

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-307

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-307

NDA APPROVAL

Eli Lilly and Company
Attention: Elizabeth C. Bearby, Pharm.D.
Director, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your new drug application (NDA) dated December 26, 2007, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Effient (prasugrel) 5 and 10 mg Tablets.

We acknowledge receipt of your submissions dated January 9, 15, 25, 28 and 30, February 4, 6, 19, 25 and 28, March 20 (two), 21, 24, 25 and 28, April 2, 7 (two), 14, 15, 17, 22 (two), 24 (two), 25, 28 and 30 (three), May 6, 9 (two), 10, 12 (two), 14, and 16, June 11 (two), 17, 20 (two) and 25 (two), July 22 and 30, August 8, 14, 19, 25 and 28, September 4, 11, 18, 22, 24 and 26, October 3 (two), 10 (two) and 23, November 4, 12, 13, 17 and 21, December 3, 5, 11, 12, 18 (two) and 23, 2008, and January 1, 5, 7, 15, 19, 20, 27 (two) and 29, February 6, 12, 13, 19 and 23, March 5, 10 (two), 11, 12, 13 and 23, April 24, May 4, 21 and 22, June 4, 10, 12, 13, and 25, July 8 (two), 9 (three), 2009.

This new drug application provides for the use of Effient (prasugrel) 5 and 10 mg Tablets for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI)
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI

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.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to enclosed labeling (text for the package insert, and Medication Guide). Upon receipt, we will transmit that version to the

National Library of Medicine for public dissemination. For administrative purposes, please designate this submission “**SPL for approved NDA 22-307.**”

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*.

Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 22-307.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROPRIETARY NAME

The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Cardiovascular and Renal Products do not object to the use of the proprietary name Effient for this product.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application. The studies needed to assess the value of Effient in acute coronary syndrome in children would be impossible to conduct because the disease does not exist in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct post-marketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

We have determined that an analysis of spontaneous post-marketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of major bleeding and a signal of a serious risk of increased incidence of malignancies.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a non-clinical or observational study) will be sufficient to assess this known risk of bleeding and signal of risk of increased malignancies. Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

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. Descriptive statistics should be reported.

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

Final Protocol Submission:	09/2009
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:	06/2008
Trial Completion Date:	12/2012
Final Report Submission:	01/2013

Submit the protocols to your IND, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a

safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any post-marketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We remind you of your post-marketing commitments in your submission dated July 10, 2009. These commitments are listed below:

3. You commit to develop a new formulation of the Effient (prasugrel) drug product that (b)(4). You commit to submit the data to support this new formulation as a supplemental new drug application (sNDA). The submission will provide information on the development, manufacture, control, and stability of the new formulation. In addition, you commit to develop a robust and sensitive method to quantify very low level (b)(4) in the reformulated product, and submit this information to the sNDA.

sNDA Submission Date:

(b)(4)

4. You commit to performing a clinical trial in the fasting and fed state, to compare the pharmacokinetics of single 60-mg doses of the marketed and new prasugrel formulations with respect to concentrations of the prasugrel active metabolite and effects on platelet inhibition.

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

Trial Completion Date: 08/2009

Final Report Submission: 12/2009

5. You commit to performing, in the presence and absence of a proton pump inhibitor, a clinical trial to compare the pharmacodynamics of single 60-mg doses of the marketed and new prasugrel formulations with respect to concentrations of the prasugrel active metabolite and effects on platelet inhibition.

We understand that the protocols for these trials have been submitted and the trial has been completed.

Final Report Submission: 12/2009

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.

Trial Completion Date: 12/2012

Final Report Submission: 01/2013

Submit clinical protocols to your IND 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, number of patients entered into each study. All submissions, including supplements, relating to these post-marketing study commitments should be prominently labeled “**Post-marketing Study Commitment Protocol**,” “**Post-marketing Study Commitment Final Report**,” or “**Post-marketing Study Commitment Correspondence**.”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on July 10, 2009, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, an implementation system, and a timetable for submission of assessments of the REMS.

The information needed for assessment (REMS Assessment Plan) should include the following data:

- Patients’ understanding of the serious risks of Effient (prasugrel)
- Patients’ understanding, via a patient survey, of the Medication Guides

- A report on periodic assessments of the distribution and dispensing of the Introductory Letter and Prescriber Brochure.
- A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
- A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address non-compliance.
- Prescribers' understanding, via a prescriber's survey, of the safety messages and adherence to the boxed warning.
- A description of specific measures that would be taken to increase awareness if surveys of healthcare prescribers indicate that prescriber awareness is not adequate.

You are expected to submit a detailed description of methodology and the instruments used in the prescriber and patient surveys. A complete description of survey protocols is to be submitted to FDA 90 days prior to conducting surveys. The survey protocol submission should include:

- The sample size and confidence interval associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of prescribers/patients surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- An explanation of controls used to minimize bias
- An explanation of controls used to compensate for the limitations associated with their methodology
- An explanation of what will be done with the resulting data from the surveys
- The survey instruments (questionnaires and/or moderator's guide).
- Any background information on testing survey questions and the correlation to the messages in the Medication Guide.

The requirements for assessments of an approved REMS also include, in 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. 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 updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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.

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

NDA 22-307 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 22-307
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 22-307
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

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

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

PRODUCT EXPIRATION

An expiration dating period of 18 month is granted for Effient tablets, 5 and 10 mg stored in bottles at 25°C (USP Controlled Room Temperature). Effient 10 mg tablets stored in blisters will have an expiration dating period of 12 months.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package inserts 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 www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

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
Suite 12B05
5600 Fishers Lane
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).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, please call:

Meg Pease-Fye, M.S., R.A.C.
Regulatory Project Manager
(301) 796 - 1130

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Final Product Labeling
REMS
Medication Guide
Introductory Letter
Prescriber’s Brochure

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

/s/

Robert Temple
7/10/2009 02:33:24 PM