DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022307/S-015

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Anindita Sen, MS, PhD
Advisor, Global Regulatory Affairs-US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Sen:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 9, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel hydrochloride) 5 mg and 10 Tablets.

We also refer to our letter dated January 9, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for prasugrel. This information pertains to the risk of decreased absorption of prasugrel when used concomitantly with morphine.

This supplemental new drug application provides for revisions to the labeling for prasugrel. The agreed upon changes to the language included in our January 9, 2018 letter, and our February 28, 2018 e-mail, containing revisions to our January 9, 2018 required language, are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~):

1. In **HIGHLIGHTS**, a new section was added:

   ----------DRUG INTERACTIONS----------
   - Opioids: Decreased exposure to prasugrel. Consider use of parenteral anti-platelet agent (7.3)

2. Under **DRUG INTERACTIONS**, a new section was added:

   7.3 Opioids
   As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of prasugrel's active metabolite presumably because of slowed gastric emptying *[see Clinical Pharmacology (12.3)]*. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added to the "Drug Interactions" section:

   Morphine – Co-administration of 5 mg intravenous morphine with 60 mg loading dose of prasugrel in healthy adults decreased the Cmax of prasugrel's active metabolite by 31%

with no change in AUC, T_{max}, or inhibition of ADP-induced platelet aggregation. ADP induced platelet aggregation was higher up to 2 hours following 60 mg loading dose of prasugrel in stable patients more than 1 year after an ACS who were co-administered morphine. In the patients with a 2-hour delay in the onset of platelet aggregation (5 of 11), T_{max} was delayed and prasugrel active metabolite levels were significantly lower at 30 min (5 vs 120 ng/ml) following co-administration with morphine.

4. The revision date, version number and Table of Contents were updated.

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), 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 include 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).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, please call:

Lori Anne Wachter, RN, BSN, RAC
Safety Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
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/

MARY R SOUTHWORTH
03/09/2018