DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21515/S-022

SUPPLEMENT APPROVAL

Biovail Technologies, Ltd.
Attention: Robert W. Ashworth, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, NJ 08807

Dear Dr. Ashworth:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 3, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Wellbutrin XL (bupropion HCl) Extended-Release Tablets.

We acknowledge receipt of your submission of February 18, 2010, which constituted a complete response to our action letter of December 1, 2009.

These "Prior Approval" supplemental new drug applications provide for revisions to the product labeling:

- **CLINICAL PHARMACOLOGY: Metabolism** and **PRECAUTIONS: Drug Interactions**- Addition of pharmacokinetic information from a series of studies concerning drug interactions between bupropion and ritonavir and lopinavir/ritonavir.
- **PRECAUTIONS: Drug Interactions**- Addition of ticlopidine and clopidogrel as examples of drugs that are substrates of or inhibitors/inducers of CYP2B6 and thus may interact with bupropion. Addition of statement that bupropion increases the C_{max} and AUC of citalopram by 30% and 40%, respectively.
- **DOSAGE AND ADMINISTRATION** and the **Medication Guide (WELLBUTRIN XL only) -** An update to the statement "Do not chew, divide, or crush tablets" to add "as this may lead to an increased risk of adverse effects, including seizures".
- **MEDICATION GUIDE:** Addition of the statement "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088", as required by FDA Final Rule issued 10-28-2008 Toll Free Number for Reporting Adverse Events on Labeling for Human Drug Products.
- Minor editorial changes to provide consistency between PIs.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling

text, and with the minor editorial revisions listed under the **CLINICAL PHARMACOLOGY: Metabolism** section of labeling listed below.

1. We have re-reviewed our requested revision, and based on the data provided in the study report, the erythrohydrobupropion exposure shoud be 48% instead of (b) (4). The last sentence of the paragraph should now read as follows:

   "The exposure of the hydroxybupropion metabolite was decreased by 23%, the threohydrobupropion decreased by 38%, and the erythrohydrobupropion decreased by 48%."

2. The threohydrobupropion exposure should be 50% instead of (b) (4). The following paragraph should now read as follows:

   "In a second healthy volunteer study, ritonavir at a dose of 600 mg twice daily decreased the AUC and the Cmax of bupropion by 66% and 62%, respectively. The exposure of hydroxybupropion metabolite was decreased by 78%, the threohydrobupropion decreased by 50%, and the erythrohydrobupropion decreased by 68%."

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format that includes the changes approved in this supplemental application.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, email your Regulatory Project Manager, at Juliette.Toure@FDA.HHS.GOV.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21515	SUPPL-22	BIOVAIL LABORATORIES INTERNATIONAL SRL	WELLBUTRIN XL(BUPROPION HCL)EXTENDED REL

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

/s/

THOMAS P LAUGHREN
05/25/2010