CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

MEDICAL REVIEW(S)

MEMORANDUM

DATE: September 21, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 21-412

SUBJECT: Action Memo for NDA 21-412, for the use of Zolpidem Tartrate orally disintegrating tablets

NDA 21-412, for the use of Zolpidem Tartrate orally disintegrating tablets, was submitted on 121/31/01. The application was submitted under section 505(b)(2) of the F,D, & C Act, with Ambien as the reference drug.

The division issued a tentative approval (TA) letter on 5/26/05, because Ambien was still subject to patent protection at that time. That letter also contained five post-marketing commitments (PMCs), as well as a statement that the Agency was adopting an interim dissolution specification. In addition, the sponsor had not submitted a proposed tradename, and the letter informed the sponsor that a proposed tradename would need to be submitted and found acceptable by the Agency before the drug could be marketed with that name.

The sponsor responded to the TA letter in a submission dated 7/20/06. This submission has been reviewed by Dr. Carole Davis, medical officer, and Drs. Donald Klein and Martha Heimann, chemists.

The sponsor has made several interim submissions between the time of the TA letter and their response to the TA letter. In a 7/27/05 amendment, the sponsor addressed two of the 5 PMCs; Dr. Klein has found these responses acceptable. In another CMC submission, the sponsor proposed analytical methods that Dr. Klein has also found to be acceptable. Dr. Heimann has also found several minor CMC changes (to controls for the drug substance and some excipients) acceptable, and has recommended that the product be given a 24 month expiry (the TA letter granted only an 18 month expiry). In addition, the sponsor submitted a proposed tradename, [redacted] on 3/24/06. That name was rejected by the Agency because of potential medication errors with several approved products; the sponsor was informed of this decision. The sponsor proposed a new name that is currently under review by the Division of Medication Errors and Technical Support (DMETS). b(4)

Since the TA letter was issued, we have determined that several changes need to be made to product labeling for all hypnotic drug products. In particular, we have drafted language that describes the occurrence of angioedema with these products, and have changed the position in labeling of the statement that the

failure of insomnia to remit in 7-10 days may be indicative of other primary medical or psychiatric illness. Further, we will ask sponsors of these products to include in labeling standard language about the occurrence of "sleep driving" and other complex behaviors that can occur at night while the patient is supposed to be asleep. However, at this time, we have not finalized the language for this section; for this reason, we will inform the sponsor that when this language becomes available, they will need to adopt it in their labeling.

We find, again, that the product could otherwise be approved, but Ambien still enjoys patent protection. For this reason, I will issue the attached second Tentative Approval letter, with appended draft labeling.

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Russell Katz
9/21/2006 09:55:49 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 21-412
Submission Number	NOOO
Submission Code	Complete Response
Letter Date	July 20, 2006
Stamp Date	July 21, 2006
PDUFA Goal Date	September 21, 2006
Reviewer Name	Carole L. Davis
Review Completion Date	September 14, 2006
Established Name	Zolpidem Tartrate
(Proposed) Trade Name	Zolpidem Tartate Orally Disintegrating Tablets
Therapeutic Class	Sedative - Hypnotic
Applicant	Biovail Technologies Ltd., 3701 Concorde Parkway, Chantilly, VA 20151
Priority Designation	Standard, 505(b)(2)
Formulation	Orally Disintegrating Tablets; 5 mg, 10 mg
Dosing Regimen	PRN; Healthy adults - 10 mg @ HS; Elderly - 5 mg @ HS
Indication	Short-term Treatment of Insomnia
Intended Population	Adult

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation is in agreement with the other review disciplines for a Tentative Approval action of this NDA. Approval is tentative until the patent expiration of Ambien, the referenced product.

1.2 Recommendation on Post-marketing Actions

1.2.1 Risk Management Activity

No risk management activities are designated for this NDA.

1.2.2 Required Phase 4 Commitments

Commitment #1	
Description:	Optimize the dissolution method and specifications using 50 rpm paddle speed and a different dissolution medium (e.g., pH 5.8 buffer).
Final Study Report:	The final study report will be submitted to the Agency within one year from the date of approval for the final selection of the dissolution specification.
Commitment #2	
Description:	Generate data on biobatches and next 3 production batches for both 5 and 10 mg strengths using the selected more optimized dissolution method.
Final Study Report:	The final study report will be submitted to the Agency within one year from the date of approval for the final selection of the dissolution specification. .
Commitment #3	
Description:	Prior to commercial drug product manufacturing, the applicant will provide a copy of the commercial Batch Record.
Final Study Report:	The final study report will be submitted to the Agency within two years of approval.

1.2.3 Other Phase 4 Requests

No other Phase 4 requests are designated for this NDA.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Biovail Laboratories, Inc. ("Biovail") wishes to market an orally disintegrating formulation of zolpidem tartrate. Zolpidem tartrate is already commercially available through another sponsor and is marketed under the name Ambien. This application seeks approval for marketing zolpidem tartrate with a change in dose format from a conventional immediate-release formulation to an orally disintegrating tablet (ODT) for the indication currently covered by the approved NDA for Ambien (NDA 19,908) for the short-term treatment of insomnia. Biovail seeks approval based on bioequivalence alone, and references the innovator's existing and approved indication and the body of efficacy and safety data (referenced from the Searle and Co.) in support of the indication.

This tablet is designed to disintegrate rapidly in the mouth when it comes in contact with saliva, and then release drug-containing microspheres that are swallowed. The stated rationale is to "allow for better patient convenience and compliance, as it may be administered with or without water." This is a 505(b)(2) application that includes primarily CMC and biopharmaceutics information to support this new formulation. The application refers to the approved product, Ambien, for most biopharmaceutics, and for all pharm/tox and clinical data.

The original submission for NDA 21,412, zolpidem tartrate, 10 mg orally disintegrating tablets (ODT), was made under 505(b)(2) on December 29, 2001. The ODT design has 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 application was reviewed and designated Approvable, for the 10 mg tablet only, contingent upon the expiration of the exclusivity patent for Ambien, held by sanofi-aventis.

In the 2001 review of the NDA, the Office of Pharmacology and Biopharmaceutics (OCPB) concluded that the Biovail rapidly dissolving tablets, and the marketed Ambien tablets, were bioequivalent (90% CI's of Cmax & AUC within 80-125%) during fed or fasting conditions, and that Biovail's rapidly dissolving tablets could be taken with or without water.

The conclusion was that no new Phase 2 or Phase 3 studies in patients demonstrating efficacy or safety need be conducted with the new 10-mg tablet in light of the bioequivalence data. However, Biovail only provided for a 10-mg dose in their first submission, in 2001, yet Ambien was marketed as a 5 and 10-mg strength. This presented a problem that prevented approval because the recommended starting dose for zolpidem in the elderly was 5-mg, and safety information in labeling did not address the 10-mg strength alone for this age group. Safety data in the Ambien labeling was based on combined data on the 5 and 10-mg strengths. Biovail does not have right of reference to the safety database that belongs to the innovator. Therefore, Biovail could not use the existing Ambien labeling as a basis for their product without either an available 5-mg strength or safety data uniquely based on the 10-mg strength. The proposed labeling

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Biovail decided that they would develop a 5-mg formulation, in addition to the 10-mg formulation, so they could base their product labeling on the existing Ambien labeling without having to produce new clinical safety data. Biovail proposed manufacturing a ——— b(4)
———, and provided formulations, for ——— 5 and 10 mg tablets which was acceptable to the FDA (see e-mails of August 29 and September 10, 2003, Dr. Donald Klein, CMC reviewer).

Biovail subsequently submitted two new pharmacokinetic studies to support the ——— b(4)
formulation:

- to show bioequivalence between Biovail's 10 mg tablet of zolpidem tartrate, and two of Biovail's 5 mg tablets,
- to demonstrate bioequivalence of Biovail's 10 mg tablet, with or without water, compared to Ambien 10 mg (with water).

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 clinicolpidemal efficacy and safety.

1.3.2 Efficacy

Approval for this application is based on bioequivalence data alone and they are submitted under the provisions of section 505(b)(2) of 21CFR. There are no new clinical efficacy or substantive safety studies submitted with this application. Biovail references Ambien for all other clinical efficacy issues. Ambien is indicated for the short-term treatment of insomnia.

1.3.3 Safety

Approval for this application is based on bioequivalence data alone and they are submitted under the provisions of section 505(b)(2) of 21CFR. There are no new clinical efficacy studies, or substantive safety studies submitted with this application, or expected safety concerns. There are no new safety findings with the new bioequivalent rapidly dissolving formulation. A clinical review of this application considered prior to TA of May 16, 2005 focused only on deaths, serious adverse events and adverse dropouts related to the Biovail studies 2840 and 2841 (see Section 7). These studies were conducted only for PK evidence supporting their orally disintegrating formulation, and their 5 mg dosage, respectively. All other evidence of safety is referenced by Biovail to the previously approved Ambien research. Primary safety issues for Ambien incorporated into their labeling are the following: drowsiness, dizziness, lightheadedness, difficulty with coordination, and daytime drowsiness.

Special concerns possible with this group of drugs include: memory problems, tolerance, dependence, withdrawal, changes in behavior and thinking, and sedation of the unborn baby when used in the late stages of pregnancy.

The FDA is planning new class labeling requirements that will include all the drugs in the sedative/hypnotic class. The labeling changes will include additions to the Warnings sections on sleep driving and other complex behaviors, and angioedema. Also, in the Abuse and Dependence section, definitions of abuse, physical dependency, tolerance and addiction will be required.

1.3.4 Dosing Regimen and Administration

The recommended dosage of Biovail's zolpidem tartrate ODT for the indication of short-term treatment of insomnia is one 10 mg tablet (with or without water) at bedtime. In the elderly, the recommended dose is 5 mg (with or without water) at bedtime.

1.3.5 Drug-Drug Interactions

Biovail references drug-drug interaction information to the Ambien research and label.

1.3.6 Special Populations

As stated in the Ambien label: No dosing adjustment is required for patients with compromised renal function. Dosing should be modified for patients with hepatic insufficiency.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Zolpidem tartrate, manufactured by Biovail, is a non-benzodiazepine hypnotic of the imidazopyridine class, and is available in a 5 mg (white with off-white speckles) and 10 mg (blue with white speckles) tablet strengths for oral administration. Both are round tablets with a dimple on both sides, debossed with a "ZT" on one side and, depending on the strength, either a "5" or a "10" on the other side.

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

While zolpidem is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbituates, or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines (See label information for full details).

2.2 Currently Available Treatment for Indications

The referenced product, Ambien (zolpedim tartrate), is currently marketed in the US for the treatment of insomnia by sanofi-aventis.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, zolpedim tartrate, is currently marketed in the US as the referenced product, Ambien for the treatment of insomnia.

2.4 Important Issues with Pharmacologically Related Products

The most common side effects of the group of medications known as the "sedative/hypnotics", or simply, sleep medicines include: drowsiness, dizziness, lightheadedness, difficulty with coordination, and daytime drowsiness.

Special concerns possible with this group of drugs include: memory problems, tolerance, dependence, withdrawal, changes in behavior and thinking, and sedation of the unborn baby when used in the late stages of pregnancy.

2.5 Pre-submission Regulatory Activity

Biovail received a FDA Approvable letter for the 10 mg tablet of zolpedim tartrate dated October 31, 2002. A FDA Approvable letter for the 10 mg tablet was dated February 21, 2003. Teleconferences were held between Biovail and the FDA on May2 and June 30, 2003 to discuss FDA safety concerns about the lack of a 5 mg dose and issues around [redacted] : E-mail dialogue in August and September, 2003 related to proposals to reformulate the 5 and 10 mg zolpedim tratrate orally disintegrating tablets (ODT) formulations, and the contents of the complete response submission. b(4)

NDA 21,412 was transferred from the Division of Neuropharmacological Drug Products (DNDP) to the Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP) in December, 2003. The approval for the design for two additional biostudies for the new formulation, and the response to Biovail's request for biowaver were granted on January 30, 2004. The Complete Response to the FDA Approvable letter was submitted by Biovail on November 24, 2004.

The Tentative Approval of the under 21CFR 314.105 was received by Biovail on May 26, 2005. They submitted a Complete Response (CR) supplement, consistent with the definition of a Class 1 Re-submission, 90 days prior to expiration of the Ambien patent. It identifies changes on the conditions under which the Biovail product was tentatively approved.

Labeling revisions to bring the proposed label into accord with the referenced compound, Ambien was requested. Biovail submitted their current labeling proposal (reviewed in Section 10.2) on July 20, 2006 in the Class 1 Resubmission.

At this time, Biovail does not yet have an approved proprietary name for the ODT dosage form. The trade name ——— was submitted on March 24, 2006. It was reviewed by the Division of Medication Errors and Technical Support (DMETS) but not recommended due to potential confusion with several approved products. The Division of Neurology Products agreed with the decision, and the sponsor was notified. The sponsor plans to submit additional names for consideration. b(4)

Biovail received tentative approval (TA) for their 505 (b)(2) NDA application on May 26, 2005.

2.6 Other Relevant Background Information

No other relevant background information is available for the current review.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC data in this NDA have been reviewed by Donald Klein, PhD., from the chemistry group, and he has concluded that adequate information has been provided to support an Tentative Approval recommendation. All methods validation studies by FDA laboratories have been completed and the methods are deemed suitable for regulatory purposes (D. Klein, Review # 5, May 10, 2006).

In the original NDA, Biovail's Chantilly, Virginia facility was proposed as the sole site for commercial manufacturing. That site remains a proposed site for all steps of the drug product manufacture, but information has been added on two additional Biovail commercial manufacturing facilities. The Biovail facility in Dublin, Ireland has been added as a manufacturing site of drug product, and the Biovail site in the Dorado, Puerto Rico facility has been included as a manufacturing site for the tablet ——— packaging of the Zolpidem ODT formulation. b(4)

Based on the available long-term stability data, an expiration dating period of 24 months is assigned for Zolpidem Tartrate Orally Disintegrating Tablets.

3.2 Animal Pharmacology/Toxicology

Biovail refers all animal pharmacology/toxicology issues to the referenced product, Ambien.

3.3 Review Data Summary

Consults/Reviews Summary
Dateline of Documents:

December 31, 2001	Original NDA submission
July 25, 2002	Biopharmaceutics Review #1

October 25, 2002	Clinical Review #1 - for ODT formulation
October 29, 2002	CMC Review #1
October 31, 2002	Approvable (AE) letter #1
December 20, 2002	Biopharmaceutics Review #2
December 20, 2002	Resubmission, response to AE letter #1
February 14, 2003	CMC Review #2
February 20, 2003	Clinical Review #2 - Draft Labeling Review
February 21, 2003	Approvable letter #2
May 18, 2003	CMC Review #3 – Categorical exclusion under 21 CFR 25.31(a)
February 02, 2004	Biopharmaceutics Review #3
November 24, 2004	Resubmission, response to AE letter #2
May 10, 2005	Microbiology approval
May 19, 2005	Biopharmaceutics Review #4 – Review of Studies 2840 & 2841
May 20, 2005	Clinical Review #3 – Review of Studies 2840 & 2841
May 26, 2005	Tentative Approval (TA) letter
October 31, 2005	CMC Review #4 - Phase 4 Commitments
March 23, 2006	Methods Validation (DPA Laboratory)
May 10, 2006	CMC Review #5 - Methods Validation
July 11, 2006	DMETS – Tradename " —— ' unacceptable b(4)
July 20, 2006	Resubmission, response to TA letter
August 31, 2006	Office of Compliance – Manufacturing Facilities acceptable
September 6, 2006	CMC Review #6 – Approval of Application

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The submissions reviewed include the Amendment of March 25, 2006, the Response to the Tentative Approval letter of July 21, 2006.

Biovail provided results on two bioequivalent studies: Study 2840, and Study 2841. These studies were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) on May 19, 2005. The review by Paul Andreason, M.D., Clinical Reviewer, was completed May 20, 2005 and the studies were deemed acceptable for the Tentative Approval. The studies were not conducted for the collection of efficacy or safety data. The clinical information available on those studies is only the listing of adverse events and withdrawals. That information is included in the following sections.

4.2 Tables of Clinical Studies

Bioequivalence Studies.

2840 (B04-668PK-N04F1)	A Three-Way Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Comparative	Randomized 3-treatment, 3-period, 3-sequence crossover

	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	design under single dose fasting conditions, with and without water

Study 2840 included 36 subjects. Each subject received 3 doses of zolpidem 10-mg (Ambien 10-mg, zolpidem ODT 10-mg with water, and zolpidem 10-mg without water).

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)

Study 2841 included 36 healthy subjects. Each subject received two doses of zolpidem 10-mg (one tablet of 10-mg ODT, and two tablets of 5-mg ODT) separated by one week.

4.3 Review Strategy

The clinical review is focused on the safety data from the two bioequivalence studies. The focus is primarily on deaths, serious adverse events and adverse dropouts. This is because the safety profiles for zolpidem tartrate has already been established in much larger controlled clinical trials of Ambien. Biovail's zolpidem tartrate ODT formulations are bioequivalent to the already marketed Ambien product, and are basing their application claim on bioequivalence.

The previous clinical reviews (dated from December 29, 2001 to May 20, 2005) of medical reviewers Paul J. Andreason, M.D. and Thomas P. Laughren, M.D. are incorporated into this review. It was felt by these reviewers that the clinical issues were adequately addressed in the sponsor's Complete Response to Approvable Letter, and that Biovail's zolpidem tartrate ODT could be approved, from a clinical standpoint, after agreement to the proposed draft labeling and agreement to the phase 4 commitment to optimize the dissolution specifications that were noted in the OCPB review.

4.4 Data Quality and Integrity

DSI inspected the clinical (Miami) and analytical (Ontario) sites for study 109297, the pivotal bioequivalence study supporting this NDA. While there were some minor violations, overall, the data from this study were judged to be acceptable.

4.5 Compliance with Good Clinical Practices

Not assessed during the current review.

4.6 Financial Disclosures

Not assessed during the current review.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

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.

The biopharmaceutics data in the original submission, consisting of data from 3 PK studies, and the two additional bioequivalence studies were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The OCPB reviews concluded that: (1) the studies demonstrated that the new formulation is bioequivalent to Ambien, in both fed and fasted conditions; (2) the proposed dissolution method is acceptable; (3) bioequivalence was demonstrated between the two dosage strengths of zolpidem tartrate — ODT. Recommendations were made for a different specification, and some minor modifications of the sponsor's proposed changes to labeling, and these changes were subsequently made by the company and incorporated into the current submission. The OCPB has also designated two Phase 4 Commitments (Section 9.3.2)

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Zolpidem tartrate is proposed by Biovail for the indication of short-term treatment of insomnia. There are no changes in the indication from that of the referenced product, Ambien.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Common Adverse Events

The safety profiles for common and drug related adverse events, cognitive effects, withdrawal effects and laboratory profile of zolpidem have been established in much larger clinical trials of Ambien. The Biovail zolpidem tartrate ODT formulations are bioequivalent to the already

marketed Ambien product, so the same profile of adverse events would be anticipated in the use of this product.

7.2 Adequacy of Patient Exposure and Safety Assessments

Biovail references the data of the controlled clinical studies listed in the Ambien label.

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

Biovail references the data listed in the Ambien label for laboratory findings, vital signs, electrocardiograms (ECGs), immunogenicity, human carcinogenicity, special safety studies, withdrawal phenomena and/or abuse potential, human reproduction and pregnancy data, assessment of effect on growth, overdose experience, postmarketing experience.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended dosage of Biovail's zolpidem tartrate ODT for the indication of short-term treatment of insomnia is one 10 mg tablet (with or without water) at bedtime. In the elderly, the recommended dose is 5 mg.

8.2 Drug-Drug Interactions

Biovail references drug-drug interaction information to the Ambien research and label.

8.3 Special Populations

Biovail references drug-drug interaction information to the Ambien research and label.
The Ambien label states:

> No dosing adjustment is required for patients with compromised renal function.
> Dosing should be modified for patients with hepatic insufficiency.

8.4 Pediatrics

This NDA has applied for the indication of short-term insomnia treatment of adults only. No pediatric studies have been submitted.

8.5 Advisory Committee Meeting

No Advisory Committee Meetings have been held or scheduled for this NDA.

8.6 Literature Review

No literature review has been submitted or conducted for this NDA during the current review.

8.7 Postmarketing Risk Management Plan

No postmarketing risk management activities are designated for this NDA.

8.8 Other Relevant Materials

No other relevant materials are designated for this NDA.

9 OVERALL ASSESSMENT

9.1 Conclusions

Biovail's zolpidem tartrate is bioequivalent to Ambien, and is expected to have efficacy and safety equivalent to Ambien.

9.2 Recommendation on Regulatory Action

The clinical recommendation is in agreement with the other review disciplines for a Tentative Approval action of this NDA. Approval is tentative until the patent expiration of Ambien, the referenced product.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No postmarketing risk management activities are designated for this NDA.

9.3.2 Required Phase 4 Commitments

In the Tentative Approval (TA) letter of May 26, 2005, the following Phase 4 commitments were listed to fulfill the Post-marketing requirements:

Commitment #1 (Requested by Clinical Pharmacology and Biopharmaceutics)
Description: Optimize the dissolution method and specifications using 50 rpm paddle speed and a different dissolution medium (e.g., pH 5.8 buffer).

Final Study Report: The final study report should be submitted to the Agency within one year from the date of approval.

Commitment #2 (Requested by Clinical Pharmacology and Biopharmaceutics)
Description: Generate data on biobatches and next 3 production batches for both 5 and 10 mg strengths using the selected more optimized dissolution method.
Final Study Report: The final study report should be submitted to the Agency within one year from the date of approval.

Commitment #3 (Requested by Chemistry, Manufacturing and Controls)
Description: Using the retained photostability testing samples (non-debossed 5 mg (2 Lots) and 10 mg (2 Lots) tablets), the dissolution and disintegration will be reported within three months of approval.
Final Study Report: The final study report should be submitted to the Agency within three months of approval.

Commitment #4 (Requested by Chemistry, Manufacturing and Controls)
Description: Prior to commercial drug product manufacturing, the applicant will provide a copy of the commercial Batch Record.
Final Study Report: The final study report should be submitted to the Agency within two years of approval.

Commitment #5 (Requested by Chemistry, Manufacturing and Controls)
Description: Using the retained drug product release samples: Dublin (3 Lots of 5 mg, and 3 Lots of 10 mg); and Chantilly (3 Lots of 5 mg), the Identification (UV).
Final Study Report The final study report should be submitted to the Agency within three months of approval.

The commitments have been reviewed by Don Klein (CMC) – 10/31/05 review memo, and the Commitments #3, and #5 submissions for the commitments on photostability and Identification (UV) testing have already fulfilled the requirements.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are planned for this NDA.

9.4 Labeling Review

The labeling in the Class 1 Re-submission (July 21, 2006) is the same as the labeling in the May 26, 2006 Tentative Approval letter, except as designated in Section 10.2.

9.5 Comments to Applicant

1) Designation of a proprietary tradename, and approval of the tradename by DMETS, is still required prior to marketing Biovail's zolpidem tartrate.

2) Please be advised that the 2 warnings below are being added to the PI (Package Insert) for all sedative/hypnotic drug products as a class labeling change.

WARNINGS:

Sleep Driving:

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as sleep-driving may occur with Ambien alone at therapeutic doses, the use of alcohol and other CNS depressants with Ambien appears to increase the risk of such behaviors, as does the use of Ambien at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Ambien should be strongly considered for patients who report a "sleep-driving" episode.

Angioedema:

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

Another label change requested in our SR 2/14/06 CBE (Changes Being Effected) letter, dated February 14, 2006, is to add the following 2 paragraphs to the Drug Dependence and Addiction section:

Drug Abuse and Dependence:

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over

time. Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

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

10 APPENDICES

10.1 Review of Individual Study Reports

Review of individual study reports was completed prior to the issuance of the previous Tentative Approval for this NDA, and has not been repeated in the current review. No new clinical studies were submitted since the previous Tentative Approval.

10.2 Labeling Review

10.2.1 Labeling history:

The following changes have been made to Biovail's zolpidem tartrate labeling since the original NDA was submitted on December 29, 2001.

1. NDA amendment of December 20, 2002. Response to Approvable letter.
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]

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2. NDA amendment of February 7, 2003
   - Incorporation of Agency recommended changes to the pharmacokinetics section.

3. NDA amendment of November 24, 2004, Complete Response to Approvable letter of February 21, 2003
   - Formulation change (change in inactive ingredients)
   - Data from two new pharmacokinetic studies.

4. SPL submission of March 24, 2006, not yet reviewed because of incompatibility with the electronic document room.

5. Class 1 Resubmission with annotated labeling – the currently proposed label

10.2.2 Summary of Line by Line Labeling Review

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4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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10/13/2006 05:22:39 PM
MEDICAL OFFICER
I agree with tentative approval for this application. Please see the 9/21/06 memo by Dr. Russell Katz, Neurology Division Director, regarding this action. Please also see the 9/21/06 NDA action letter to the sponsor.

Review and Evaluation of Clinical Data
NDA #21-412

Sponsor:	**Bioavail Laboratories Inc**
Drug:	**Zolpidem Tartrate ODT**
Material Submitted:	**Response to Approvable Letter**
Correspondence Date:	**November 24, 2004**

I. Description of Compound

Drug Category:	**Hypnotic**
Forms available for proposed study:	**Orally Disintegrating Tablet (ODT) 5 and 10-mg strengths**
Date of Review Completion	**May 20, 2005**

II. Background

Bioavail wishes to market an orally disintegrating formulation of zolpidem. Zolpidem is already commercially available through another sponsor and is marketed under the name Ambien. Bioavail seeks approval based on bioequivalence alone.

Bioavail only provided for a 10-mg dose in their first submission, yet Ambien was marketed as a 5 and 10-mg strength. This presented a problem that prevented approval because the recommended starting dose for zolpidem in the elderly was 5-mg and safety information in labeling did not address the 10-mg strength alone for this age group. Safety data in the Ambien labeling was based on combined data on the 5 and 10-mg strengths. Bioavail therefore could not use the existing Ambien labeling as a basis for their product without either an available 5-mg strength or safety data uniquely based on the 10-mg strength.

Bioavail decided that they would develop a 5-mg formulation in addition to the 10-mg formulation so that they could base their product labeling on the existing Ambien labeling without having to produce new clinical safety data.

III. Data Reviewed

Bioavail provided results on two bioequivalence studies.

2040 (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**

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)

These studies were reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). My clinical review is therefore focused on the safety data from the two bioequivalence studies. My review is further focused on deaths, serious adverse events and adverse dropouts. This is because the safety profiles for common and drug related adverse events, cognitive effects, withdrawal effects and laboratory profile of zolpidem have been established in much larger clinical trials of Ambien, and these zolpidem ODT formulations are bioequivalent to the already marketed Ambien product.

Safety Results

Study 2840 included 36 subjects. Each subject received 3 doses of zolpidem 10-mg (Ambien 10-mg, zolpidem ODT 10-mg with water and zolpidem 10-mg without water.). There were no deaths or serious adverse events. There was one dropout but no dropouts due to adverse events.

There Study 2841. 36 healthy subjects were enrolled in the study. All completed the study. In this study each subject received two doses of zolpidem 10-mg (one dose of 10-mg ODT and two tablets of 5-mg ODT) separated by one week. There were no deaths serious adverse events or dropouts due to adverse events.

There were no adverse events in the two small studies that were unexpected or unlabeled and likely drug related.

III. Conclusions and Recommendations

I believe that the sponsor has adequately addressed the clinical issues in their Complete Response to Approvable Letter. I believe that zolpidem ODT can be approved from a clinical standpoint after agreement to the proposed draft labeling and agreement to the phase IV commitment to optimize the dissolution specifications that are noted in the OCPB review.

I agree with the draft labeling changes proposed by OCPB except for the complete deletion of the phrase "Do NOT chew, break, or split the tablet." I agree that the word chew should be deleted, but "Do NOT break or split the tablet," should remain because this is not possible to do accurately. The sponsor considered [redacted] b(4)

CMC notes that the cartons [redacted] b(4)

[redacted] This was confusing and leads one to believe that the contained formulation (5 or 10-mg) is the usual adult dosage. This could be clarified by changing these to lines to the same type face to read, "For the usual adult dosage see accompanying Package Insert." b(4)

5/20/97

Paul J. Andreason, M.D.

cc: NDA#
HFD-120
HFD-120/
P Andreason

T Laughren

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: February 20, 2003

FROM: Paul J. Andreason, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Draft labeling for Zolpidem Tartrate 10-mg tablets

TO: File, NDA 21-412
[Note: This memo should be filed with the February 7, 2003 submission of this NDA.]

The sponsor (Bioavail) submitted a full response to the Division's approvable letter of October 31, 2002 on December 20, 2002. OCPB recommended several changes in labeling including language stating that the 10-mg tablet could not be broken. Unfortunately, the sole availability of zolpidem tartrate in a 10-mg tablet leads to a label that is confusing at best and might lead to unsafe dosing at worst.

The recommended initial dose of zolpidem for the elderly, debilitated patients, and patients with hepatic impairment is 5-mg. These recommendations for these patient groups are stated clearly yet the label goes on to say that zolpidem tartrate is only available in the 10-mg size. Elsewhere in labeling it states that zolpidem tartrate tablets should not be broken. Given that breaking tablets, in general, is a widely accepted practice, recommending an unavailable dose invites dividing an available tablet to achieve the dose. There are at least two possible solutions to this problem for Bioavail:

1. If the sponsor chooses to only market the 10-mg dose form, then clearer language that it is impossible to give this formulation to the elderly, debilitated, or patients with hepatic impairment needs to be incorporated in labeling at all points where a 5-mg dose is recommended.
2. Formulate a zolpidem tartrate 5-mg tablet

The adverse event tables also reflect data for doses of zolpidem $\leq$ 10-mg. Since zolpidem tartrate is only available in the 10-mg size, then the tables should only reflect adverse events at the 10-mg dose. This is a problem for Bioavail since they are submitting this NDA as a 505(b)2 application that relies on the innovating company's data. Bioavail therefore does not have access to the data from which the current zolpidem adverse event tables were generated. There are at least two possible solutions to this problem for Bioavail:

1. Acquire a letter of reference to the innovator's data or acquire new 10-mg only data to generate a new 10-mg only adverse event table
2. Formulate a 5-mg zolpidem tartrate tablet.

I recommend that the Division take an approvable action on this submission and inform the sponsor of the above problems and potential solutions. Other potential solutions may be viable that are not outlined in this memo.

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/s/

Paul Andreason
2/20/03 03:09:49 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: October 30, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approvable action for NDA for zolpidem tartrate rapidly dissolving tablets

TO: NDA 21-412 for zolpidem tartrate rapidly dissolving tablets
[Note: This memo should be filed with the 12-31-01 original submission.]

Background

Zolpidem tartrate is currently approved in an immediate release tablet formulation that is intended to be swallowed whole, under the name Ambien, in 5 and 10 mg strengths. This application is for a rapidly dissolving formulation for the same indication, in a 10 mg strength, for oral administration. This tablet is designed to disintegrate rapidly in the mouth when it comes in contact with saliva, and then release drug-containing micospheres that are swallowed. The stated rationale is to "allow for better patient convenience and compliance, as it may be administered with or without water." This is a 505(b)(2) application that included primarily CMC and biopharmaceutics information to support this new formulation. It refers to the approved product for most biopharmaceutics, and for all pharm/tox and clinical data.

CMC

The CMC data in this NDA have been reviewed by Donald Klein, Ph.D., from the chemistry group, and he has concluded that adequate information has been provided to support an approvable action. Several CMC deficiencies have been included in the approvable letter.

Name

The sponsor did not propose a proprietary name for this new product. However, we have asked the sponsor to adopt the accepted established name for this type of product, i.e., "orally disintegrating."

Biopharmaceutics

The biopharmaceutics data, consisting of data from 3 PK studies, were reviewed by Maria Sunzel, Ph.D., from OCPB. OCPB has concluded that: (1) these studies demonstrated that this new formulation is bioequivalent to Ambien, in both fed and fasted conditions; and, (2) the proposed dissolution method is acceptable, however, they have recommended a different specification. They have also recommended some minor modifications of the sponsor's proposed changes to labeling.

DSI Audit

DSI inspected the clinical (Miami) and analytical (Ontario) sites for study 109297, the pivotal bioequivalence study supporting this NDA. While there were some minor violations, overall, the data from this study were judged to be acceptable.

Clinical

There were n=102 normal volunteers who were exposed to this new zolpidem formulation at a dose of 10 mg in this program. There were no deaths or SAEs, and only 2 adverse dropouts. There was no important new safety information that would impact on the labeling for zolpidem.

Conclusion/Recommendations

I agree with the recommendation of all review disciplines for an approvable action for this NDA, and also with the recommended changes to labeling.

cc:
Orig NDA 21-412
HFD-120/DivFile
HFD-120/TLaughren/RKatz/AMHomonnay

DOC: NDA21412.01

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/s/

Thomas Laughren
10/30/02 08:33:38 AM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

NDA #:	21-412
Sponsor:	Biovail Laboratories Inc.
Material Reviewed	NDA 21-412
Submission Date:	December 29, 2001
Drug	Zolpidem tartrate rapidly dissolving tablets
Proposed Indication:	Insomnia
Dosage Forms, Strengths, and Route of Administration:	10-mg rapidly dissolving tablets Oral administration

Clinical Review

Approval for this application is based on bioequivalence data alone and they are submitted under the provisions of section 505(b)(2) of 21CFR. There are no new clinical efficacy or substantive safety studies submitted with this application. Clinical review of this application focuses only on deaths, serious adverse events and adverse dropouts.

The sponsor 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 were submitted for any pilot study).

There were no deaths or serious adverse events. Two of 102 patients in the three studies dropped out due to the adverse event of nausea, vomiting, and headache.

Conclusion

I recommend that the NDA be approved from a clinical standpoint. There are no new safety findings or expected safety concerns with the new bioequivalent rapidly dissolving formulation.

OCPB review concluded 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 Cmax & 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 need be conducted with the new 10-mg tablet in light of the bioequivalence data.

10/25/02

Paul J. Andreason, M.D.
Medical Review Officer, DNDP

Cc/
NDA 21-412
HFD-120/

P Andreason
T Laughren
M Shin

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/s/

Paul Andreason
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Thomas Laughren
10/28/02 08:46:41 AM
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