CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-693

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-693

Biovail Laboratories, Inc.
Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs
700 Route 202/206 North
Bridgewater, New Jersey 08807

Dear Dr. Weet:

Please refer to your new drug application (NDA) dated March 10, 2004, received March 11, 2004, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for tramadol hydrochloride orally disintegrating tablets, 50 mg.

We acknowledge receipt of your submissions dated March 10, November 9, 12, 16, and 22, December 10, 13, 21, and 22, 2004 and January 5, and 10, 2005.

We completed our 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 issue:

- Labeling according to 21 CFR 314.50(e)(2)(ii) has not been submitted to the application for review (immediate container and carton label).

Information needed to resolve approvability issues:

- According to 21 CFR 314.50(e)(2)(ii) copies of the label and all labeling for the drug. Labeling should include text for immediate container and carton labels.

Furthermore, before this application may be approved, however, you must submit draft printed label (package insert) revised as follows:

- Throughout the labeling, reference to the reference listed drug be replaced by "orally swallowed immediate release tramadol tablet.

Reference is made to the letter dated January 10, 2005 in response to the Division labeling letter of January 7, 2005, requesting an alternate proprietary name for your tramadol hydrochloride orally disintegrating tablets. We have completed review of your newly proposed trade name and find it unacceptable. If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidances specify that labeling to be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format with proposed revisions clearly indicated. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

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

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), you may request an informal meeting or telephone conference with this division to discuss what 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 Kathleen Reedy, Regulatory Project Manager, at (301) 827-2533.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, M.D.
Deputy Director
Division of Analgesic, Anti-inflammatory,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

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

/s/

Sharon Hertz
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