CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-864

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-864

APPROVABLE LETTER

Wyeth Pharmaceuticals
Attention: Robert DiGregorio, D.O., F.A.C.O.O.G.
Director I, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DiGregorio:

Please refer to your new drug application (NDA) dated May 27, 2006, received May 27, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lybrel™ (levonorgestrel and ethinyl estradiol) Tablets.

We acknowledge receipt of your submissions dated: September 1, 27, November 28, December 21, 2005; January 27 (2), February 7, 8, 10, 16, 21, March 6 (2), 13, 21 (2), 24, 29 (3), April 6, and 20, 2006.

We also acknowledge receipt of your submissions dated May 22 and June 22, 2006. 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 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:

1. The application does not contain sufficient stability data to support approval of the product manufactured using the revised ——— method. Submit 3 months of real time and accelerated stability data on the three lots of drug product manufactured by the revised ——— method.

b(4)

2. Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application.

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 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 John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 796-0932.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D., F.A.C.S.
Acting Deputy Director
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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