CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-873

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-873

Berlex, Inc.
Attention: Nancy F. Velez
340 Changebridge Road
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Velez:

Please refer to your new drug application (NDA) dated December 22, 2004, received December 23, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone/ethinyl estradiol) for Oral Contraception (OC) and Premenstrual Dysphoric Disorder (PMDD).

We acknowledge receipt of your submissions dated February 18, March 15, 23, April 29, May 20 (2), June 23, July 25, August 26, 30, September 14, October 28 (2), November 1, 3, 10, 11, 16, 17, 22, and 30, December 2, 6, 9, 13 and January 6, 10, (2), 12, 13, 16, 19, 20, 2006.

The submissions dated December 2, 6, 9, 2005 and January 10, 2006 were not reviewed for this action. Because these submissions contain important information relevant to a determination of the safety of YAZ for the proposed indications, this application is approvable pending our review of these submissions and a satisfactory conclusion as to their content.

In addition, labeling remains unresolved. We anticipate that extensive discussions will be needed to arrive at mutually acceptable language regarding the proposed indication for PMDD and the importance of distinguishing PMDD from Premenstrual Syndrome (PMS). We also encourage you to submit a proposal for a patient package insert which incorporates this distinction in lay language. Lastly, we suggest you consider additional training and educational activities related to ensuring the appropriate use of YAZ in those patients comprising the target populations.

When you respond to this letter, 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.

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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with the Division of Reproductive and Urologic 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, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
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/

Daniel A. Shames
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