DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021864/S-007

**SUPPLEMENT APPROVAL**

Wyeth Pharmaceuticals, Inc.
c/o Pfizer, Inc.
Attention: Carl Louison
Senior Manager, Worldwide Safety & Regulatory
235 East 42nd Street
New York, NY 10017

Dear Mr. Louison:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on April 18, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lybrel® (levonorgestrel and ethinyl estradiol) tablets.

We also refer to our letter dated, March 18, 2016, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Lybrel. This information pertains to the risk of venous thromboembolic events (VTE) based on the findings of the postmarketing commitment study with Lybrel.

This supplemental new drug application provides revisions to the labeling for Lybrel, consistent with our March 18, 2016, letter and electronic communication dated May 16, 2016. Labeling revisions to the prescribing information are as follows (additions are noted by underline):

Under the Warnings and Precautions "Venous Thrombosis and Thromboembolism," the addition of the following paragraph:

A post-marketing observational study evaluated the risk of venous thromboembolism with Lybrel use in two large US automated healthcare claims databases. The study was not completed as planned due to low accrual of Lybrel users in these databases and discontinuation of the product from the market due to low usage. At study discontinuation, the crude incidence rate of venous thromboembolism among Lybrel users (n=12,281) was 17.6 per 10,000 person-years, compared to 8.8 per 10,000 person-years among the users of cyclic oral contraceptives containing 20 mcg of ethinyl estradiol and a progestogen, and 5.1 per 10,000 person-years among the users of cyclic oral contraceptives containing the progestin levonorgestrel and 20 mcg of ethinyl estradiol. Adjustment for important risk factors or confounders (such as obesity, cardiovascular disease and other diseases) for venous thromboembolism could not be performed due to the small sample size. Although the study results suggest an elevated risk of venous thromboembolism with current Lybrel use compared to cyclic oral hormonal contraceptive use, reliable interpretation of the results is significantly limited due to the small sample size and

concerns over unmeasured and uncontrolled confounding, as well as questions about the suitability of the comparator selection and the validity of the venous thromboembolism definition.

## APPROVAL & LABELING

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

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert, text for the patient package insert, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

## REPORTING REQUIREMENTS

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 Meredith Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

*{See appended electronic signature page}*

Christine P. Nguyen, MD
Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

---

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

---

/s/

---

CHRISTINE P NGUYEN
06/16/2016