CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-676

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-676

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

Dear Ms. Velez:

Please refer to your new drug application (NDA) dated October 16, 2003, received October 17, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for YAZ (drospirenone 3 mg/ethinyl estradiol 0.02) Tablets.

We acknowledge receipt of your submissions dated November 18, 25, December 4, January 29, February 18, March 18, April 8, 16 (2), 19, 21, 23, 26, 28, May 6, 14, 21, 26, 27, June 9, 10, 11, 24, 29, 30, July 1, 8, 9, 22, August 3, 4, 6 (2), 11, 13, 17, 23, September 8, 24, October 7, 21, November 4 (4), and November 8, 2004. These submissions were reviewed for this action.

We have completed our review of this application, and it is approvable. Before the application may be approved, however, it will be necessary for you to (1) demonstrate a clinical benefit for the 24-day regimen over that provided by a 21-day regimen to offset the increased potential risk associated with the additional 3 days of drospirenone/ethinyl estradiol or (2) propose a 21-day regimen for consideration. This can be accomplished by any of the following:

1. Provide evidence that the proposed 24-day contraceptive dosing regimen provides a clinical benefit over that provided by a 21-day regimen. This evidence could consist of demonstrating fewer "escape ovulations" with the 24-day regimen compared to the 21-day regimen.

2. Demonstrate that the 24-day regimen is safe and effective for either of the two secondary indications that are presently under investigation, premenstrual dysphoric disorder (PMDD) and acne.

3. Submit an application amendment for the 21-day dosing regimen for the contraceptive indication. The amendment should include acceptable labeling, acceptable financial disclosure information for the investigators who participated in Study 303860, acceptable CMC information regarding final packaging of the 21-day regimen, and a safety update. You can consider a dosing regimen that includes 7 days of placebo tablets instead of 7 tablet–free days.

Regardless of the option chosen, your submission should also include [redacted]

Should you continue to pursue approval of the 24-day dosing regimen, your submission should also include a proposal to conduct a large, adequately powered post-marketing surveillance study to compare the incidence of serious thrombotic and thromboembolic events in users of this product to that in users of other combination oral contraceptives that do not contain drospirenone. This type of study would not be necessary should you choose to pursue a 21-day dosing regimen.

Labeling remains unresolved. Further discussions regarding this topic will occur in the next review cycle.

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.

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 fully to the deficiencies described above. We will not process a partial reply as a major amendment nor will the review clock be reactivated until the deficiencies have been fully addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Reproductive and Urologic 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, call Charlene Williamson, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug 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/

Donna Griebel
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