CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-692

Biovail Technologies, Ltd.
700 Route 202-206 North
Bridgewater, NJ 08807

Attention: John F. Weet, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Weet:

Please refer to your new drug application (NDA) dated December 31, 2003, received December 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Trade name (tramadol HCL) Extended-Release Tablets.

We acknowledge receipt of your submissions dated February 25, March 31, April 30, August 3, 6(2), 20, 26, and 30, September 1, 8, 9, 17, 23, 28, and 30(2), October 6, 13, 25, and 28(2), and November 11 and 22, 2004, and March 7 and 9, April 26 and 29, June 6 and 10, July 18, 25, and 28(2), August 8, 17, and 23(2), September 1(2) and 8, 2005.

The March 7, 2005, submission constituted a complete response to our October 29, 2004, action letter.

This new drug application provides for the use of TRADENAME ER for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container and carton labels) Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this/these submission(s) "**FPL for approved NDA 21-692.**" Approval of this submission by FDA is not required before the labeling is used.

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.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages birth to 16 years until September 30, 2010.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of for the management of moderate to moderately severe chronic pain in pediatric patients ages birth to 16 years.

   Final Report Submission: September 30, 2010

Submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitments**".

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.**"

In addition, you have agreed to the following interim dissolution specifications:

Time	**Dissolution Specification**
2 hours	
4 hours	
8 hours	
10 hours	
16 hours	

In order to validate your proposed in vitro/in vivo correlation (IVIVC), and the associated in vitro dissolution specification, we encourage you to provide the following information:

1. The mathematical models (equations) and the control files that you used for predicting the plasma concentration time profiles for IVIVC; and

2. Evidence that the IVIVC is predictive of alterations in the rate of drug release, i.e., external validation using the release formulations that would probe the acceptance limits of the IVIVC. Such an external validation could be done with the material from Study

2553 or new lots of product that have release rates/bioavailabilty that are different from the clinically studied product. You are encouraged to seek guidance from the Agency as to what would be an appropriate comparator for this external validation.

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(s) directly to:

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

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

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, call Parinda Jani, Chief, Project Management Staff, at (301) 827-2538.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-692

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-692

Biovail Laboratories, Incorporated
Attention: John B. Dubeck, Esquire
Keller and Heckman, LLP
1001 G Street, N.W., Suite 500-W
Washington, D.C. 20001

Dear Mr. Dubeck:

Please refer to your new drug application (NDA 21-692) dated December 31, 2003, received December 31, 2003, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ralivia ER (tramadol hydrochloride extended release) 100, 200, and 300 mg tablets.

We acknowledge receipt of your submissions dated February 25, August 6, 20, 26 and 30, September 1, 9, 17, 23 and 30, and October 5 and 6, 2004.

We also acknowledge receipt of your submission dated September 30, 2004. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

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

You have not provided evidence of an acceptable risk to benefit ratio for this product. Specifically, the following deficiencies were identified:

Efficacy:

1. The proposed indication "for the treatment of moderate to moderately severe pain", is not supported by the data presented in the NDA.

   a. This is the same indication described in the Ultram® (tramadol hydrochloride immediate release) label. The labeled indications for Ultram® are based on clinical trials performed to support approval, which included studies in both acute pain and chronic pain models. Ralivia ER has not provided a similar set of clinical trials. Furthermore, upon review of the data presented in your NDA, Ralivia ER is not bioequivalent to the reference listed product. Therefore, the indications for Ralivia ER cannot be identical to Ultram® and your proposal to label Ralivia ER with the same indications as Ultram® is not justified.

b. When the pain variable was considered as the single primary endpoint to support this indication, Study 021 failed the primary analysis. Studies 023, 015 and 014 succeeded in the primary analyses using the Last Observation Carried Forward (LOCF) as the method of imputation for missing data. However, your analyses were not supported by sensitivity analyses conducted to adjust for substantial number of patient dropouts.

2. The proposed indication, [redacted] is not supported by the data presented in the NDA. None of the trials reached significance for the three co-primary endpoints as pre-specified in the pivotal osteoarthritis protocols.

3. The data provided to support dose response is inadequate. Primary efficacy analyses showed inconsistent results for different doses among trials, although all doses failed sensitivity analyses. No dose showed robust evidence of efficacy.

Safety:

1. The analysis of adverse events as submitted in the Integrated Summary of Safety (ISS) is inadequate. All adverse events were not included in your analyses. As stated in your NDA submission, cases of adverse events were eliminated from the ISS.

2. An increase in serious thromboembolic events was noted in the flexible dosing group versus placebo.

3. The proposed label submitted for Ralivia ER is not adequate to address the safety concerns associated with Ralivia ER. Specifically, the label does not include serious adverse events as well as adverse events identified with Ralivia ER but not found in the Ultram® label.

Information needed to resolve deficiencies:

Provide additional data to support the risk/benefit ratio:

[redacted]

2. Provide additional information regarding the increased number of serious thromboembolic events.

3. Submit a revised label that addresses the safety findings in the Ralivia ER NDA and which delineates any additional safety and efficacy findings with Ralivia ER, including a description of the carcinogenicity studies you have conducted.

In addition, when the above issues are addressed in your response, we also request the following information and analyses:

1. Provide an analysis of outliers and dropouts due to laboratory, vital signs or EKG (including QT intervals) abnormalities, as appropriate. This should include a presentation of the extent of these abnormalities.

2. Provide an analysis of the measures of central tendency as well as shifts from normal to abnormal, as appropriate.

3. Provide a statistical analysis of the results of C_{min} testing, to include the calculation of 90% confidence intervals, in the studies where C_{min} was available.

4. Acceptance of the dissolution specifications is pending upon the review of *in vitro-in vivo* correlation (IVIVC) results.

5. For patients with renal or hepatic impairment, you relied on Ultram labeling along with your studies to develop dosing recommendations. Please provide a more detailed explanation on how final conclusions regarding dosage reduction in these patients were reached in each condition.

6. To further evaluate age effect, provide additional data on Ralivia ER exposure-response in elderly (65-75 yrs) and older (>75 yrs) subjects.

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
   - 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.

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 314.120. 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 the Division of Anti-inflammatory, Analgesic, and Opthalmologic Drug Products 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 this application is approved.

If you have any questions, contact Nancy Clark, PharmD, Regulatory Project Manager, at (301) 827-2516.

Sincerely,

{See appended electronic signature page}
Brian E. Harvey, M.D., Ph.D.
Acting Director
Division of Anti-inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Brian Harvey
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