



NDA 22307/S-007

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Peter Morrow, MS
Director, Global Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Supplemental New Drug Application (sNDA) dated June 1, 2012, received June 1, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel hydrochloride) 5 mg and 10 mg Tablets.

We acknowledge receipt of your amendments dated September 18 and November 14 and 27, 2012.

This Prior Approval supplemental new drug application provides for the additional bleeding risk factor of “moderate to severe renal dysfunction” to the label for prasugrel.

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. These changes are as follows:

Full Prescription Labeling

- Under the Section 5 **WARNINGS AND PRECAUTIONS** subsection, **5.1 General Risk of Bleeding**, the following paragraph was changed to add “or moderate to severe renal impairment”:

“Propensity to bleed (e.g., recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment) [*see Adverse Reactions (6.1) and Use in Specific Populations (8.7 and 8.8)*].”

- In **USE IN SPECIAL POPULATIONS** subsection **8.7, Renal Impairment**, the following paragraph now appears as follows, adding the higher risk of bleeding:

“No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage renal disease, but such patients are generally at higher risk of bleeding [*see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].”

- The above changes to the FPI are also reflected in the **HIGHLIGHTS**.
- Other minor and editorial changes were made throughout the label.

Medication Guide

- In the “**What is the most important information I should know about Effient?**” subsection, “**Your risk of bleeding while taking Effient may be higher if you also:**”, the following was added:

“have moderate to severe kidney problems”

- Under the section, “**What should I tell my doctor before taking Effient?**” the following bullet was added:

“have kidney problems”

- Finally, under the section, “**How should I take Effient?**”, the following bullet was added:

“Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.”

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 and Medication Guide), 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 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).

POSTMARKETING REQUIREMENTS UNDER 505(o)

We remind you of your post-marketing requirements listed in our action letter dated July 10, 2009. These requirements are listed below:

- 95-2 You will gather baseline cancer history and cancer adverse event data from the ongoing trial TRILOGY, a 10,300-subject trial being conducted in patients with acute coronary syndrome who are being managed medically (without coronary revascularization). The final report on cancers in this trial is to be submitted to IND 63,449.

The timetable you submitted on July 8, 2009 states that you will conduct this trial according to the following timetable:

Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

POSTMARKETING COMMITMENTS REPORTABLE UNDER SECTION 506B

We also remind you of your post-marketing commitment listed in our action letter dated July 10, 2009. This commitment is listed below:

- 95-6 You commit to the collection of samples at baseline for genotyping CYP450 enzymes in TRILOGY subjects, to allow a comparison of effectiveness and bleeding in prasugrel and clopidogrel subgroups by metabolizer status. These data will be submitted with the final study report of TRILOGY. The periodic reports will include the fraction of subjects who consented to genetic testing.

We understand that the protocols for these trials have been submitted.

Final Protocol Submission: Received 06/20/2008
Trial Completion Date: 12/2012
Final Report Submission: 01/2013

Submit clinical protocols to your IND (63,449) for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)

5901-B Ammendale Road
Beltsville, MD 20705-1266

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/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. 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>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director of Safety
Division of Cardiovascular and Renal Products
Office of New Drugs
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/

MARY R SOUTHWORTH
11/30/2012