CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-412

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-412

Biovail Laboratories International SRL
c/o John Dubeck, Esq.
Keller and Heckman Law Offices
1001 G Street, NW, Suite 500 W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your new drug application dated and received December 31, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for zolpidem tartrate orally disintegrating tablets, 5 mg and 10 mg.

Your submission of November 7, 2006 constituted a complete response to our September 26, 2006 action letter.

We also acknowledge receipt of your submission dated December 22, 2006, received on December 26, 2006.

This NDA provides for the use of zolpidem tartrate orally disintegrating 5 mg and 10 mg tablets for the short-term treatment of insomnia.

We have completed our review of this application, as amended on November 7, 2006, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the deficiencies outlined below.

We note that these deficiencies were conveyed to you electronically on December 6, 2006, and that your December 22, 2006 submission was your intended response. However, given the timing of your response, we are deferring review of the December 22, 2006 submission to the next review cycle to allow for substantive review. Please incorporate the December 22, 2006 submission by specific reference as part of your response to this letter.

Carton and Container Labeling

To assure that we have considered all of your current proposals for labeling, please submit all carton and container labeling proposed to be used with TOVALT. The following comments are based on our review of the labels you submitted on August 9, 2006.

Blister Labels

1.

2.

3.

b(4)

4.

Carton Labels

5.

6. b(4)

7.
8.

Package Insert

After review of available post-marketing adverse event reports, we have determined that additional modifications are needed in the class labeling for the sedative-hypnotic group. These modifications, which pertain to the risks for severe allergic reactions and sleep-driving (and other complex behaviors), are being required for all drug products that are indicated for the treatment of insomnia.

For clarity, we have included text in its entirety for the WARNINGS section of your package insert. We have also included revised text for the PRECAUTIONS: Information for patients subsection of the package insert.

1. **"WARNINGS" section**

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Tovalt ODT. Because some of the important adverse effects of Tovalt ODT appear to be dose related *(see Precautions and Dosage and Administration)*, it is important to use the smallest possible effective dose, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative-hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character); similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation, and depersonalization. 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 Tovalt ODT alone at therapeutic doses, the use of alcohol and other CNS depressants with Tovalt ODT appears to increase the risk of such behaviors, as does the use of Tovalt ODT at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Tovalt ODT should be strongly considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with sleep-driving, patients usually do not remember these events.

Amnesia, anxiety and other neuro-psychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative-hypnotics.

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

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

Tovalt ODT, like other sedative/hypnotic drugs, has CNS-depressant effects. [Note to Sponsor: Please underline the following sentence.] Due to the rapid onset of action, Tovalt ODT should only be taken immediately prior to going to bed. Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential

impairment of the performance of such activities that may occur the day following ingestion of Tovalt ODT. Tovalt ODT showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when Tovalt ODT is administered with such agents because of the potentially additive effects.

Severe anaphylactic and anaphylactoid reactions

Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including Tovalt ODT. 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 Tovalt ODT should not be rechallenged with the drug.

2. **"PRECAUTIONS: Information for patients" subsection**

Patient information is printed at the end of this insert. To assure safe and effective use of Tovalt ODT, this information and instructions provided in the patient information section should be discussed with patients.

SPECIAL CONCERNS

"Sleep-Driving" and other complex behaviors

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

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required. Please be advised that class labeling changes for the sedative-hypnotic drug group are currently under review by the Agency (see above). We will keep you informed of any additional changes if they occur.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Neurology Products and two copies of both the promotional materials and the package insert directly to:

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

Timing of Response

We remind you that the listed reference drug product upon which you based your application, Ambien of Sanofi Synthelabo, is subject to a period of patent protection which expires on April 21, 2007 (U.S. Patent No. 4382938) and, therefore, final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until this period has expired. Your application contains a Paragraph III Patent Certification to this patent under Section 505(b)(2)(A)(iv) of the Act.

Please submit a response to all items listed in this letter and identify additional changes to this product as appropriate. Your response should include updated labeling, chemistry, manufacturing and controls data, and a safety update. You should respond to this letter no sooner than 60 or 180 days prior to the expiration of Ambien's patent (see above). You should determine the timing of your response by referring to resubmission classifications and associated FDA review times described in the Guidance for Industry: Classifying Resubmissions in Response to Action Letters available at http://www.fda.gov/cder/guidance/index.htm.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director, Division of Neurology 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/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-412

Biovail Laboratories International SRL
c/o John Dubeck, Esq.
Keller and Heckman Law Offices
1001 G Street, NW, Suite 500 W
Washington, DC 20001

Dear Mr. Dubeck:

Please refer to your new drug application dated and received December 31, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for zolpidem tartrate orally disintegrating tablets, 5 mg and 10 mg.

We acknowledge receipt of your additional submissions dated:

May 25, 2005 May 26, 2005 June 9, 2005 July 27, 2005 March 24, 2006
July 20, 2006 August 9, 2006

Your submission of July 20, 2006 constituted a complete response to our May 26, 2005 action letter.

This NDA provides for the use of zolpidem tartrate orally disintegrating 5 mg and 10 mg tablets for the short-term treatment of insomnia.

We have completed the review of this application, as amended, and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the enclosed labeling (text for the package insert and patient information sheet), and is tentatively approved under 21 CFR 314.105. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product upon which you based your application, Ambien of Sanofi Synthelabo, is subject to a period of patent protection which expires on October 21, 2006 (U.S. Patent No. 4382938) and, therefore, final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until this period has expired (and/or exclusivity if it is granted, has expired). Your application contains a Paragraph III Patent Certification to all of these patents under Section 505(b)(2)(A)(iv) of the Act. This certification states that this application seeks approval for uses of zolpidem tartrate as a hypnotic agent for the treatment of insomnia after the expiry of US Patent No. 4,382,938 (October 21, 2006).

Timing of Response

Please submit a response to all items listed in this letter and identify changes, if any, in the conditions under which your product was tentatively approved. Your response should include updated labeling, chemistry, manufacturing and controls data, and a safety update. You should respond to this letter no sooner than 60 or 180 days prior to the expiration of Ambien's patent and/or exclusivity (see above). You should determine the timing of your response by referring to resubmission classifications and associated FDA review times described in the Guidance for Industry: Classifying Resubmissions in Response to Action Letters available at http://www.fda.gov/cder/guidance/index.htm.

Failure to submit the response will prompt a review of the application that may result in rescission of this tentative approval letter.

Package Insert

The attachment to this letter provides the labeling that the Agency asks you to adopt for zolpidem tartrate orally disintegrating tablets upon approval of this application. The base document used for our attached labeling is your July 20, 2006 proposed zolpidem tartrate orally disintegrating tablets package insert. Although sections of this proposal are taken verbatim from the labeling proposed by you in the NDA, other sections have been revised.

Since issuance of our May 26, 2006 letter, the Agency has determined that class labeling modifications are needed for the sedative-hypnotic group. Because these changes are applicable for all drug products indicated for the treatment of insomnia, we have included these modifications in our attached labeling for zolpidem tartrate ODT. Specifically, we have revised the INDICATIONS and USE section to clarify the duration of the studies on which Ambien's approval was based, the WARNINGS section to add information about angioedema, and the DRUG ABUSE AND DEPENDENCE section to clarify definitions about abuse and addiction. Please be aware that the Agency is currently considering the implementation of a Medication Guide for the sedative-hypnotic group in an effort to minimize the risk for certain adverse events.

We ask that, when you respond to this letter, you submit labeling for zolpidem tartrate orally disintegrating tablets that includes all previous revisions, as reflected in the most recently approved Ambien package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes and identify which version of zolpidem tartrate labeling was used as the base document. Also, please assure that spacing of the text is readable.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Carton and Container Labeling

b(4)

Chemistry, Manufacturing and Controls

Stability
Based on the stability data provided, a 24-month expiration dating period is assigned for Zolpidem Tartrate Orally Disintegrating Tablets.

Methods Validation

We have completed validation of the regulatory methods. Methods are acceptable for control and regulatory purposes. However, we expect your continued cooperation to resolve any problems that may be identified.

Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

As described in our May 26, 2006 letter, we remind you of the following comments regarding dissolution method and specifications.

- Based on the dissolution data of the biobatches, OCPB does not believe that your 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. We note that this issue had been previously conveyed to you, including the better choice of pH 5.8 phosphate buffer at 50 rpm, and we note your agreement to revise these specifications. Therefore, 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:

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

Outstanding Phase 4 Postmarketing Commitments

We remind you of the following postmarketing study commitments acknowledged in our May 26, 2005 letter, which are still open.

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 should 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 the 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 for the final selection of the dissolution specification.

Commitment #4
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.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Commitment Protocol", "Postmarketing Study Commitment Final Report", or "Postmarketing Study Commitment Correspondence."

Fulfilled Postmarketing Commitments

We have reviewed your July 25, 2005 submission and conclude that the below commitments are fulfilled.

Commitment #3
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.

Commitment #5
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) results.

Tradename

We remind you that, on July 26, 2006, you were informed by phone and by email that your proposed tradename, ——— was unacceptable. We note that, on August 9, 2006, you submitted an alternate tradename. That submission is currently under review. b(4)

Promotional Material

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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

Other

Any significant change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letter before the expiration of Ambien's patent and/or exclusivity if granted, has expired, you should amend your application accordingly.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed before final approval.

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

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

23 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-412

Biovail Technologies, Ltd.
Jacqueline Little, M.Sc.
Director, Regulatory Liaison
CNS and Pain
700 Routes 202/206 North
Bridgewater, NJ 08807

Dear Ms. Little:

Please refer to your new drug application dated and received December 31, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Tartrate orally disintegrating 5 mg and 10 mg tablets.

We acknowledge receipt of your submissions dated:

November 24, 2004				
December 22, 2004	February 15, 2005	March 11, 2005	May 4, 2005	May 16, 2005
January 17, 2005	February 22, 2005	April 5, 2005	May 9, 2005	May 18, 2005
January 26, 2005	March 7, 2005	April 26, 2005	May 13, 2005	May 23, 2005

Your submission of November 24, 2004 constituted a complete response to our February, 21, 2003 action letter.

This NDA provides for the use of Zolpidem Tartrate orally disintegrating 5 mg and 10 mg tablets for short-term treatment of insomnia.

We have completed the review of this application, as amended, and have concluded that based upon the information you have presented to date, the drug product is safe and effective for use as recommended in the enclosed labeling (text for the package insert and patient package insert), and is tentatively approved under 21 CFR 314.105. This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

The listed reference drug product upon which you based your application, Ambien of Sanofi Synthelabo, is subject to a period of patent protection which expires on October 21, 2006 (U.S. Patent No. 4382938) and, therefore, final approval of your application under section 505(c)(3) of the Act (21 U.S.C. 355(c)(3)) may not be made effective until this period has expired. Your application contains a Paragraph III Patent Certification to all of these patents under Section 505(b)(2)(A)(iv) of the Act. This certification states that this application seeks approval for uses of zolpidem tartrate as a

hypnotic agent for the treatment of insomnia after the expiry of US Patent No. 4,382,938 (October 21, 2006).

At least 90 days prior to October 21, 2006 , submit an amendment to this application identifying changes, if any, in the conditions under which your product was tentatively approved. This information should include updated labeling, chemistry, manufacturing and controls data, and a safety update.

Failure to submit this amendment will prompt a review of the application that may result in rescission of the tentative approval letter.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Phase 4 Postmarketing Commitments and Agreements

We remind you of your postmarketing study commitments acknowledged in your e-mail correspondence dated May 26, 2005, to Dr. Renmeet Gujral, of this Division. These commitments are listed below.

Commitment #1

Description:	Optimize the dissolution method and specifications using (b) (4) paddle speed and a different dissolution medium (e.g., (b) (4)).
Final Study Report:	The final study report should 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 (b) (4) 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 for the final selection of the dissolution specification.

Commitment #3

Description:	Using the retained (b) (4) (b) (4)ng samples (non-debossed 5 mg ((b) (4)) and 10 mg (b) (4)) 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

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

Description: Using the retained drug product release samples ((b) (4)((b) (4) of 5 mg and 3 Lots of 10 mg); and (b) (4)((b) (4) of 5 mg), the Identification (UV) results 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

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence.**"

Additionally, we remind you of the following agreements:

Chemistry, Manufacturing, and Controls

- An 18 month expiration is granted.

Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

- Based on the dissolution data of the biobatches, OCPB does not believe that your current proposal for dissolution method (b) (4) and the choice of dissolution medium (b) (4) are optimal for this product since the dissolution is very rapid (b) (4) and the method does not appear to be discriminatory. We note that this issue had been previously conveyed to you, including the better choice of pH (b) (4) at (b) (4) and we note your agreement to revise these specifications. Therefore, the currently proposed method (dissolution medium (b) (4) and agitation speed) and the dissolution specifications can, at best, be allowed only as interim specifications.

- Following are the interim dissolution method and specifications:
  Method: (b) (4)
  Speed: (b) (4)
  Mediu-(b(b) (4)
  Temperature: 37 ± 0.5°C
  Specification: Q = (b) (4) 30 minutes

Tradename

If you wish to market this drug with a tradename, you will be required to submit a proposed tradename and receive Agency acceptance of the tradename. Additionally, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Any significant change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letter before October 21, 2006, you should amend your application accordingly.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before final approval.

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at (301) 594-5535.

Sincerely,

(See appended electronic signature page)

Russell Katz, M.D.
Director
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/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-412

Keller and Heckman LLP
U.S. Agent for Biovail Technologies Ltd.
Attention: John B. Dubeck, Esq.
1001 G Street, Ste 500-W
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your new drug application (NDA) dated December 29, 2001, received December 31, 2001, submitted under section 505(b)/pursuant to 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Orally Disintegrating Tablets, 10 mg.

We acknowledge receipt of your amendments dated December 20, 2002; and February 3, 6, and 7, 2003.

Your amendment of December 20, 2002, constituted a complete response to our October 31, 2002, action letter.

This NDA provides for the use of zolpidem orally disintegrating tablets for the short-term treatment of insomnia.

We have completed the review of this application, as amended, and it is approvable. While we recognize that the review team and members of your firm have negotiated, and agreed to, language for product labeling, a closer inspection of that agreed-to wording reveals that it is misleading in the following ways, which must be adequately addressed before this application may be approved:

1. [redacted]

b(4)

2.

We believe that these problems would be definitively, and most appropriately, resolved by making a 5 mg dosage strength available. We would be happy to discuss with you the requirements for approval of such a strength.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Senior Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
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/

Russell Katz
2/21/03 01:52:59 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-412

Keller and Heckman LLP
U.S. Agent for Biovail Technologies Ltd.
Attention: John B. Dubeck, Esq.
1001 G Street, Ste 500-W
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your new drug application (NDA) dated December 29, 2001, received December 31, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Orally Disintegrating Tablets, 10 mg.

We acknowledge receipt of your amendments dated February 19, March 27 (2), June 28, July 19 and 31, August 28 and October 2, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry Issues

1. ——— has been sent a DMF deficiency letter on September 4, 2002 stating that DMF ——— is inadequate for Zolpidem Tartrate. Please be advised that DMF ——— must be adequate prior to the approval of NDA 21-412. b(4)

2. Please provide the source used to yield Glyceryl Monostearate, NF and Stearoyl Monogolglycerides, EP. This information is needed to reduce the potential risk posed by Bovine Spongiform Encephalopathy (BSE).

3. Due to the complexity of the manufacturing process, please provide the executed batch record of a commercial batch and the respective Certificate of Analysis (COA). The COA should adhere to your proposed specifications and test methods.

4. We recommend you tighten the specification limit for the Total Impurities such that the limit is consistent with the analytical data submitted for the pivotal batches (Lots 24870801, 24880801, and 24890801).

5. We recommend you tighten the specification limit for the Moisture such that the limit is consistent with the analytical data submitted for the pivotal batches (Lots 24870801, 24880801, and 24890801).

6. Please provide a revised drug product specification table to reflect the requested change in the dissolution specification limit, as stated in the September 26, 2002 Information Request Letter.

7. Please update your primary stability data in support of your proposed 24 month drug product expiration date.

8. Please submit a drug product stability protocol.

9. We acknowledge the October 2, 2002 amendment where you provide data that identified Impurity ——— ——— As a result, please remove the specification for Impurity — from the stability testing (page 377 in Volume 1.4). b(4)

10. We recommend tightening the stability specification limits: Moisture; Impurity — Total Impurities; Dissolution, based on the submitted stability data (through 9 months). b(4)

Biopharmaceutics Issues

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) finds the proposed *in vitro* dissolution method acceptable; however, the proposed specification should be changed to Q = — in 30 minutes. b(4)

Labeling Issues

1.

2.

3. b(4)

4.

b(4)

5.

6.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you should have any questions, please call Ms. Anna Marie H. Weikel, R.Ph., Regulatory Affairs Manager, at (301) 594-5535.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
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/

Russell Katz
10/31/02 12:17:17 PM