DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022307/S-003

SUPPLEMENT APPROVAL

Eli Lilly and Company
Attention: Peter Morrow, M.Sc.
Director, Global Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Mr. Morrow:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 15, 2011, 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 amendment dated August 10, and September 13 2011 and your risk evaluation and mitigation strategy (REMS) assessment dated January 31, 2011.

This supplemental new drug application provides for proposed modifications to the approved REMS and labeling revised as follows:

The following changes were made to the labeling:

1. In **HIGHLIGHTS/RECENT MAJOR CHANGES**, the following was added:

   Hypersensitivity with angioedema (5.5) 06/2011

2. In **HIGHLIGHTS/WARNINGS AND PRECAUTIONS,** the following bullet was added:

   - Hypersensitivity: Hypersensitivity including angioedema has been reported with Effient including in patients with a history of hypersensitivity reaction to other thienopyridines (5.5).

3. In **FULL PRESCRIBING INFORMATION: CONTENTS***, the following section was added:

   5.5 Hypersensitivity including Angioedema

4. Under **WARNINGS AND PRECAUTIONS** a new section was added:

5.5 Hypersensitivity Including Angioedema

Hypersensitivity including angioedema has been reported in patients receiving Effient, including patients with a history of hypersensitivity reaction to other thienopyridines *[see Contraindications (4.3), Adverse Reactions (6.2)]*

5. Under **PATIENT COUNSELING INFORMATION/Other Signs and Symptoms Requiring Medical Attention**, a new bullet was added:

   - Inform patients that they may have hypersensitivity reactions including rash, angioedema, anaphylaxis, or other manifestations. Patients who have had hypersensitivity reactions to other thienopyridines may have hypersensitivity reactions to Effient.

6. The revision date and version number were updated.

The following changes were made to the Medication Guide:

1. Under the **What is the most important information that I should know about Effient? Do not take Effient if you**: section, the second bullet was changed from:

   - have a history of stroke or "mini-stroke" (also known as transient ischemic attack or TIA)

To:

   - have had a stroke or "mini-stroke" (also known as transient ischemic attack or TIA)

2. Under **What is the most important information that I should know about Effient?**, the third bullet was changed from:

   Get medical help immediately if you think you may be having a stroke or TIA. You may experience the following while having a stroke or TIA: sudden slurring of speech, sudden weakness or numbness in one part of your body, sudden blurry vision, or sudden severe headache.

To:

   Get medical help right away if you think you may be having a stroke or TIA. Symptoms that you may be having a stroke or TIA include:

   - **sudden slurring of speech,**
   - **sudden weakness or numbness in one part of your body,**
   - **sudden blurry vision, or sudden severe headache.**

3. Under the **What is the most important information that I should know about Effient?**, the fourth bullet was changed from:

> **If you are having a stroke or TIA, your doctor will probably stop your Effient.**

To:

> **If you have a stroke or TIA while taking Effient, your doctor will probably stop your Effient. Follow your doctor's instructions about stopping Effient. Do not stop taking Effient unless your doctor tells you to.**

4. Under the **Your risk of bleeding while taking Effient may be higher if you also:** section, the fourth bullet was deleted.

5. Under the **Your risk of bleeding while taking Effient may be higher if you also:**, the fifth bullet was changed from:

- take other medicines that increase your risk of bleeding, including:
  • Coumadin*, Jantoven* (warfarin sodium) also known as "blood thinner" or anticoagulant

To:

- take other medicines that increase your risk of bleeding, including:
  • warfarin sodium (Coumadin*, Jantoven*)

6. Under the **Your risk of bleeding while taking Effient may be higher if you also:**, the seventh bullet was changed from:

- other medicines to prevent or treat blood clots, such as Pradaxa* (dabigatran)

To:

- other medicines to prevent or treat blood clots

7. Under the **Your risk of bleeding while taking Effient may be higher if you also:**, the eighth bullet was changed from:

> long term (for 2 weeks or longer) daily use of non-steroidal anti-inflammatory drugs NSAIDs)), such as Aleve* (naproxen), Advil*, or Motrin* (ibuprofen)

To:

regular daily use of non-steroidal anti-inflammatory drugs (NSAIDs)

8. Under **What should I tell my doctor before taking Effient?,** the second bullet was changed from:

    - have a history of stroke or "mini stroke" (also known as transient ischemic attack or TIA)

To:

    - have had a stroke or "mini stroke" (also known as transient ischemic attack or TIA)

9. Under **What should I tell my doctor before taking Effient?,** the third bullet was changed from:

    - any allergies you may have to medications, including Plavix (clopidigrel)

To:

    - are allergic to any medicines including clopidogrel (Plavix) or ticlopidine hydrochloride (ticlid)

10. Under **What are the possible side effects of Effient?**, a new bullet was added:

    - **Serious allergic reactions.** Serious allergic reactions can happen with Effient, or if you have had a serious allergic reaction to the medicines clopidogrel (Plavix) or ticlopidine hydrochloride (Ticlid). **Get medical help right away if you get any of these symptoms of a severe allergic reaction while taking Effient:**

        • swelling or hives of your face, lips, in or around your mouth, or throat
        • trouble breathing or swallowing
        • chest pain or pressure
        • dizziness or fainting

11. Under the **General Information about Effient,** the section was changed from:

    Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Effient for a condition for which it was not prescribed. Do not give your Effient to other people, even if they have similar symptoms. It may harm them. This Medication Guide summarizes the most

important information about Effient. If you would like more information about Effient, talk with your doctor or pharmacist. For more information, call 1-800-545-5979 or go to the following website:
www.Effient.com

To:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Effient for a condition for which it was not prescribed. Do not give your Effient to other people, even if they have the same symptoms you have. It may harm them. This Medication Guide summarizes the most important information about Effient. If you would like more information about Effient, talk with your doctor or pharmacist. For more information, call 1-800-545-5979 or go to the following website:
www.Effient.com

12. Under **What are the active ingredients in Effient?**, the statement "*The brands listed are trademarks of their respective owners and are not trademarks of Daiichi Sankyo, Inc. or Eli Lilly and Company.", was relocated to the end of the Medication Guide.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental application, as amended, and 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, 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).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Effient was originally approved on July 10, 2009, and REMS modifications were approved on April 16, 2010 and December 6, 2010. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of a revised Medication Guide and communication plan (Prescriber Brochure) to include information about the risk of hypersensitivity reactions and other editorial changes.

Your proposed modified REMS, submitted on June 15, 2011, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 10, 2009.

There are no changes to the REMS assessment plan described in our July 10, 2009 letter.

We remind you that assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved

REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022307 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022307
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022307
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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
Division of Drug Marketing, Advertising, and Communications
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 Division of Drug Marketing, Advertising, and Communications (DDMAC), 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 for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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
09/26/2011