MEMORANDUM OF TELECON

DATE: April 9, 2009

APPLICATION NUMBER: NDA 22-307

BETWEEN:

Name: John Towns and Joerg Pfeifer
Phone: (317) 276-4079
Representing: Eli Lilly and Company

AND

Name: Patrick Marroum, Biopharmaceutics Expert Reviewer, ONDQA
Kasturi Srinivichari, Pharmaceutical Assessment Lead, ONDQA
Sharmista Chatterjee, Chemistry/Manufacturing Sciences Reviewer, ONDQA
Rebecca McKnight, Project Manager, ONDQA

SUBJECT: To provide clarification to Eli Lilly (Lilly) on the following three items from the Agency's 04/03/09 correspondence:

1. Tablet form conversion for both 5 and 10 mg prasugrel tablets as measured by XRPD to be Not More Than — This recommendation is based on review of the stability data of batches manufactured with the proposed commercial controls that show form conversion did not exceed — en during storage at accelerated conditions for 6 months for most batches Moreover, the current limit of NMT — was set prior to the implementation of the recent stringent controls which allow manufacturing of prasugrel tablets with — — %). b(4)

   Eli Lilly Comments: Eli Lilly wished to submit data that supported tablet form conversion of Not More Than (NMT) — Of the — batches manufactured, one batch had form conversion greater than — The one batch that exceeded the limit was a challenge lot, and had form conversion of — b(4)

   Agency Response: Eli Lilly provided commercial scale-up data that supported tablet form conversion of NMT — . The Agency informed Eli Lilly that the form conversion limit of NMT — would not be changed.

2. Dissolution to be Q= — at 30 minutes. The rationale for this recommendation is based on data from the new dissolution method as provided in the December 18th, 2008 amendment. This acceptance criterion will minimize the probability of the release of batches with markedly different release characteristics that might result in bioinequivalent lots.

   Eli Lilly Comments: There were no additional comments.

3. An expiration dating period of — months for prasugrel hydrochloride tablets packaged in both bottles and blisters can be granted considering the limited bottle data provided.

b(4)

Eli Lilly Comments: Lilly requested to submit the 12-month stability data for bottles in order to seek expiry dating of —— months. The request for extended expiry is to ——

Agency Response: Lilly may submit the data for Agency review.

Rebecca McKnight
Regulatory Health Project Manager
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Rebecca A. McKnight
5/13/2009 03:18:31 PM
PROJECT MANAGER FOR QUALITY

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 14, 2009
To:	Norman Stockbridge, M.D., Ph.D., Director Division of Cardiovascular and Renal Products (DCRP)
Through:	Claudia Karwoski, Pharm.D., Acting Director Office of Surveillance and Epidemiology (OSE)
From:	OSE EFFIENT Risk Management Team: Scientific Lead: Gita Akhavan-Toyserkani, Pharm.D., MBA, Senior Drug Risk Management Analyst, DRISK Team Members: Marcia Britt, Ph.D., Regulatory Health Specialist, DRISK Mary Dempsey, Risk Management Program Coordinator, DRISK Kellie Taylor, Pharm.D., Safety Evaluator Team leader, DMEPA Tara Turner, Pharm.D., Safety Evaluator, DMEPA Mary Willy, Ph.D., Senior Risk Management Analyst Acting Team Leader, DRISK Zarna Patel, PharmD, Division of Drug Marketing, Advertising and Communication (DDMAC) Michelle Sarafik, PharmD DDMAC
Subject:	Review of proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	EFFIENT ™ (prasugrel hydrochloride) Tablets 5mg and 10 mg
Submission Number:	0000
Application Type/Number:	NDA 22-307
Applicant/Sponsor:	Eli Lilly and Company (Lilly)
OSE RCM #:	2008-227

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1 INTRODUCTION

This review follows a request from the Division of Cardiovascular and Renal Drug Products (DCRP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Effient (prasugrel HCL).

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a 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)). Given the increased risk of serious bleeding events with prasugrel compared to clopidogrel, OSE and DCRP have determined that a REMS is necessary for prasugrel to ensure that the benefits of the drug outweigh the risks of major bleeding. These risks may be mitigated by avoiding prescribing prasugrel to certain patient populations (e.g., history of previous stroke or TIA) and by informing patients to contact their physician if they experience bleeding. The elements of the REMS will consist of a Medication Guide, a Communication Plan, and a timetable for the submission of assessments of the REMS.

2 BACKGROUND

Effient (prasugrel HCL), a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered prodrug whose active metabolite irreversibly inhibits platelet activation and aggregation. The proposed indication for prasugrel is for the reduction of acute myocardial infarction in acute coronary syndrome (ACS) patients with unstable angina or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI) and patients with ST-segment elevation myocardial infraction (STEMI)who are managed with primary or delayed PCI.

As described in more detail in our October 2008 review, the safety concerns for prasugrel include increased risk of bleeding, the potential risk of tumor stimulation, and the risks associated with an unstable formulation. The formulation issue is an uncertainty that cannot be managed through risk mitigation strategies and will not be addressed in this review. The Cardiovascular and Renal Drugs Advisory Committee met on February 3, 2009 to discuss prasugrel for the treatment of ACS. The potential risk of tumor stimulation was also discussed and the Committee opined that the signal was not strong; therefore, the Advisory Committee recommended describing the potential risk of tumor stimulation only in the Adverse Event section of the labeling. The increased risk of serious bleeding is most concerning and is being addressed by including the information in a Boxed Warning.

The Agency also determined prasugrel requires a REMS to ensure the benefits of the drug outweigh the risk of bleeding. The Sponsor submitted a proposed REMS for Effient on January 19, 2008 which consisted of a Medication Guide and a timetable for assessments. On January 30, 2009, the Sponsor was notified that a Medication Guide-only REMS did not adequately warn healthcare providers about the increased risk of bleeding, particularly fatal bleeding in certain patient populations. The Sponsor was

informed that an updated REMS was required which included a Medication Guide, Communication Plan, and a timetable for submission of assessments of the REMS. The Sponsor submitted a revised REMS proposal on March 12, 2009. The current proposed REMS addresses the risk of bleeding and the need for appropriate patient selection to minimize this risk.

3 MATERIALS REVIEWED

- DDMAC comments on REMS for Effient (NDA 22-307) dated March 17, 2009.
- Modified Proposed REMS for Effient (NDA 22-307) dated March 12, 2009.
- Regulatory Response to FDA Request to Change Carton and Labels for Effient (NDA 22-307, Sequence 0095) dated March 11, 2009.
- Proposed REMS for Effient (NDA 22-307) dated January 19, 2009.
- OSE review of Risk Management for Effient (NDA 22-307) dated October 7, 2008.
- Proposed Labeling for Effient (NDA 22-307) dated December 26, 2008.
- DRISK Review of Patient Labeling (NDA 22-307) dated April 3, 2009

4 PROPOSED REMS

4.1 GOALS

The Sponsor has proposed the following goal:

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b(4)

The proposed REMS goal is vague and does not target safety-related health outcomes related to safety risks. The primary purpose for requiring a REMS for Effient is to communicate and educate about the serious risks associated with Effient, specifically the risk of major bleeding.

We recommend that the sponsor revise the proposed goal to target the achievement of particular health outcomes related to safety risks and list specific objectives for achieving this goal. An example is provided below:

> *Goal: To mitigate the serious risk of bleeding associated with the use of EFFIENT by:*
>
> 1. *Informing patients of the serious risks associated with EFFIENT, particularly the increased risk of bleeding.*
> 2. *Communicating to prescribers about the increased risk of bleeding associated with EFFIENT and the need for appropriate patient selection.*

4.2 REMS ELEMENTS

4.2.1 Medication Guide

The sponsor has proposed to supply Medication Guides that will be dispensed with each prescription for Effient. The Medication Guide was submitted to the FDA on November 12, 2008 and has been reviewed; comments on the Medication Guide have been provided in a separate DRISK review[1].

The Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) reviewed the labeling. On March 06, 2009, DMEPA requested the Sponsor affix one Medication Guide to each commercial retail bottle, enclose several Medication Guides in each carton, locate the Medication Guide statement on the principal display panel rather than the side panel, and revise the language on the carton and container labels. The Sponsor submitted a response and agreed to the following[2]:

- The U.S. Package Insert (USPI) and Medication Guide will be printed on the same paper, separated by a perforation between the two documents, and glued to each bottle.
- A USPI and multiple Medication Guides will be enclosed in each carton of blister packs.
- The location of the medication Guide will be on the front panel.
- The language of the front panel will be revised to state "Dispense accompanying Medication Guide to each patient."
- The language on the carton label will be revised to state "Dispense the enclosed Medication Guide to each patient."

The Sponsor will provide a Medication Guide with Effient for dispensing with each prescription. For outpatient pharmacy dispensing, each bottle will have the Medication Guide affixed and pharmacists will be instructed to dispense Effient in the original container. Hospital packs, which are intended for initiate dosing, will contain sufficient copies of the Medication Guide so that one can be given to each patient. As such the distribution and dispensing of the Medication Guide is acceptable and will be in accordance with the requirements of 21 CFR 208.24.

4.2.2 Communication Plan

As Lilly has stated in their proposal, the Dear Health Care Provider (DHCP) Letter and Prescriber Brochure will inform prescribers of the serious risk of bleeding associated with the use of Effient.This element of the REMS is not intended to continue over the lifetime of the product; it will function only to disseminate appropriate safety information to healthcare providers as they become familiar with a new thienopyridine, to include:

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[1] DRISK Review of Patient Labeling (NDA 22-307) dated April 3, 2009

[2] DMEPA aware of the response and concurred with the changes on April 8, 2009

- the serious risk of bleeding associated with Effient
- appropriate patient selection (emphasizing patients in whom Effient should not be used)

4.2.2.1 Dear Healthcare Provider Letter

The sponsor will disseminate the DHCP Letter approximately 30-45 days after approval. The letter will be sent to health care providers likely to initiate, continue, or manage patients on Effient therapy. This will include interventional cardiologists, clinical cardiologists, primary care and internal medicine physicians, pharmacists, and other specialists commonly involved in decisions related to continuation or discontinuation of oral antiplatelet medications for acute coronary syndrome patients managed with PCI (e.g. gastroenterologists, cardiac surgeons, general and oral surgeons). The Sponsor plans to write a separate letter for each specialty group.

The purpose of this letter is to inform healthcare providers of the serious risk of bleeding associated with Effient and the importance of appropriate use and appropriate patient selection. Therefore, we do not believe it is necessary that a separate letter is written for each group of healthcare providers as the information to be provided appears to be similar regardless of their specialty.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the DHCP letter and reminds the sponsor that REMS materials are not appropriate for use in a promotional manner. The DHCP Letter has been revised to remove any promotional claims. Please see attached DHCP Letter for additional track changes (Appendix C).

4.2.2.2 Prescriber Brochure

The Sponsor has proposed a prescriber brochure which presents complete information from the labeling including efficacy, pharmacology, clinical trial overview, as well as safety information. The proposed prescriber brochure does not focus on communicating key safety messages, guidance on proper patient selection and providing information on bleeding risks and management.

The purpose of the prescriber brochure is to emphasize the key safety messages and highlight the information on the risk of bleeding described in the labeling. We recommend the Sponsor revise the prescriber brochure (see Appendix C).

During the firs[redacted]after launch, the sponsor has proposed leaving the prescriber brochure with potential prescribers upon completion of the initial presentation of the product by a representative of the sponsor. These prescribers will include all prescribing healthcare providers called on by sponsor representatives such as interventional cardiologists, clinical cardiologists, emergency medicine physicians, internal medicine and primary care physicians, and other physician specialties involved in the care of ACS patients managed with PCI (e.g. surgeons, gastroenterologists). b(4)

4.2.3 Elements to Assure Safe Use

The REMS for Effient does not include Elements to Assure Safe Use.

4.2.4 Implementation System

Because the REMS for Effient does not include any Elements to Assure Safe Use, an implementation system is not required.

4.2.5 Assessment of the REMS

The sponsor proposes to submit a REMS Assessment to FDA at the following acceptable timetables:

1st FDAAA Assessment:	18 months after REMS approval
2nd FDAAA Assessment:	3 years after REMS approval

The sponsor will need to include an assessment within the 7th year following the approval of the REMS. We recommend the sponsor submit assessments to FDA within 60 days of the noted time intervals.

The Sponsor will ascertain patients' understanding of the Medication Guide and assess the distribution and dispensing of the DHCP letter, prescriber brochure, and the Medication Guide. Lilly will also need to assess whether prescribers understand the safety messages and are adhering to the boxed warning. The Sponsor should submit to FDA for review a detailed plan to evaluate the prescribers' and patients' understanding about the safe use of Prasugrel 60 days prior to conducting the assessment. If the Sponsor plans to do this by survey, the submission should include, at a minimum:

- 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
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with their methodology
- Explain 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.

Information needed for assessments (REMS Assessment Plan) is not required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS supporting document.

5 CONCLUSION & RECOMMENDATIONS

We have completed our review of the most recent proposed REMS as described in the Sponsor's submission of March 12, 2009. We have the following recommendations and comments:

Comments and recommendations for the Sponsor

1. We recommend the goal be revised to target the achievement of particular health outcomes related to safety risks and list specific objectives for achieving this goal. An example is provided below:

   Goal: To mitigate the serious risk of bleeding associated with the use of EFFIENT by:

   - *Informing patients of the serious risks associated with EFFIENT, particularly the increased risk of bleeding.*
   - *Communicating to prescribers about the increased risk of bleeding associated with EFFIENT and the need for appropriate patient selection.*

2. The timetable for submission of assessments will need to include an assessment within the 7th year following the approval of the REMS.
3. Please see attached REMS document for additional track changes (Appendix A).
4. Revise the proposed DHCP Letter as outlined in Appendix B. We do not believe it is necessary that a separate letter is written for each group of healthcare providers as the information to be provided appears to be similar regardless of their specialty.
5. Regarding the Prescriber Brochure:
   a. The proposed prescriber brochure does not focus on communicating key safety messages, guidance on proper patient selection, and providing information on bleeding risks and management. In Appendix C, we have provided the key safety information that needs to be the focus of the Prescriber Brochure.
   b. The prescriber brochure must be disseminated to all new prescribers for a period for 2 years. This should be reflected in the proposed REMS.
6. Your REMS Assessment Plan (e.g., information needed for assessments) should include a plan to assess whether prescribers understand the safety messages and are adhering to the boxed warning.
7. Submit to FDA the methodology that will be used to assess prescribers' and patients' understanding about the safe use of Prasugrel 60 days prior to conducting the assessment. If the Sponsor plans to do this by survey, the submission should include, at a minimum:
   a. The sample size and confidence interval associated with that sample size
   b. How the sample will be determined (selection criteria)
   c. The expected number of prescribers/patients surveyed
   d. How the participants will be recruited
   e. How and how often the surveys will be administered
   f. Explain controls used to minimize bias
   g. Explain controls used to compensate for the limitations associated with their methodology

h. Explain what will be done with the resulting data from the surveys
i. The survey instruments (questionnaires and/or moderator's guide).
j. Any background information on testing survey questions and the correlation to the messages in the Medication Guide.

8. Submit the amended REMS, REMS Supporting Document, and appended materials for review incorporating the comments above and in the appended documents.

Comments and recommendations for DCRP

- The comments and recommendations for the sponsor (above) are considered preliminary comments.
- The information needed to assess the effectiveness of the REMS (REMS Assessment Plan) will need to be incorporated into the approval letter.

12 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

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