DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-307/S-001

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 December 18, 2009 Supplemental New Drug Application (sNDA), received December 18, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Effient (prasugrel) 5 and 10 mg tablets.

We also acknowledge receipt of your submissions dated January 19, February 26, March 26, and April 2 and 15, 2010; and your risk evaluation and mitigation strategy (REMS) assessment dated April 1, 2010.

This Prior Approval supplemental new drug application provides for changes to the formulation (b) (4) that existed in the initially approved formulation. This re-formulation also provides for the following changes to the package insert:

1. The section, **DOSAGE FORMS AND STRENGTHS**, was updated with new debossing information and appears as follows:

   "Effient 5 mg is a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5121" on one side and 3 parallel arched lines followed by a "5" on the other.

   Effient 10 mg is a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "5123" on one side and 3 parallel arched lines followed by a "10" on the other."

2. In Section 11, **DESCRIPTION**, the following inactive ingredients were added, "low-substituted hydroxypropyl cellulose", "sucrose stearate", and "glyceryl behenate". The following inactive ingredients were deleted, "croscarmellose sodium" and "vegetable magnesium stearate".

   The following text was also deleted from Section 11, "During manufacture and storage, partial conversion from prasugrel hydrochloride to prasugrel free base may occur".

3. Section 16, **HOW SUPPLIED/STORAGE AND HANDLING**, was amended to read as follows:

   "Effient (prasugrel) 5 mg is supplied as a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5121" on one side and 3 parallel arched lines followed by a "5" on the other.

   5 mg tablets are supplied as follows:
   Bottles of 30 - NDC 0002-5121-30
   Blisters ID 24* - NDC 0002-5121-52

   Effient (prasugrel) 10 mg is supplied as a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "5123" on one side and 3 parallel arched lines followed by a "10" on the other.

   10 mg tablets are supplied as follows:
   Bottles of 30 – NDC 0002-5123-30
   Blisters ID 90* - NDC 0002-5123-77
   (*Identi Dose®, unit dose medication, Lilly)
   Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].

   Dispense and keep product in original container. Keep container closed and do not remove desiccant from bottle. Do not break the tablet".

This supplement also provides for the following change to the medication guide:

The section, **What are the ingredients in Effient?**, was revised to read as follows:

"Inactive Ingredients: mannitol, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, sucrose stearate, and glyceryl behenate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10 mg tablet)."

Finally, this supplement also provides for proposed modifications to the approved REMS.

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

An expiration dating of **18 months** is granted, based on the submitted stability data for the 5 mg and 10 mg strengths of Effient (prasugrel) tablets packaged in bottles and blisters, when stored at 25°C (USP controlled room temperature).

CONTENT OF LABELING

Please submit revised content of labeling [21 CFR 314.50(l)(1)(i)], at the time the new formulation is being released, in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). For administrative purposes, please designate this submission, "**SPL for approved NDA 22-307/S-001**".

We request that the revised labeling approved today be available on your website within 10 days of the new formulation being marketed.

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:

1. An open-label trial of *ex vivo* reversal of platelet inhibition by exogenous platelets as a function of time and plasma level of prasugrel active metabolite in 28 normal volunteers administered a single 60-mg loading dose of prasugrel plus aspirin 325 mg. The methods should be similar to those described by Vilahur *et. al.,* 2007. J. Thromb Haemost 5:82.

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

   Final Protocol Submission: Received 09/29/2009
   Trial Completion Date: 08/2011
   Final Report Submission: 09/2011

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:

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**."

POSTMARKETING COMMITMENTS

We remind you of your agreement in your April 15, 2010 submission to the following post-marketing commitment:

1633 – 1 You agreed to have, on an interim basis, an acceptance criterion for the dissolution test of Q of (b)(4)% in 20 minutes for this formulation for one year. You also agreed to collect 15 minutes dissolution data for the remaining primary stability time points (18 and 24 months), and within 14 months of approval date submit these data to the FDA for re-evaluation and setting of the final dissolution acceptance criterion for your re-formulated product.

Submission Date: 06/2011

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**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Effient (prasugrel) was originally approved July 10, 2009. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. The proposed modification to the REMS consists of a revised Medication Guide as described above and also revised language in the timetable for submission of assessments of the REMS.

Your proposed modified REMS, submitted April 1, 2010, and appended to this letter, is approved. The communication plan and the dates in the timetable for submission of assessments of the REMS will remain the same as that approved on July 10, 2009. In addition, there are no changes to the REMS assessment plan described in our July 10, 2009, letter.

Prominently identify submissions containing 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:

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, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and 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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see 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.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA 22-307 for this drug product, not to this NDA. In the future, do not make submissions to this NDA except for the final printed labeling requested above.

If you have any questions, please call:

Alison Blaus
Regulatory Project Manager
(301) 796 - 1138

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22307	SUPPL-1	ELI LILLY AND CO	EFFIENT

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

/s/

ALISON L BLAUS
04/16/2010

NORMAN L STOCKBRIDGE
04/16/2010