# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-742**

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Mylan Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea Miller
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your new drug application (NDA) originally submitted April 30, 2004, and resubmitted May 30, 2007 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for nebivolol 2.5, 5, and 10 mg Tablets.

We acknowledge receipt of your submissions dated May 30, July 26 (two) and 27, August 16, September 17, 25, and 27, October 17, 19 (two), 23, and 30, and November 1, 2007 (two).

The May 30, 2007 submission constituted a complete response to our May 31, 2005 action letter.

We have completed our review of this application, as amended, and it is approvable.

During a recent inspection of the manufacturing facility for this application, our field investigator conveyed deficiencies to the facility representative. Satisfactory resolution to these deficiencies is required before this application may be approved.

We have included agreed-upon labeling text as an enclosure. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

We acknowledge your agreement to conduct a postmarketing placebo-controlled withdrawal study following at least three months of treatment.

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 the Division of Cardiovascular and Renal 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

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 a meeting or telephone conference with the Division of Cardiovascular and Renal 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 the application is approved.

If you have any questions, please call Dan Brum, Pharm.D., MBA, Regulatory Project Manager, at (301)796-0578.

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Enclosed agreed-upon labeling text

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

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/s/

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Robert Temple
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# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-742

Mylan Bertek Pharmaceuticals Inc.
Attention: Ms. Andrea B. Miller
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Miller:

Please refer to your new drug application (NDA) dated April 30, 2004 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nebivolol 2.5, 5, and 10 mg Tablets.

We acknowledge receipt of your submissions dated June 4, 22, 23, 24, 25 and 28, July 8, 9, 13, 14, and 15, August 23, September 9 and 27, October 27, November 12 (two), 16, 19, 23 (two), and 30, and December 6, 10, 15, and 21, 2004 and January 4 (two) and 20, February 3, 4, 8, 11, 21, 22, and 24, March 14, 15, and 17, and April 8 and 12, 2005.

We also acknowledge receipt of your submissions dated May 24, 2005 (two). These submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have 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 address the following issues:

A highly statistically significant and dose-related increase in benign and malignant Leydig cell tumors was observed in male mice. The findings appear with exposure only several times the clinically attained blood levels. This effect may be endocrinologically mediated. Other possibly endocrinologically mediated effects were also seen in long-term toxicology studies of rats—reductions in adrenal and ovary weights, dystocia, and interference with cyclicity. If an endocrine mechanism can be established and if this mechanism is not relevant to human use, e.g., because it is not active at clinical doses, the mouse findings may not be of concern. It will therefore be necessary for you to establish the mechanism by which nebivolol is responsible for these findings and demonstrate that these findings are not relevant in humans.

After review of the data submitted on February 21 and 22, 2005, we recommend the following dissolution method and specifications:

| Condition | FDA Recommendation |
|---|---|
| Dissolution Medium | 0.01N HCL |
| Paddle Speed | 50 rpm |
| USP Apparatus II | |
| Volume | 900 mL |
| Specifications | [redacted] in 30 minutes |

Given the extent of the additional information needed, final labeling cannot be considered at this time. As the additional requested information becomes available, revision of the proposed labeling will be required. However, in the interim, we will continue to discuss the draft labeling in order to reach a timely agreement once the deficiencies noted above have been resolved.

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.

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 the Division of Cardio Renal 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 the application is approved.

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

*{See appended electronic signature page}*

Robert Temple, M.D.
Director
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/

Robert Temple
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