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) mg 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)(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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