetic Parameters	Zolpidem Tartrate 10 mg Flash Dose tablet (A) Mean ± SD	Ambien® 10 mg tablet (B) Mean ± SD
AUC_{0-t}	632.63 ± 325.50	631.28 ± 293.97
AUC_{0-inf}	645.88 ± 337.72	644.02 ± 305.68
C_{max}	82.41 ± 26.65	94.08 ± 32.35
T_{max}	2.80 ± 1.31	3.22 ± 1.66
$t_{½}$	3.03 ± 1.03	3.12 ± 0.94
K_{el}	0.259 ± 0.096	0.246 ± 0.085

The two formulations were bioequivalent (acceptance criteria 80-125%) in the fed state both with regard to C_{max} and AUC, see main review for the tabulated results. An analysis of gender differences on the PK parameters was performed. No apparent differences in the PK (C_{max} &AUC) were observed between the male and female volunteers.

Safety:
A total of 4 AEs were reported by 3 (8.8%) of the 34 subjects that received at least 1 dose of zolpidem tartrate. The reported AEs were vomiting (n=1), headache (n=1), dizziness (n=1), and right upper quadrant pain (n=1). Two AEs (elevated AST & elevated ALT) were detected in the clinical laboratory tests. These elevations occurred in a male, subj. 30 (Screen: ALT 24 IU/L, AST 17 IU/L; End of study: ALT 306 IU/L, AST 121 IU/L; Repeat 1 week post study: ALT 114 IU/L, AST 34 IU/L, no further lab tests reported). One subject (female, subj. 12) terminated the study prematurely after the first dosing period (rapidly dissolving tablet, test) due to AEs (vomiting, dizziness, & headache). There were a number of abnormal laboratory values that occurred at both screening and after the study (not reported as AEs).

Comments:
This study demonstrated bioequivalence between the 10 mg zolpidem tartrate rapidly dissolving tablets (test) and the currently marketed 10 mg Ambien tablets (reference) after single evening doses in the fed state (high fat content). The peak zolpidem concentrations also occurred at a similar time (t_{max}) for both products after the evening dose intake. Food delayed the time to peak zolpidem levels (t_{max}) by approximately 1.5 h for after dose intake of either formulation, which is in accordance with previous observations reported in the label of the approved IR tablets. Peak plasma zolpidem concentrations were also lower compared to Study #549PK, where both formulations were given in the fasting state (also see main review).

7.3.3 Bioequivalence evaluation of zolpidem tartrate rapidly dissolving tablets, with *vs.* without concomitant water intake

Volume 18-23

Study title:
Study #109299 (Protocol B01-551PK-ZOLN04): A two-way, crossover, open-label, single-dose, fasting, evening administration, comparative bioavailability study of zolpidem tartrate flash dose 10 mg tablets administered with and without water in normal healthy non-smoking male and female subjects

Study Objective:
- To compare the rate and extent of absorption of 10 mg zolpidem rapidly dissolving ('flash dose') tablets administered with (test) or without (reference) water after a single evening dose in healthy volunteers during fasting conditions.

Study Design and Methods: b(4)
34 healthy male and female subjects (>18 years old) were to receive a single evening dose of 10 mg zolpidem tartrate rapidly dissolving tablet (lot # 24870801; batch size: ——→ tablets) administered with (test) or without (reference) water in this open-label, two-period, randomized, cross-over study. The subjects were admitted to the clinic, and were served dinner that was followed by a > 4-h 'fast', prior to and after the 10 PM evening dose intake. Water-intake was *ad lib*, but not allowed for ± 1 h of dose intake. The subjects received the following zolpidem tartrate treatments:

Treatment A (test): One 10 mg rapidly dissolving tablet was placed on the tongue and sucked for 1 min or longer, until completely dissolved. Water (240 mL) was ingested within 1 min.

Treatment B (reference): One 10 mg rapidly dissolving tablet was placed on the tongue and sucked for 1 min or longer, until completely dissolved. Water intake was not allowed until 1 h post-dose.

The subjects remained in the clinic for approximately 24 h. No concomitant medications were allowed during the trial. The safety monitoring consisted of AE reporting throughout the trial, and pre- and post-study assessments that included vital signs, clinical laboratory & urinalyses, and physical examinations. There was a washout period of 7 days between treatments.

Blood samples for drug analyses were collected at 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 10, 12, 16, 20 & 24 h post-dose. Zolpidem plasma concentrations were determined by HPLC with ——→ detection. The limit of quantitation of zolpidem was 1.0 ng/mL (see separate analytical section in Appendix). The pharmacokinetic parameters (C_{max}, t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t½) of zolpidem were calculated by non-compartmental methods. Descriptive statistics for the parameters, analysis of variance, ratio of least squares mean, and 90% confidence intervals of the log transformed C_{max}, AUC_{0-t} and $AUC_{0\text{-infinity}}$ for the two treatments were calculated. b(4)

Results:
34 healthy male & female subjects (19M/15F, 18-68 years old) received one dose of zolpidem tartrate, and 32 subjects completed the study (2 subject withdrew consent after 1st dosing: Subj. 8, female & Subj. 26, male). The 32 subjects (18M/14F; 43.37±11.9 years, range 18-68 years old) who completed both treatments were included in the pharmacokinetic evaluation.

Pharmacokinetics:
The mean ± SD and the individual zolpidem plasma concentration-time profiles after the two single doses are depicted in Figures 1 and 2, respectively.

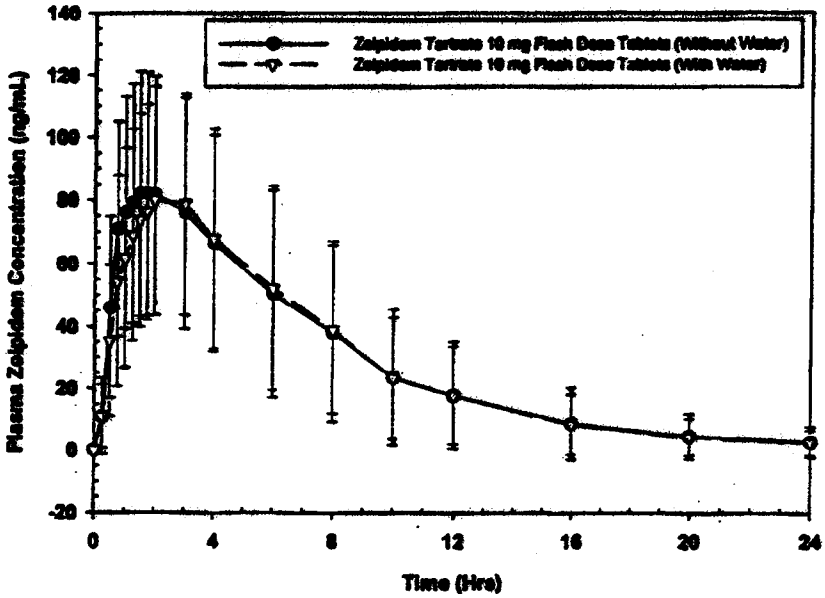
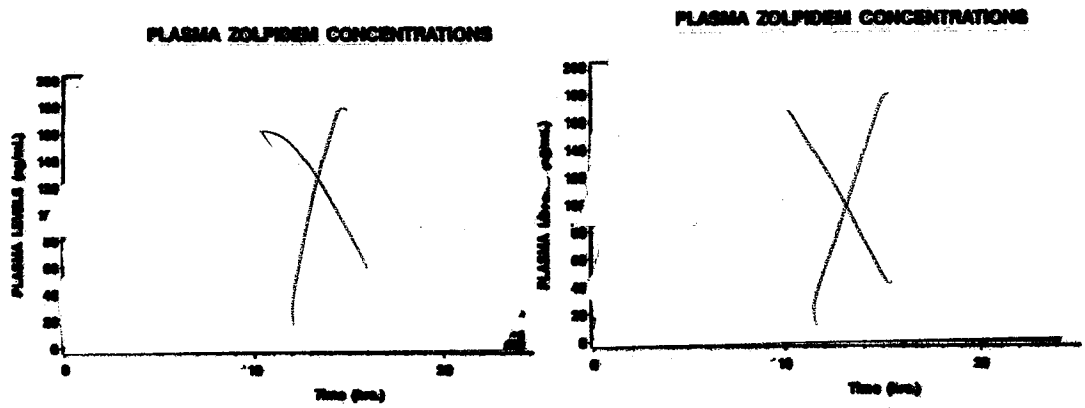


FIGURE 1. Mean (±SD) zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate rapidly dissolving tablets to healthy male & female volunteers (n=32) in the fasting state. Solid circles: With water (test); Unfilled triangles: Without water (reference) [Study 551PK]



b(4)

FIGURE 2. Individual zolpidem plasma concentration (ng/mL) *vs.* time (h) profiles after a single evening dose of 10 mg zolpidem tartrate rapidly dissolving tablets to healthy male & female volunteers (n=32) in the fasting state. Left panel: With water (test); Right panel: Without water (reference) [Study 551PK]

The pharmacokinetic (PK) parameters after the two single doses are depicted in Table 1.

TABLE 1. Mean (±SD) PK parameters after a single evening dose of 10 mg zolpidem tartrate rapidly dissolving tablets to healthy male & female volunteers (n=32) in the fasting state. Treatment A (test): With water; Treatment B (reference): Without water [Study 551PK]

Pharmacokinetic Parameters	Zolpidem Tartrate 10 mg Flash Dose tablet Treatment A-with water Mean ± SD	Zolpidem Tartrate 10 mg Flash Dose tablet Treatment B-without water Mean ± SD
AUC_{0-t}	670.24 ± 430.05	659.33 ± 393.29
AUC_{0-inf}	692.72 ± 468.11	679.04 ± 422.11
C_{max}	91.89 ± 38.31	90.61 ± 37.36
T_{max}	2.23 ± 1.51	2.36 ± 1.02
$t_{½}$	3.41 ± 1.16	3.35 ± 1.09
K_{el}	0.226 ± 0.075	0.229 ± 0.078

The zolpidem tartrate rapidly dissolving tablet given with and without water was bioequivalent (acceptance criteria 80-125%) both with regard to C_{max} and AUC, see main review for the tabulated results. An analysis of gender differences on the PK parameters was performed. No apparent differences in the PK (C_{max} &AUC) were observed between the male and female volunteers.

Safety:
Only one AE (headache) was reported by 1 (3%, Subj. 2) of the 34 subjects that received at least 1 dose of zolpidem tartrate. There were a number of abnormal laboratory values that occurred at both screening and after the study (not reported as AEs).

Comments:
This study demonstrated bioequivalence between the 10 mg zolpidem tartrate rapidly dissolving tablets taken with water (test) and without water (reference) after single evening doses in the fasting state.

7.4 Bioanalytical method

The sponsor used a High Performance Liquid Chromatography (HPLC) method with _____ detection, for the plasma analyses of zolpidem. The same method was used for the 3 *in vivo* studies, and all analyses were performed at the same laboratory (Biovail Contract Research, Toronto, Canada).

The HPLC method with _____ ection (method Z01-01) was developed and validated by Biovail Contract Research. Zolpidem and the internal standard, _____ are extracted from human plasma (0.5 mL) by solid phase extraction. The method is valid over the zolpidem plasma concentration range of _____ ng/mL. Internal SOPs for acceptance criteria, and reanalysis (including dilution of samples above upper limits of standards or malfunctioning equipment) and bioanalytical documentation are in place. b(4)

The HPLC method with _____ detection was validated in regard to linearity, intra- and inter-assay precision & accuracy, extraction recovery, dilution integrity, and stability. Linearity was established for zolpidem in the range of _____ (r >0.999; 1/conc^2, 5 standard-curves), and the relative error of back extraction for calibration standards were within -2.6 - 2% of spiked concentrations. Accuracy and precision were satisfactory over the studied QC range of _____ (Intra-day: relative error –2.7-0.4%, CV 0.6-2.5%; Inter-day: relative error –2.3-2.4%, CV 2.4-3.8%). The extraction recovery of zolpidem and the internal standard (zopiclone) was 110.2±1.5% and 104.2±0.6%, respectively. The stability was tested with regard to in-process (zolpidem stable for 4 h in plasma on the bench top), in auto-sampler (zolpidem stable for 48 h in extracted samples at room temperature) and in frozen stock solutions of methanol (zolpidem stable for 29 days at -70°C; zolpidem stable for 79 days at -25°C & zopiclone stable for 113 days at -25°C). Zolpidem in plasma was shown to be stable for 3 freeze-thaw cycles. Stored, frozen (both at -25°C & -70°C) plasma samples of zolpidem are stable up to 82 days.

A summary of the study specific details regarding the HPLC method performance is shown in Table 1 (Method Z01-01).

TABLE 1. Study summary: Method Z01-01 (zolpidem plasma analysis) Analytical and PK repeats refer to the number of samples reanalyzed (expressed as % of total number of samples in the study) due to analytical issues or verification of plasma zopiclone concentrations

Study	Analytical repeats	PK repeats	Range STD curve (ng/mL)	Study specific validation Accuracy** % / Precision*** %
#109297 (549PK)	1.3%	0.7%	1.00-512	STD curve: QC samples
#109298 (550PK)	0.5%	0.8%	1.00-512	STD curve: QC samples
#109299 (551PK)	0.9%	0.7%	1.00-512	STD curve: QC samples

b(4)

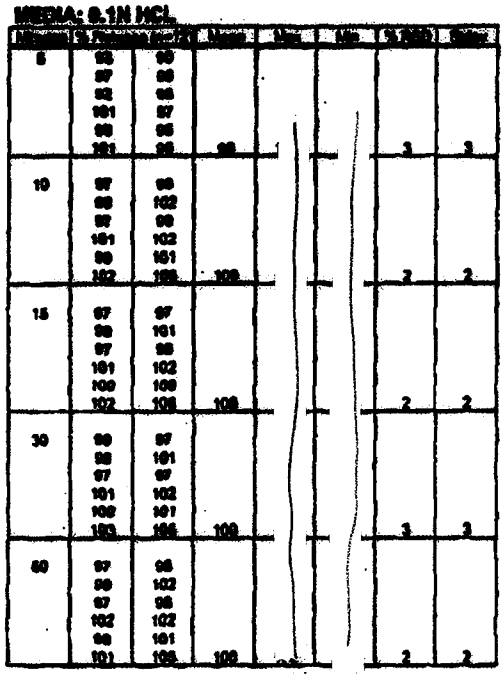
STD = standard; *LLOQ = Lower limit of quantitation; **Accuracy: relative error (%), ***Precision: coefficient of variation (CV%)

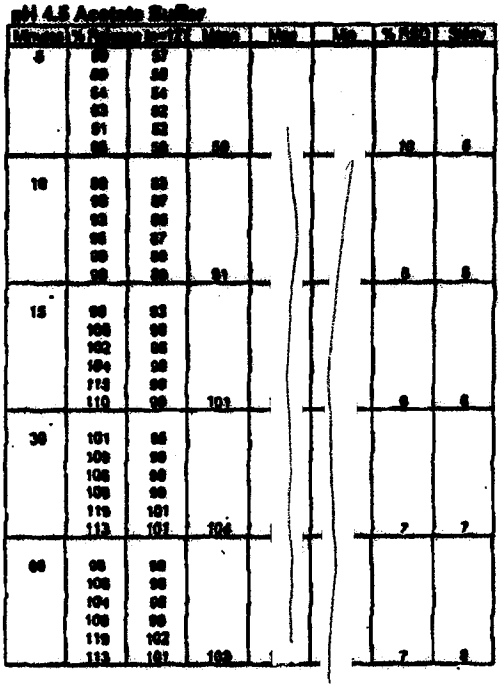
In conclusion, the bioanalytical method used for zolpidem analysis of the plasma samples from the three *in vivo* studies in NDA 21-412 is considered adequately documented and validated.

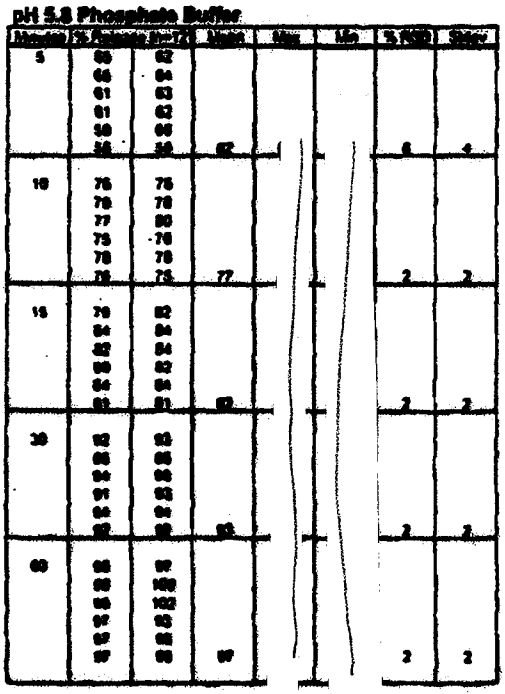
7.5 In vitro dissolution (4 pH media)

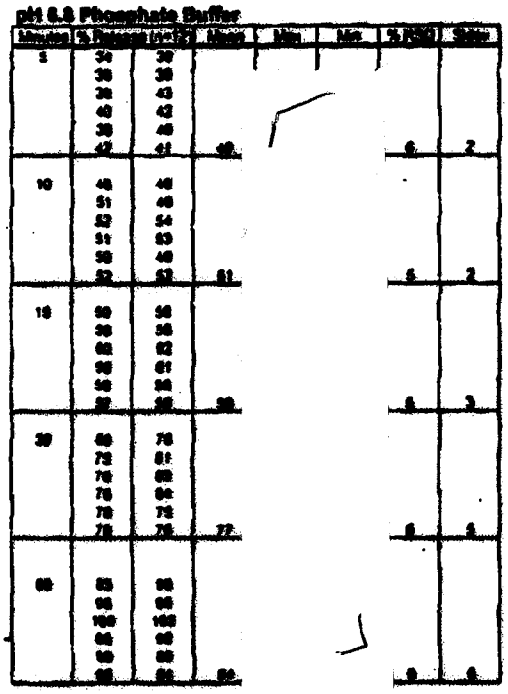
Volume 4 (CMC)

TABLE 1. Zolpidem tartrate rapidly dissolving tablets (10 mg) in vitro dissolution (% release) in 4 pH media of the biobatch tablets (Lot # 24870801, n=12).









b(4)

b(4)

7.6 Interim (9-month) stability – *in vitro* dissolution data

06/28/02 submission

Tables 1-3 contain *in vitro* dissolution data (proposed method & specification) from the ongoing stability studies of the 3 validation batches (conditions: 25°C/60%RH & 30°C/60%RH). Lot 24870801 (biobatch) was used in the *in vivo* studies.

TABLE 1. Lot 24870801 (biobatch) Interim stability – *in vitro* dissolution Upper panel: 25°C/60%RH; Lower panel: 30°C/60%RH

INTERIM STABILITY REPORT									
Product: Zolpidem Tartrate 10mg Flash Dose Tablets					Product Code: 5332				
Lot: 24870801		Manufacture Date: 14-Aug-01			Stability Protocol #: SS01013-01				
Condition: 25°C/60% RH		Storage Date: 14-Sept-01			Packaging:				
Test:		Appearance	Assay	Moisture	ID	Dissolution			
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT (Q) in 60 minutes			
						Min	Max	Mean	SD
Storage Time (months)	Initial	Complies	98.4	0.9	Positive			102	3
	1	Complies	98.5	1.0	Positive			96	3
	3	Complies	99.0	1.0	Positive			99	3
	6	Complies	98.3	0.9	Positive			96	1
	9	Complies	99.5	1.3	Positive			92	3
	12								
	18								
	24								
	36								

b(4)

INTERIM STABILITY REPORT									
Product: Zolpidem Tartrate 10mg Flash Dose Tablets					Product Code: 5332				
Lot: 24870801		Manufacture Date: 14-Aug-01			Stability Protocol #: SS01013-01				
Condition: 30°C/60% RH		Storage Date: 14-Sept-01			Packaging:				
Test:		Appearance	Assay	Moisture	ID	Dissolution			
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT (Q) in 60 minutes			
						Min	Max	Mean	SD
Storage Time (months)	Initial	Complies	98.4	0.9	Positive			102	3
	1	Complies	97.2	1.1	Positive			93	2
	3	Complies	97.8	1.2	Positive			94	4
	6	Complies	98.1	1.1	Positive			94	1
	9	Complies	99.2	1.5	Positive			95	4
	12								

b(4)

TABLE 2. Lot 24880801 Interim stability – *in vitro* dissolution Upper panel: 25°C/60%RH; Lower panel: 30°C/60%RH [+ Summary of Stage 2 (N=12 units tested)]

INTERIM STABILITY REPORT

Product:	Zolpidem Tartrate 10mg Flash Dose Tablets				Product Code: 5332					
Lot:	24880801	Manufacture Date: 15-Aug-01			Stability Protocol #: SS01013-01					
Condition:	25°C/60% RH	Storage Date: 14-Sept-01			Packaging:					
Test:		Appearance	Assay	Moisture	ID	Dissolution				
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT — Q) in 60 minutes				
						Min	Max	Mean	SD	
Storage Time (months)	Initial	Complies	97.7	0.8	Positive			98	2	b(4)
	1	Complies	94.5	0.8	Positive			95	3	
	3	Complies	96.4	0.8	Positive			92	2	
	6	Complies	98.9	0.8	Positive			90	3	
	9	Complies	96.7	1.2	Positive			88	2	
	12									
	18									
	24									
	36									

INTERIM STABILITY REPORT

Product:	Zolpidem Tartrate 10mg Flash Dose Tablets				Product Code: 5332					
Lot:	24880801	Manufacture Date: 15-Aug-01			Stability Protocol #: SS01013-01					
Condition:	30°C/60% RH	Storage Date: 14-Sept-01			Packaging:					
Test:		Appearance	Assay	Moisture	ID	Dissolution				
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT — Q) in 60 minutes				
						Min	Max	Mean	SD	
Storage Time (months)	Initial	Complies	97.7	0.8	Positive			98	2	b(4)
	1	Complies	95.9	0.9	Positive			87	3	
	3	Complies	96.3	1.0	Positive			91	3	
	6	Complies	96.3	1.1	Positive			87	2	
	9	Complies	97.0	1.5	Positive			84+	2+	
	12									

APPEARS THIS WAY
ON ORIGINAL

TABLE 3. Lot 24890801 Interim stability – *in vitro* dissolution Upper panel: 25°C/60%RH; Lower panel: 30°C/60%RH [+ Summary of Stage 2 (N=12 units tested)]

INTERIM STABILITY REPORT

Product:	Zolpidem Tartrate 10mg Flash Dose Tablets				Product Code: 5332					
Lot:	24890801	Manufacture Date: 15-Aug-01			Stability Protocol #: SS01013-01					
Condition:	25°C/60% RH	Storage Date: 14-Sept-01			Packaging:					
Test:		Appearance	Assay	Moisture	ID	Dissolution				
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT — Q) in 60 minutes				
						Min	Max	Mean	SD	
Storage Time (months)	Initial	Complies	98.6	0.7	Positive			99	3	
	1	Complies	94.0	0.8	Positive			98	3	
	3	Complies	98.0	0.8	Positive			94	5	
	6	Complies	97.8	0.8	Positive			90	3	
	9	Complies	97.3	1.2	Positive			90	2	
	12									
	18									
	24									
	36									

b(4)

INTERIM STABILITY REPORT

Product:	Zolpidem Tartrate 10mg Flash Dose Tablets				Product Code: 5332					
Lot:	24890801	Manufacture Date: 15-Aug-01			Stability Protocol #: SS01013-01					
Condition:	30°C/60% RH	Storage Date: 14-Sept-01			Packaging:					
Test:		Appearance	Assay	Moisture	ID	Dissolution				
Specifications:		Speckled Blue Tablets	90.0%-110.0% Label Claim	NMT	Positive	NLT — Q) in 60 minutes				
						Min	Max	Mean	SD	
Storage Time (months)	Initial	Complies	98.6	0.7	Positive			99	3	
	1	Complies	96.0	0.8	Positive			94	2	
	3	Complies	97.0	0.9	Positive			95	1	
	6	Complies	97.3	0.9	Positive			95	4	
	9	Complies	97.5	1.4	Positive			87+	5+	
	12									

b(4)

APPEARS THIS WAY
ON ORIGINAL

15 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

7.3 Filing memo

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

NDA Number	NDA 21-412	Brand Name	Zolpidem Tartrate Rapidly Dissolving Tablet
OCPB Division I	HFD-860	Generic Name	Zolpidem tartrate
Medical Division	HFD-120	Drug Class	Imidazopyridine derivatives
OCPB Reviewer	Maria Sunzel, Ph.D.	Indication(s)	Treatment of insomnia
OCPB Team Leader	Vanitha Sekar, Ph.D. (acting during filing of NDA) /Ramana Uppoor, Ph.D.	Dosage Form	Rapidly dissolving tablet One strength: 10 mg
Date of Submission	December 28, 2001	Dosing Regimen	10 mg immediately before bedtime (short-term treatment, up to 35 days)
Estimated Due Date of OCPB Review	*Late August, 2002*	Route of Administration	Oral
PDUFA Due Date	*October 31, 2002*	Sponsor	Biovail Laboratories, Inc.
Division Due Date	*End-Aug, 2002*	Priority Classification	Standard (new formulation) 505(b)(2)

BACKGROUND:

In 1992 the Agency approved zolpidem tartrate IR tablets (5 & 10 mg, Ambien® by Lorex (joint venture between Pharmacia & Sanofi-Synthelabo). The 10 mg dose is recommended for most patients. The lower, 5 mg dose is recommended as a starting dose for elderly, patients with impaired hepatic function, or with concomitant use of Ambien and other CNS depressants.

This new NDA contains data regarding rapidly dissolving zolpidem tartrate tablets (one strength: 10 mg, oral admin.), intended for short-term treatment of insomnia in adults. The rapidly dissolving tablets can be taken without water. The sponsor refers to the approved product for all other information regarding basic pharmacokinetics (PK), special populations, DDI, as well as clinical efficacy and safety. No phase II/III studies in patients demonstrating efficacy or safety have been conducted with the new 10 mg tablet.

The sponsor has submitted reports from 3 single-dose Phase I studies, 95 (43F/52M) of 102 healthy subjects completed the studies. The sponsor states that 6 Phase I studies were performed, where 3 studies were of pilot character. The summary contains information about one pilot study in 18 additional subjects (no reports submitted for any pilot study).

PK information for zolpidem from the submitted study reports covers the following items:

- Relative bioavailability: Rapidly dissolving tabl. *vs.* approved IR tabl. after a single 10 mg dose during fasting conditions
- Relative bioavailability: Rapidly dissolving tabl. *vs.* approved IR tabl. after a single 10 mg dose during fed conditions
- Relative bioavailability: Rapidly dissolving tabl. after a single 10 mg dose administered with or without water

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	No. studies submitted	No. studies reviewed	Comments
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			Paper submission
Tabular Listing of All Human Studies	No			Only 4 of 6 mentioned studies listed in the submission
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) -		[redacted]	[redacted]	[redacted]
Healthy Volunteers-		[redacted]	[redacted]	[redacted]
single dose:	X	4		3 studies w/TBM formulation
multiple dose:	-			
Patients-		[redacted]	[redacted]	[redacted]
single dose:	-			
multiple dose:	-			
Dose proportionality -		[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:	-			
fasting / non-fasting multiple dose:	-			
Drug-drug interaction studies -		[redacted]	[redacted]	[redacted]
in-vivo effects on primary drug:	-			
in-vivo effects of primary drug:	-			
in-vitro:	-			
Subpopulation studies -		[redacted]	[redacted]	[redacted]
ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
renal impairment:	-			
hepatic impairment:	-			
PD:		[redacted]	[redacted]	[redacted]
Phase 2:	-			
Phase 3:	-			
PK/PD:		[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:	-			
Phase 3 clinical trial:	-			
Population Analyses -		[redacted]	[redacted]	[redacted]
Data rich:	-			
Data sparse:	-			
II. Biopharmaceutics		[redacted]	[redacted]	[redacted]
Absolute bioavailability:	-			
Relative bioavailability -		[redacted]	[redacted]	[redacted]
solution as reference:	-			
alternate formulation as reference:	X			Marketed IR tablet as reference (bioequivalence analysis)
Bioequivalence studies -		[redacted]	[redacted]	[redacted]
traditional design; single dose:	(X)			See rel. bioavailability above
replicate design; single / multi dose:	-			
Food-drug interaction studies:	X	2		1) Fed state: Dissolving tabl vs. marketed IR tablet (no fasting arm in study); 2) Disintegrating tabl. with & w/o water
Dissolution:	X			In CMC section (extra copy of volume will be requested)
(IVIVC):	-			
Bio-waiver request based on BCS	-			
BCS class	-			
III. Other CPB Studies		[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			
Literature References	-			Sponsor refers to original NDA 19-906
Total Number of Studies	3		3	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	X	
Comments sent to firm?	X	• Please provide data sets (as SAS transport files) for the plasma concentration-time data, demographics and pharmacokinetic parameters (individual values) from studies B01-548PK-ZOLN04, B01-550PK-ZOLN04, and B01-551PK-ZOLN04. • In Item 6 (1st & last paragraph, page 2) it is stated that 6 (3 pilot) studies were performed, but the NDA summary only contains information regarding 4 (1 pilot) studies. Please explain this discrepancy, and please submit study report/s (please do not include copies of the signed Informed Consent forms). • The sponsor is requested to submit an extra desk copy of volume 1.4 (Chemistry), needed for the CPB review of the *in vitro* dissolution method and specifications
QBR questions (key issues to be considered)		• Has bioequivalence been established between the rapidly dissolving and commercially available IR Ambien tablets? • Are the PK of the rapidly dissolving tablet altered in the presence of food or water? • Are there any differences in PK between men and women? • Is the proposed *in vitro* dissolution method acceptable? • Does the submitted data support the proposed label text?
Other comments or information not included above		• DSI will make a full inspection of the clinical and bioanalytical sites used for the submitted study/studies. OCPB proposes study B01-548PK-ZOLN04 (fasting state; new vs. marketed tabl.) for inspection since it is regarded as the most important study in the submission. • The sponsor has included copies of the signed Informed Consent forms for all healthy volunteers from all three submitted study reports. Post-meeting note: Dr Yau (DSI) consulted the Human Subject Protection group within the DSI, who said that the signed Informed Consent forms can be submitted to the FDA (i.e. there are no provisions in the CFR that Consent Forms have to reside with the investigator).
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

cc: NDA 21-412, HFD-850 (Lee), HFD-120 (Shin, Andreason, Laughren, Klein), HFD-860 (Mehta, Marroum, Sekar, Sunzel, Uppoor), DSI (Yau)