DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-307

DISCIPLINE REVIEW LETTER

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

During our review of the Chemistry, Manufacturing and Controls section of your submission, we have identified the following deficiencies:

We have major concerns regarding the observed conversion of prasugrel HCl salt to free base in the drug product, as this can [redacted] Based on the information presented to date in your NDA, we recommend elimination of form conversion. Please propose an approach to achieve this goal, [redacted] b(4)

Our specific concerns are:

1. Analysis by the agency's clinical pharmacology reviewer of the data from study TACS showed that high (70%), intermediate (58%) and low conversion tablets (5%) are bio-inequivalent in healthy subjects pre-treated with a proton pump inhibitor, contrary to your interpretation. The difference in plasma levels also translated into clinically significant differences in platelet aggregation.

2. [redacted] b(4)

3.

Additional Questions:

[redacted] b(4)

Provide a comprehensive analysis of all such [redacted] that could be present in the drug substance or drug product addressing the following issues: b(4)

a. Is the impurity detected under normal storage conditions, and if so, at what levels?
b. Safety based on the threshold of toxicological concern as defined in the EMEA Guideline on genotoxic impurities.
c. Justification for not routinely monitoring these compounds in release and stability testing.

2. For the XRPD method:

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c. Clarify whether salt/ base conversion occurs during [redacted]
d. Clarify whether the [redacted] for the 5-mg tablets is the same one as for the 10-mg tablets. Provide full validation for the 5-mg tablets also.
e. Provide data to demonstrate whether the PLS model and the sample prediction could be improved (*e.g.*, data pre-treatment). The current acceptance criteria for precision and accuracy may not be sufficient, especially at a low level of form conversion.
f. Provide validation for the LOD and LOQ.

3. Based on the review of the information given in response to the dissolution development in the previous information request letter, your proposed dissolution specification does not discriminate changes in formulation and manufacturing process. We recommend that you revise the dissolution method (*e.g.*, higher pH dissolution media), and provide data to demonstrate that the revised dissolution specification has discriminatory power for changes in formulation and manufacturing process, such as variations in excipients, formulation changes beyond robustness ranges, changes in process parameters beyond PAR, etc…

4. For the container/closure system, clarify whether the bottle sizes are the same for [redacted] and 30-count presentations, and provide bottle sizes for each presentation. b(4)

5. Provide data to justify that the amount of [redacted] generated in the drug product poses no safety concern throughout the shelf-life.

6. Provide details about the sampling method at [redacted]

7. Provide data to support the [redacted] for the excipients as given in table 3.2.P.4.1.1-2, since it was concluded during the formulation development study that the formulation [redacted] b(4)

8. Update the excipient specification to include the LOD specification as given in response to the IR letter as additional criteria for compendial excipients. Provide details about the [redacted] that was used to derive the LOD specifications for the excipients.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call:

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

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

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

/s/

Norman Stockbridge
4/9/2008 03:45:46 PM

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Transmitted via e-mail:	Elizabeth Bearby, Ph.D.
Company Name:	Eli Lilly
Phone:	(317) 276-1203
Subject:	**Minutes of a teleconference w/FDA on March 17, 2008 NDA 22-307**
Date:	April 9, 2008
Pages including this sheet:	8

From:	**Meg Pease-Fye, M.S.**
Phone:	**301-796-1130**
Fax:	**301-796-9838**
E-mail:	**meg.peasefye@fda.hhs.gov**

Please note that you are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

Teleconference with Eli Lilly

Application Number:	NDA 22-308 IND 63,449
Sponsor:	Eli Lilly
Drug:	Effient (Prasugrel)
Type of Meeting:	Agency requested
Meeting Date:	March 17, 2008
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Recorder:	Meg Pease-Fye, M.S.

List of Attendees:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D	Division Director
Ellis Unger, M.D.	Deputy Division Director
Thomas Marciniak, M.D.	Team Leader, Medical Officers
Shari Targum, M.D.	Team Leader, Medical Officers
Karen Hicks, M.D.	Medical Officer
Albert DeFelice, Ph.D.	Team Leader, Pharmacology
Charles Resnick, Ph.D.	Team Leader, Pharmacology
Belay Tesfamariam, Ph.D.	Pharmacology Reviewer
Patricia Harlow, Ph.D.	Pharmacology Reviewer
John Koerner, Ph.D.	Pharmacology Reviewer
Edward Fromm, R. Ph.	Chief, Project Management Staff
Meg Pease-Fye, M.S.	Regulatory Health Project Manager
Alison Blaus	Regulatory Health Project Manager

Eli Lilly

Cheryl Anderson, Pharm.D.	Director, Regulatory
Norma Ascroft, Pharm.D.	Scientific Director, Regulatory
Elizabeth Bearby, Pharm.D.	Scientific Director, Regulatory
[redacted]	Advisor, Global Product Safety
	Advisor, Medical
William Macias, M.D.	Director, Medical
Peter, Morrow M.S.	Associate Director, Regulatory
Jeff Riesmeyer, M.D.	Fellow, Medical
J. Anthony Ware, M.D.	Cardiovascular Platform Leader
Govinda Weerakkody, Ph.D.	Advisor, Statistician
Joseph Wernicke, M.D.	Fellow, Global Product Safety

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Daiichi Sankyo Co., Ltd:

Rich Cuprys, M.S.	Regulatory
Allen Feldman, M.D.	Vice President, Risk Management
Howard Hoffman, M.D.	Regulatory
Helene Petitjean, M.D.	Associate Director, Clinical Development
Francis Plat	Clinical Development

BACKGROUND

Lilly submitted their NDA containing data from their study, H7T-MC-TAAL, TRITON-TIMI 38 on December 26, 2008 The Agency requested this meeting in order to convey information required for review. Lilly submitted the following slides summarizing non-clinical carcinogenicity studies, and the clinical data supporting the reporting of neoplasia in the TRITON study:

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2 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

_____ Personal Privacy (b6)

b(4)

DISCUSSION

After introductions, Dr. Marciniak began by stating that the review team has concerns regarding carcinogenicity findings in the pre-clinical data, as well as excess malignancy in the clinical study. Although not all are statistically significant, there appears to be in the mouse carcinogenicity study:

- more liver adenomas and cancers in female mice

- a trend in uterine neoplasm, supported by a similar trend in rats
- a trend in intestinal carcinomas
- a trend in lung cancers

When Lilly responded that only the hepatocellular adenoma was statistically significant, Dr. Marciniak responded that the data all show unfavorable trends for prasugrel. Lilly stated that the mechanism of action explains the liver tumors and Dr. Marciniak opined that this does not necessarily explain away the problems.

Regarding the human neoplasms, the Division noted a general increase in most solid cancers excluding non-melanoma skin cancers. Lilly asked why the Division had excluded skin cancers in their findings. The Division responded that non-melanoma skin cancers were considered treatable and not considered as threatening as other solid tumors. The Division found problems with the way the cancers were coded. Dr. Stockbridge suggested that Lilly submit to the Agency the patients IDs of the problems they located and the Division will request the ones not found on this list. Lilly agreed to do this.

Dr. Marciniak added that the Division is still missing the verbatim adverse events. He stated that the terms he received were labeled "AE Modified" and that these are identical to the "AE Term," neither of which matched what the investigator originally wrote on the case report forms. The Division still wished to see what the investigator wrote at the site. Lilly explained that what was provided was the final AE term approved by the investigator after the data clarification process. There was general discussion about the requested data and how to obtain it. Lilly was concerned about a potential diagnostic bias toward bleeding complications (citing slides 4, 5, 6 and 7 which summarizes data provided in the NDA), noting that they focused on diagnosing new neoplasms (citing slide 15, identifying bleeds and non-bleeds by cancers). The population was then divided by hemorrhagic versus non-hemorrhagic bleeds that occurred prior to cancer diagnosis. The Division had considered this already and asked how the antecedent bleed rates compared and asked if Lilly was matching the site of the bleed to the neoplasm. Dr. Stockbridge recommended that we reconcile our interpretation of the data and send Lilly a list. Dr. Marciniak requested that Lilly submit the exact datasets and classification used to generate the Powerpoint slides, and match them for bleeds and events.

ACTION ITEMS
Lilly will forward to the Division the list of patient IDs of subjects with cancers within one week.

Date Minutes Drafted: April 3, 2008
Date Minutes Finalized: April 7, 2008

Recorder: *{See appended electronic signature page}*
Meg Pease-Fye, M.S.

Chair Concurrence: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Reviewed:
T. Marciniak 04.03.08
E. Unger 04.04.08
N. Stockbridge 04.04.08

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

/s/

Norman Stockbridge
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Margaret Pease-Fye
4/7/2008 09:27:24 AM