CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

SECTION 14 – PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

List of Patents

The Orange Book (20th Edition) lists one unexpired patent for Ambien® Tablets. Attached in this section is the Patent Certification for this patent:

APPEARS THIS WAY
ON ORIGINAL

BIOVAIL
LABORATORIES INCORPORATED

PATENTS AND EXCLUSIVITY STATEMENT

Zolpidem Tartrate Rapidly Dissolving Tablets 10 mg

Paragraph III Certification

In the opinion and to the best knowledge of Biovail Laboratories Incorporated there is one unexpired patent listed pursuant to 21 USC § 355(b)(1) or (c) related to formulations and methods of use of zolpidem tartrate.

The Orange Book (21th Edition) lists the following unexpired patent for drugs containing the active ingredient zolpidem tartrate.

Patent Number	Patent Expiration Date
4,382,938	October 21, 2006

I, Biovail Laboratories Incorporated, state that this application seeks approval for uses of zolpidem tartrate as hypnotic agent for the treatment of insomnia after the expiry of US Patent No. 4,382,938 i.e., after October 21, 2006.

Eugene Melnyk
President
BIOVAIL LABORATORIES INCORPORATED

Date

BIOVAIL LABORATORIES INCORPORATED
Chelston Park Building 2 Collymore Rock St. Michael, BB11, Barbados, W.I.
Tel (246) 437-7088 Fax (246) 437-7085

Patent and Exclusivity Search Results from query on 019908 002.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019908	002	4382938	OCT 21,2006	U-74

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

APPEARS THIS WAY
ON ORIGINAL

Sent by email 4/9/07
NDA 21412

Good Morning:
We have the following comments regarding labeling requirements:

CMC:

- Clarify whether the blister labels that were submitted on February 20, 2007 (Attachment 2) are intended to be representative of the unit dose blister. If so, you will need to revise the label such that all required information is legible when reduced to the same size as the unit dose blister. If the labels provided in Attachment 2 are not unit dose blister labels, clarify where the label will be used and submit samples of the unit dose blister label.

Clinical:

- As you may know, the FDA March 14, 2007 Press Release for ALL sedative/hypnotics sponsors announced that Medication Guides will be required for all products indicated fro insomnia. To assist you, the FDA has written the section of the Med Guide ' "What is the most important information I need to know..."
  This section must be contained verbatim in your Medication Guide. Please insert this section into your Med Guide.

What is the most important information I should know about Tradename?

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

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

Important:
1. Take [TRADENAME] exactly as prescribed

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

2. Do not take TRADENAME if you:

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

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

We remind you that you are responsible for writing the rest of the content and submitting the full Med Guide for our review by July 1, 2007.

Please acknowledge receipt of this message.

Any questions, please contact me. Thanks,

Cathleen

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov

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

/s/

Cathleen Michaloski
4/10/2007 11:49:49 AM
CSO

Regulatory Project Manager
Labeling Review

Date of Review: January 4, 2007

NDA: 21-412

DRUG: zolpidem tartrate orally disintegrating tablets (ODT)

Sponsor: John Dubeck, Keller and Heckman (US Agent) for Biovail Laboratories International, SRL

Background: The original submission for N DA 21-412, zolpidem tartrate 10 mg ODT was made under 505(b)(2) on December 29, 2001. Approval for this application is based primarily on bioequivalence data. However, the sponsor was advised on January 30, 2004 to design a small study to establish that the new formulation for the 5 mg ODT was sufficiently similar to the 10 mg ODT. This study requirement was fulfilled and a tentative approval was granted on May 26, 2005. The application is submitted under the provisions of section 505(b)(2) of 21CFR. There is no additional new clinical efficacy or substantive safety studies submitted with this application. Biovail references Ambien for all other clinical efficacy issues. The first action on the application was 'approvable' on October 31, 2002, and a second 'approvable' action was made on February 21, 2003. Tentative Approvals were granted on May 26, 2005 and recently on September 26, 2006.

The last submission dated November 7, 2006 contained class labeling changes requested by the Agency and stated in the Agency letter dated September 26, 2006. This review addresses those changes.

REVIEW

21-412 / N 000
Submission Dated: November 7, 2006
Reviewed by Medical Officer: Yes, acceptable

The submission provides for class labeling additions to the Indication and Usage section to clarify the duration of the studies on which Ambien's approval (reference drug) was based, the WARNINGS section to add information about angioedema, and the DRUG ABUSE AND DEPENDENCE section to clarify definitions about abuse and addiction.

CONCLUSIONS

1. The submission only provides for labeling revisions as noted above.
2. The medical officer has reviewed the revised PI and found it acceptable.

Cathleen Michaloski, BSN, MPH

28 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Gujral, Renmeet

From: Jacqueline Little [Jacqueline.Little@biovail.com]
Sent: Monday, May 23, 2005 10:33 AM
To: Gujral, Renmeet
Cc: Jack West
Subject: RE: NDA 21-412 Phase IV commitment
Importance: High

Hi Renmeet,

Biovail commits to the two requests in your email. The attached letter with that commitment is being submitted to the NDA this morning.

In order to help us optimize the dissolution method, Biovail requests that your reviewer provide clarification of the rationale for the suggested pH 5.8 buffer. In the Complete Response we offered our rationale for the use of 0.1 N HCl as more physiologically relevant because dissolution occurs in the stomach where the active ingredient is released and absorbed. The active ingredient is not released in the buccal cavity. Also the pKa of zolpidem tartrate is approximately 6.

Best regards,

Jacqueline

Jacqueline Little, M.Sc.
Director, Regulatory Liaison
CNS & Pain
Biovail Technologies, Ltd.
700 Routes 202/206 North
Bridgewater, NJ 08807
Tel 908-927-1753
Mobile 908-216-1190
Fax 908-927-1553
e-mail: Jacqueline.Little@biovail.com

-----Original Message-----
From: Gujral, Renmeet [mailto:GujralR@cder.fda.gov]
Sent: Friday, May 20, 2005 3:36 PM
To: Jacqueline Little
Subject: NDA 21-412 Phase IV commitment

Hi Jacqueline,

Your proposed dissolution method and specification is only acceptable as an interim specification, since we do not consider the dissolution medium proposed to be optimal for this product. Please let me know if Biovail will commit to the following Phase IV commitment to optimize the dissolution

method:

1. Optimize the dissolution method and specifications using 50rpm 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 final selection of the dissolution specification.

Sincerely yours,
Renmeet

Renmeet Gujral, Pharm.D., LT USPHS
Regulatory Project Manager
Division of Neuropharmacological Drug Products, HFD-120
Center For Drug Evaluation and Research, FDA
Office of Drug Evaluation I
Ph: (301) 594-5535
Fax: (301) 594-2859
Email: gujralr@cder.fda.gov

BIOVAIL

VIA OVERNIGHT COURIER

May 23, 2005

Russell G. Katz, MD, Director
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation & Research
Food & Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD, 20852

RE: NDA 21-412
Zolpidem Tartrate Orally Disintegrating Tablets
Biovail Post-Approval Commitment to Optimize Dissolution

Dear Dr. Katz:

Reference is made to the original NDA submitted under 505(b)(2) on December 29, 2001; the FDA Approvable Letter dated February 21, 2003; and to the Complete Response to the FDA Approvable Letter submitted November 24, 2004.

In response to an FDA request provided by Renmoet Gujral, PharmD, Regulatory Project Manager in an email on May 20, 2005, Biovail commits to the following Phase IV commitment to optimize the dissolution method:

1. Optimize the dissolution method and specifications using 50rpm 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 final selection of the dissolution specification.

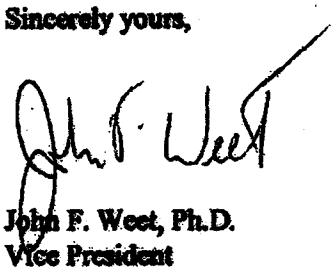
Biovail
700 Route 202/206 North
Bridgewater, New Jersey USA
08807

T 908 927 1740
F 908 927 1749
josh.wood@biovail.com

Our client Biovail Laboratories International SRL has requested that we provide this information. If you should have any questions regarding this submission, please address any inquiries to Jacqueline Little, whose contact information follows.

Jacqueline Little, M.Sc.
Director, Regulatory Liaison
CNS and Pain
Biovail Technologies, Ltd.
700 Route 202-206 North
Bridgewater, NJ 08807
(908) 927-1753 (phone)
(908) 927-1553 (fax)

Sincerely yours,



John F. Weet, Ph.D.
Vice President
Regulatory Affairs
Biovail Technologies Ltd.

Gujral, Renmeet

From: Klein, Donald N
Sent: Wednesday, May 18, 2005 3:47 PM
To: Gujral, Renmeet
Cc: Oliver, Thomas F
Subject: N21-412: CMC Review: Issues for the Letter

Rimmy,

In the event BioPharm and Medical approve this NDA, the following need to be in the Approval Letter:

1. An 18 month expiration is granted.

2. The test method validation has not been completed.

3. There are 3 post-approval commitments on the first page of the Executive Summary.

My review is in DFS, T.Oliver will probably sign off tomorrow.

Don

APPEARS THIS WAY
ON ORIGINAL

Gujral, Renmeet

From: Joseph Quitasol [Joseph.Quitasol@biovail.com]
Sent: Sunday, May 15, 2005 8:21 PM
To: KLEIND@cder.fda.gov
Cc: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Last remaining CMC issue for N21-412

mmsinfo.txt (482 B)

Don,

We commit to follow the current protocol in the NDA. I will confirm by sending a you a copy of the current protocol first thing Monday morning.

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Sunday, May 15, 2005 5:04 PM
To: Joseph Quitasol
Cc: Gujral, Renmeet; Jacqueline Little
Subject: Last remaining CMC issue for N21-412

Joe,
Biovail needs to provide a post-approval stability protocol or commit to follow the current protocol in the NDA.

I suggest Biovail address this issue ASAP.

Don

-----Original Message-----
From: Joseph Quitasol [mailto:Joseph.Quitasol@biovail.com]
Sent: Saturday, May 14, 2005 8:01 PM
To: KLEIND@cder.fda.gov
Cc: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Zolpidem ODT NDA 21-412 - Stability Update

Don:

Agree

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Saturday, May 14, 2005 4:46 PM
To: Joseph Quitasol
Cc: Gujral, Renmeet; Jacqueline Little
Subject: RE: Zolpidem ODT NDA 21-412 - Stability Update

b(4)

Joe and Jacqueline:
Follow-up to DMF —— being withdrawn on 5/12/05.

Even though the DMF —— was withdrawn on 5/12/05, the two Dublin drug

product lots that contain ——— drug substance, will be viewed as
supportive stability data in determining the expiration date. Also, the
——— stability data is considered supportive stability as we had
discussed prior to the 11/2004 Resubmission.

b(4)

-----Original Message-----
From: Klein, Donald N
Sent: Friday, May 13, 2005 2:23 PM
To: 'Joseph Quitasol'
Cc: Gujral, Renmeet; 'Jacqueline Little'
Subject: RE: Zolpidem ODT NDA 21-412 - Stability Update

Joe,
Just to make sure: Biovail is remaining with the following proposed
Disintegration Specifications (1/26/05 Amendment):

Release: NMT ———

Stability: NMT ———

b(4)

Correct?

Don

-----Original Message-----
From: Joseph Quitasol [mailto:Joseph.Quitasol@biovail.com]
Sent: Thursday, May 12, 2005 4:12 PM
To: KLEIND@cder.fda.gov
: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Zolpidem ODT NDA 21-412 - Stability Update

Don,

Attached please find the stability update for Dublin (12 months) and Dorado
(6 months). Chantilly (6 months) will follow by May 23, 2005.

The data show acceptable stability.

The disintegration showed passing the limit of NMT ——— for samples at
25/60. There were 2 batches with OOS at 45/75. The 30/60 samples were tested
and passed the specification limit. We will initiate more testing for
samples at — Dublin started to report actual
(numerical) results and Dorado has been reporting actual results.

b(4)

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Tuesday, May 10, 2005 4:09 PM
To: Joseph Quitasol
: Gujral, Renmeet; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

Joe,

Send it ASAP.

Yi

-----Original Message-----
From: Joseph Quitasol [mailto:Joseph.Quitasol@biovail.com]
Sent: Tuesday, May 10, 2005 4:06 PM
To: KLEIND@cder.fda.gov
Cc: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

Don,

We keep the raising the bar. For more good news, we just received the stability data from Dublin and we are just waiting for the Dorado data. We
might be able to send the stability data before the 13th of May (Friday).

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Tuesday, May 10, 2005 3:58 PM
To: Joseph Quitasol
Cc: Gujral, Renmeet; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

3,

That is before 9AM/Weds.

Don

-----Original Message-----
From: Joseph Quitasol [mailto:Joseph.Quitasol@biovail.com]
Sent: Tuesday, May 10, 2005 3:52 PM
To: KLEIND@cder.fda.gov
Cc: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

Don,

Attached please find the responses to the 5-06-05 CMC Information Requests.
Official hard copy will follow.

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Tuesday, May 10, 2005 9:35 AM
To: Joseph Quitasol
Cc: Gujral, Renmeet; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

Joe and Jacqueline,

Since the Review Clock is running out this cycle, will you be able
to submit responses to the 5/6 CMC Information Requests by tomorrow 9AM.
This is not critical but it would be helpful for our internal discussion
(5/11).

-----Original Message-----
From: Klein, Donald N
Sent: Monday, May 09, 2005 5:11 PM
To: 'Joseph Quitasol'
Cc: Gujral, Renmeet; 'Jacqueline Little'
Subject: RE: Additional CMC IR for N21-412 Resubmission

Joe,
It is certainly a point of discussion. Submit your reply. I'm talking with Tom Oliver on Weds. morning. Don

-----Original Message-----
From: Joseph Quitasol [mailto:Joseph.Quitasol@biovail.com]
Sent: Monday, May 09, 2005 5:08 PM
To: KLEIND@cder.fda.gov
Cc: GujralR@cder.fda.gov; Jacqueline Little
Subject: RE: Additional CMC IR for N21-412 Resubmission

Hi Don:

We are reviewing and preparing the responses to the CMC IRs. One issue that
we want to clarify:

...r the description of the 5 mg tablet: "[redacted]". We note that the
tablets have speckles...please double check the description. b(4)

Thank you.

Joe

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Friday, May 06, 2005 3:12 PM
To: Jacqueline Little; Joseph Quitasol
Cc: Gujral, Renmeet
Subject: Additional CMC IR for N21-412 Resubmission

Hello again on Friday Afternoon:
I inadvertently forgot this CMC Information Request in the earlier
E-mail.

Don

-----Original Message-----
From: Klein, Donald N
Sent: Friday, May 06, 2005 2:09 PM
To: 'Jacqueline Little'; 'Joseph Quitasol'
Cc: Gujral, Renmeet
Subject: RE: N21-412 Resubmission: CMC IRs

The Responses may be submitted as available instead of sending the responses
together.

on
-----Original Message-----
From: Jacqueline Little [mailto:Jacqueline.Little@biovail.com]
Sent: Friday, May 06, 2005 1:12 PM
To: Klein, Donald N; Joseph Quitasol
Cc: Gujral, Renmeet
Subject: RE: N21-412 Resubmission: CMC IRs

Hi Don,

The responses will come from Ireland and I believe they have left for the
day but I will get an idea of the timing on Monday and let you know. I understand the urgency.

Regards,

Jacqueline

-----Original Message-----
From: Klein, Donald N [mailto:KLEIND@cder.fda.gov]
Sent: Friday, May 06, 2005 12:52 PM
To: Joseph Quitasol
Cc: Gujral, Renmeet; Jacqueline Little
Subject: N21-412 Resubmission: CMC IRs

Joe and Jacqueline,
Not to ruin your Friday afternoon, but we are trying to approve the
CMC section this review cycle. Attached are CMC Information Requests that
need to be addressed.

Don

Homonnay Weikel, Anna M

From: Homonnay Weikel, Anna M
Sent: Tuesday, February 04, 2003 1:46 PM
To: 'Niall Morrissey'
Cc: Homonnay Weikel, Anna M
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

FDA AP labeling proposal.doc

As discussed during last Friday's telecon, I am forwarding the FDA labeling proposal for the PK subsection of the labeling. It has been reformatted and revised. Please indicate your concurrence or otherwise within the next few days, if possible.

Thank You

Anna Marie H. Weikel, R.Ph.
Divison of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

-----Original Message-----
From: Niall Morrissey [mailto:nmorrissey@biovail.ie]
Sent: Thursday, January 30, 2003 9:31 AM
To: 'Homonnay Weikel, Anna M'
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

This schedule is suitable to Biovail thank you. We will call at the time indicated.

In addition to the list of Biovail participants provided yesterday I would
like to add the following Biovail colleagues from the field of Analytical
Chemistry: Rosanna Garcia (Director Analytical Services) and Breda Burke (Analytical Manager).

Thank you

-----Original Message-----
From: Homonnay Weikel, Anna M [mailto:HOMONNAYA@cder.fda.gov]
Sent: Wednesday, January 29, 2003 06:41
To: 'Niall Morrissey'; Homonnay Weikel, Anna M
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

I've scheduled a teleconference for Friday morning, the 31st, from 11:00 - 1:30 AM EST. The FDA participants will be Susanna Uppoor, Ph.D., Biopharmaceutics Teamleader; Vaneeta Tandon, Ph.D., Biopharmaceutics Reviewer; and myself. The number to call is (301) 827-2804. Is this okay?

Thanks

Anna Marie H. Weikel, R.Ph.
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

-----Original Message-----
From: Niall Morrissey [mailto:nmorrissey@biovail.ie]
Sent: Wednesday, January 29, 2003 1:03 PM
To: 'Homonnay Weikel, Anna M'
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

Beth Ferguson is on vacation at present.
Biovail would welcome a teleconference with you and your colleagues Friday
morning January 31st (USA Eastern Time). Biovail's confirmed list of active
participants will be Dr. Paul Maes (Vice President Pharmaceutics), Alexander
Rochefort (Vice President Regulatory Affairs), Dr. Sury Sista (Director
Pharmacokinetics), Siobhan Fogarty (Senior Director R&D) and finally myself.

Is a Friday morning January 31st (USA Eastern Time) suitable for the
Division. If so can you recommend a phone-in time ? Can you provide a list of
participants from the Neuropharm division ?
Thank you
Niall Morrissey

-----Original Message-----
From: Niall Morrissey
Sent: Wednesday, January 29, 2003 02:25
To: 'Homonnay Weikel, Anna M'
Cc: 'beth.ferguson@biovail-btl.com'
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

Biovail would welcome the opportunity to discuss the issues relating to the
tablet dissolution method via a teleconference.
I am currently accumulating a short list of likely attendees from
appropriate disciplines within Biovail to participate in this
teleconference. I will be in contact very shortly with a list of
participants.
Thank you
Niall Morrissey
-----Original Message-----
From: Homonnay Weikel, Anna M [mailto:HOMONNAYA@cder.fda.gov]
Sent: Tuesday, January 28, 2003 08:14
To: 'Niall Morrissey'
Subject: RE: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

I left a message today with Beth at the Virginia office about needing to
schedule a teleconference to discuss your proposed dissolution specs. I do
not agree and would like to talk it over with you this week or early next

week if possible. Could someone get back to me about this?

Thank You

Anna Marie H. Weikel, R.P.
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
FDA Center for Drug Evaluation and Research
Senior Regulatory Project Manager
(301) 594-5535

-----Original Message-----
From: Niall Morrissey [mailto:nmorrissey@biovail.ie]
Sent: Tuesday, January 14, 2003 5:14 AM
To: 'homonnaya@cder.fda.gov'
Subject: NDA 21-412, Zolpidem Tartrate Orally Disintegrating Tablets

Arrangements have been made to dispatch 2 additional paper review copies of
Biovail's amendment dated December 20th 2002 entitled "Response to the FDA's
Oct.31st, 2002, Approvable Letter". I would however be most grateful if you
could confirm that you received all the contents of my original December 20th submission as indicated on the cover letter accompanying the amendment,
i.e. three identical complete paper copies (one archive and 2 review copies)
and a complete electronic submission containing all the paper information in
electronic form via a CD-ROM formatted in accordance with the FDA's Jan.1999 "Guidance for industry, Providing Regulatory Submissions in Electronic Format - NDAs". I am concerned that your Divison may not have received the CD-ROM electronic version. If not I would be happy to resubmit
this CD-ROM if needs be.
Thank you very much.

Niall Morrissey
Biovail Technologies Limited,

3 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

SI:-

MEMORANDUM

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

DATE: July 25, 2002

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 29,02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-412,
Ambien® (zolpidem tartrate) Rapidly Dissolving Tablets,
Sponsored by Biovail Technologies Ltd.

TO: Russell G. Katz, M.D.
Director
Division of Neuropharmacological
Drug Products (HFD-120)

At the request of HFD-120, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study 109297: "A Two-Way Crossover, Open-Label, Single-Dose, Fasting, Evening Administration, Comparative Bioavailability Study of Zolpidem Tartrate Flash Dose 10 mg Tablets Versus Ambien® 10 mg Tablets in Normal Healthy Non-Smoking Male and Female Subjects" (B01-549PK-ZOLN04)

The clinical and analytical portions of the study were conducted at _____, and at Biovail Contract Research (BCR), Ontario, Canada. b(4)

Following the inspections at _____ and BCR (5/3-7/02), Form 483 was issued. The Form 483 items and our evaluation of them follows:

Clinical Site: [redacted] b(4)

1. **Inadequate record keeping:**
   a. **No reason for changing Subject 34's blood pressure history.**

      Subject 34's history for high blood pressure was changed from "Yes" to "No" without documented justification. Subject 34's ECG screen and vital signs were normal for the study.

   b. **The justification provided to the IRB for discontinuation of Subject 014 from the study was inaccurate.**

      Subject 014 was discontinued due to a positive drug screen. Instead, the clinic informed the IRB that the dismissal was based on the "subject's best interest". However, the clinical report correctly states the reason for the dismissal. In future, the clinic should assure that the information provided to the IRB is accurate.

   c. **Subject history forms do not document that a signed informed consent form was obtained for each subject.**

      Nonetheless, the inspection revealed that the subjects signed informed consents prior to study initiation.

The above findings do not affect the study results or compromise subject safety. However, the objectionable practices in Item 1 should be corrected by the clinic for future studies.

Analytical Site: Biovail Contract Research, Ontario, Canada.

2. **Lack of freeze-thaw (F-T) stability for the first F-T cycle.**

   Both the freeze-thaw (F-T) stability samples and the comparison quality controls (QC) were F-T once. Also, calibrators in the F-T experiment underwent one F-T cycle. Therefore, analyte stability through the first F-T cycle in human plasma was not demonstrated.

   In their response to the Form 483, the firm presented data comparing F-T stability samples with freshly prepared QCs. The results indicate stability of the analytes following the first F-T cycle (Exhibit 1).

3. **Autosampler stability comparison was not meaningful in that peak responses of stability samples from different validation batches were compared.**

   However, calibration standard sets at the beginning and end of the analytical runs and QCs interspersed within the analytical runs were processed with subject samples and found to be acceptable. This indicates stability of analyte in processed samples for the duration of the analytical runs.

4. **Discrepancies in selection of pharmacokinetic (PK) repeat.**

   In addition to the log concentration vs. time profiles, concentration vs. log time plots were also used to select PK repeats. The firm, however, failed to include these plots in the submission. Also, the SOP allows [redacted] b(4)

   The finding does not impact the study, as inclusion of the original or PK repeat data for the subject samples in question, does not affect the study outcome.

5. **Documentation in laboratory notebooks was inadequate.**

   Analysts do not routinely document in the laboratory notebooks: i) the stress conditions of the stability samples (e.g., time and date of freezer storage and thaw cycles) during validation and, ii) purity and expiration dates of reference standards. In their response to the Form 483, the firm confirmed with the manufacturer that the pharmacopeial zolpidem tartrate reference standard used in the study was the current lot.

The firm promised to correct the objectionable Items 2 to 5 in their response to the Form 483.

Conclusion:

We recommend that the study data be accepted for Agency review as the above findings do not invalidate the study.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Attachments

Final Classifications:
VAI - _____ b(4)
VAI - Biovail Contract Research, Ontario, Canada

cc:
HFD-45 RF
HFD-48 Subramaniam(2)/CF
HFD-120 Hommonnay Weikel/David
HFD-860 Sunzel/Uppoor
HFR-SW150 Annes
Draft: SS 7/25/02
Edit: MKY MKY 7/26/02
DSI:5422; O:\BE\EIRCOVER\21412bio.zol.doc
FACTS ID: 294579

Table 12: Long Term Stability in Plasma at 174 Days for Zolpidem at –70° Celsius

	Amount added (ng/mL)			
	QC LOW2		QC HIGH	
	3.000	2.997	383.972	383.663
	Amount found (Peak Height Ratio)			
Preparation date	09-29-2000	03-22-2001	09-29-2000	03-22-2001
Assay date	03-22-2001	03-22-2001	03-22-2001	03-22-2001
Storage time	174 days	---	174 days	---
	0.238	0.227	30.149	30.764
	0.231	0.236	30.593	29.824
	0.236	0.226	30.116	30.310
	0.226	0.229	31.101	30.228
	0.229	0.220	29.807	29.560
	0.221	0.222	29.995	29.986
n	6	6	6	6
Mean	0.230	0.227	30.294	30.112
Std. Dev.	0.006	0.006	0.473	0.420
% C.V.	2.7	2.5	1.6	1.4
% Diff.	1.5		0.6	

AE Label

AE Label

BIOVAIL TECHNOLOGIES LTD.

DUPLICATE

RECEIVED

JUL 2 2 2002

HFD-120/ODER

July 19th, 2002

Russel G. Katz, MD
Director, Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food And Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

ORIGINAL AMENDMENT

N(22)

Re: Zolpidem Tartrate Rapidly Dissolving Tablets, 10mg
NDA 21-412
Electronic Pack Insert (Word Format)

Dear Dr. Katz,

This correspondence for archive contains an electronic copy of the current Zopidem Tartrate Rapidly Dissolving Tablet pack insert reported in Biovail's December 2001 original NDA submission. The file is contained in the 3½inch diskette secured in this binder. A hard copy of this file is presented overleaf.

An identical word document was provided to the Neuropharmacological division's Regulatory Health Manager Dr. Anamarie Hommonay-Weikel via e-mail on July 18th 2002.

If you have any additional questions relating to this submission please contact the undersigned by phone at 011-353-1-2941887, by fax at 011-353-1-2941868 or e-mail using nmorrissey@biovail.i.e

Sincerely,
On behalf of Biovail Laboratories Inc.

Niall Morrissey
Regulatory Affairs Associate
Biovail Technologies (Ireland) Limited

BIOVAIL TECHNOLOGIES LTD.
3701 Concorde Parkway, Chantilly, Virginia 20151
Tel: (703) 995-2400 Fax: (703) 995-2490

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

FAC13 2.1.0.1 SNIP

MEMORANDUM

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

DATE: March 19, 2002

TO: Director, Investigations Branch
Florida District Office
555 Winderly Place, Suite 200
Maitland, FL 32751

FROM: C.T. Viswanathan, Ph.D. CTV 3/19/02
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2002 **High Priority CDER User Fee NDA**, Pre-approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-412
DRUG: Ambien® (zolpidem tartrate) Rapidly Dissolving Tablets, 10 mg
SPONSOR: Biovail Corporation
C/O Biovail Technologies Limited
3701 Concorde Parkway
Chantilly, VA 20151

This memo requests that you arrange for an inspection of the clinical portion of the following bioequivalence study. The analytical portion of Protocol #109297 (B01-549PK-ZOLN04) was conducted elsewhere, and is the subject of a separate inspection. **Due to the user fee deadline, the inspection must be completed by July 15, 2002.**

Protocol: #109297 (B01-549PK-ZOLN04)

Clinical Site: [redacted] b(4)

Clinical Investigator:

Please check the batch numbers of both the test and the reference drug formulations used in the study with the descriptions in documents submitted to the Agency. If study formulations have not been submitted to the Agency previously, samples of both the test and reference drug formulations should be collected and mailed to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening.

Please have the records of all study subjects audited, including 100% of the informed consent forms. The subject records in the NDA submission should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A member of the GLP and Bioequivalence Investigations Branch, Division of Scientific Investigations may participate in the inspection.**

Headquarters Contact Person: Martin K. Yau, Ph.D.
(301) 827-5458

CC:
HFA-224
HFD-45/RF
HFD-48/Yau(2)/CF
HFD-120/Melaine Shin
HFD-860/Sunzel/Baweja
Draft: MKY 3/19/02
DSI:5422 O:\BE\assigns\bio21412clin.doc
FACTS 294579

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: February 25, 2002

TO: Dr. C.T. Viswanathan
Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Russell Katz, M.D
Division Director, HFD-120

FROM: Melaine Shin, R.Ph., Regulatory Management Officer, HFD-120

SUBJECT: Request for Biopharmaceutical Inspections
NDA 21-412
Ambien (zolpidem)

Study/Site Identification:

As discussed with you, the following studies/sites pivotal to approval (OR, raise question regarding the quality or integrity of the data submitted and) have been identified for inspection:

Sponsor: Biovail Corporation
C/O Biovail Technologies Limited
3701 Concorde Parkway
Suite 800
Chantilly, Virginia 20151
(703) 995-2400

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
#109297 (B01-549PK-ZOLN04)		Biovail Contract Research (A Division of Biovail Corporation) 460 Comstock Road Toronto, Ontario, Canada M1L 4S4 Tel No.: 416-752-3636 Fax No.: 416-752-7610 Study Director: Shafik Dharamshi, MD Director of Bioanalytical Lab: Brent Matthews, B.Sc.

b(4)

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by July 31, 2002. We intend to issue an action letter on this application by October 31, 2002.

Should you require any additional information, please contact Melaine Shin.

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
3/5/02 03:05:37 PM

MEMORANDUM OF MEETING MINUTES

Application:	NDA 21-412 Zolpidem Rapidly Dissolving Tablets, 10mg
Meeting Date:	February 14, 2002
Time:	11:00AM
Location:	WOCII Conference Room E
Application:	NDA 41-412
Type of Meeting:	45-Day Filing Meeting
Meeting Chair:	Russell Katz, M.D.
Meeting Recorder:	Melaine Shin, R.Ph.

FDA Attendees, titles, and Office/Division:

Russell Katz, M.D.	Division Director
Thomas Laughren, M.D.	Clinical Team Leader
Paul Andreason, M.D.	Medical Officer
Maria Sunzel, Ph.D.	OCPB Reviewer
Hasmukh Patel, Ph.D.	CMC Team Leader
Donald Klein, Ph.D.	CMC Reviewer
Melaine Shin, R.Ph.	Regulatory Management Officer
Martin Yau, Ph.D.	DSI

Discussion Points:

CMC

- It's filable.
- The sponsor is asking for a 2-year expiration date, but only submitted 3-month stability data and would need to submit more stability data.

OCPB

- It's filable.
- Need data sets (as SAS transport files) for the plasma concentration-time data, demographics and pharmacokinetic parameters (individual values) from studies B01-549PK-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. The sponsor needs to explain this discrepancy and submit study report/s (not including copies of the signed Informed Consent forms).
- The sponsor needs to submit an extra desk copy of volume 1.4 (Chemistry), needed for the CPB review of the *in vitro* dissolution method and specifications.
- The sponsor submitted copies of the signed informed consent forms for all healthy volunteers from all three submitted study reports. Dr. Yau from DSI would check with the Human Subject Protection group to find out how to handle these forms.

Clinical

- **It's filable.**

Post Meeting Notes

- **Dr. Yau informed the Division that the signed informed consent forms can be submitted to the FDA and there are no provisions in the CFR that consent forms have to reside with the investigator.**

Action Items:

- **Contact the sponsor to convey OCPB's requests.**
- **CMC will send the consult to Microbiology.**
- **It's due on 10/31/02 and all the primary reviews will be completed by end of August, 2002.**

Chair Concurrence: _____ **Minutes Preparer:** _____
Thomas Laughren, M.D. **Melaine Shin, R.Ph.**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-412

Biovail Technologies LTD
Attention: Wayne Kreppner, M.Sc., RAC
Manager, Regulatory Affairs
3701 Concorde Parkway
Chantilly, Virginia 20151

Dear Mr. Kreppner:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: zolpidem tartrate Rapidly Dissolving Tablets 10mg

Review Priority Classification: Standard (S)

Date of Application: December 29, 2001

Date of Receipt: December 31, 2001

Our Reference Number: NDA 21-412

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 1, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 31, 2002 and the secondary user fee goal date will be December 31, 2002.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Melaine Shin, R.Ph., Project Manager, at (301) 594-5793.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Melaine Shin
1/16/02 10:51:56 AM
Sign for Mr. John Purvis

SECTION 2 – SUMMARY

Cross Ref. to Section Vol/Page

H. Clinical Data Summary and Results of Statistical Analysis

This product is being filed in accordance with section 505(b)(2) of the Food Drug and Cosmetic Act. Clinical efficacy and safety data in support of this submission is referenced from the Searle and Co. approved NDA # 19-906 for Ambien® tablets.