DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-307

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

Dear Dr. Bearby:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for prasugrel hydrochloride Tablets.

We also refer to your October 16, 2008, correspondence, received October 23, 2008, requesting a meeting to discuss the review issues for prasugrel.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: November 4, 2008
Time: 1:00pm – 2:00pm
Location: FDA - White Oak Campus, Building 22, Rm. 1421

CDER participants:

Office of New Drug Quality Assessment
Moheb Nasr, Office Director
Blair Fraser, Division Director
Kasturi Srinivasachar, Pharmaceutical Assessment Lead
Patrick Marroum, Biopharm Reviewer
Sharmista Chatterjee, Chemistry/Manufacturing Sciences Reviewer
Rebecca McKnight, Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at <rebecca.mcknight@fda.hhs.gov> so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards the following number to request an escort to the conference room: 301-796-1765.

If you have any questions, call me at (301) 796-1765.

Sincerely,

{See appended electronic signature page}

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

11/3/2008 01:02:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Brian E. Wagner, Pharm.D., Associate Director
US Regulatory Affairs
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285

RE: NDA 22-307
Effient™ (prasugrel)
MACMIS # 16862

Dear Dr. Wagner:

This letter concerns Eli Lilly and Company's (Lilly's) October 16, 2008, correspondence regarding the placement of an advertisement for Efficient™ (prasugrel) in the program book at the Academy of Managed Care Pharmacy (AMCP) 2008 Educational Conference held in Kansas City, Missouri from October 14th to October 18th, 2008. We acknowledge that in response to the promotional activity Lilly:

- Removed the branded advertisement from the AMCP website.
- Closed the AMCP exhibit booth during the meeting.
- Initiated work with AMCP to physically remove the exhibit booth.
- Instructed Lilly personnel to refer questions regarding Effient to Lilly's medical information department and acknowledge that Effient is still under FDA review.

In light of the actions taken, DDMAC considers this matter closed, but reminds you of your continuing obligation to ensure that all of your promotional materials comply with each applicable requirement of the Act and FDA implementing regulations.

If you have any comments or questions, please contact the undersigned at the 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, or

MACMIS # 16862 in addition to the NDA number. We remind you that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Lisa M. Hubbard, R.Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Lisa Hubbard
10/28/2008 10:35:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-307

INFORMATION REQUEST 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)(1) of the Federal Food, Drug, and Cosmetic Act for Effient (prasugrel) 10 mg Tablets.

We also refer to your submission dated June 20, 2008.

We have reviewed the Pharmacology/Toxicology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Two-year chronic bioassays in two rodent species are the current "gold standard" for assessing carcinogenicity of new drugs as well as other products. Results from these studies have been shown to identify virtually all known human carcinogens (Huff, 1994). Prasugrel was adequately tested in chronic bioassays using both rats and mice. When tested up to 70 times the clinical exposure, prasugrel was negative in a 2-year rat carcinogenicity study. Statistically significant increases in hepatocellular adenomas were seen in a mouse 2-year carcinogenicity study at a dose 250-fold the clinical exposure. These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk. Other data also add to the weight of evidence that prasugrel is not carcinogenic.

1) Prasugrel was tested and found to be without activity in an ICH-compliant battery of genetic toxicology tests including a bacterial mutation assay, chromosomal aberration assay in cultured mammalian cells, and *in vivo* chromosomal damage assay in mice.
2) The normally high frequencies of spontaneous tumors at the end of two years in rodents were similar in treated and control groups suggesting that prasugrel did not cause tumor promotion or progression.
3) *In silico* structure activity assessment suggests that prasugrel is not carcinogenic.

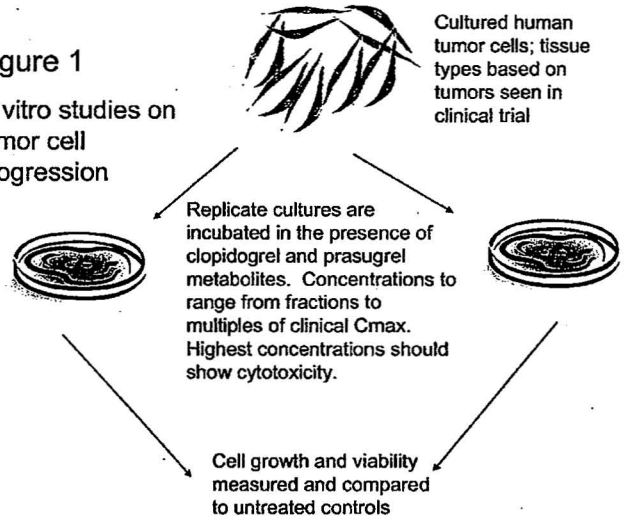
Based on classical definitions, the weight-of-evidence suggests that prasugrel is neither a "complete carcinogen" nor a "tumor promoter." The relatively short duration of the prasugrel clinical trial argues against *de novo* induction of the cancers identified in this study;

even the shortest latency periods are significantly longer. If the excess in cancers seen in the clinical trial is related to drug treatment, one would have to hypothesize that prasugrel accelerates tumor progression, *i.e.,* preexisting tumors are stimulated to grow and become clinically recognizable. Since the excesses were seen for a wide variety of tumors, a plausible explanation might be a stimulation of angiogenesis. It is perhaps noteworthy that there were differences only in solid tumors and not in hematologic cancers.

We ask you to perform *in vitro* (figure 1) and *in vivo* (figure 2) studies to help allay concerns regarding potential for drug-induced tumor progression. These are straightforward studies using established human tumor cell lines grown both in culture and in congenitally immunodeficient "nude" mice. These studies are schematically described in the attached figures. Both the active and major human metabolites (R-138727 and R-106583) of prasugrel should be tested in these model systems. Clopidogrel is similarly metabolized to its active form, although these synthesized metabolites may not be available to you.

Figure 1

In vitro studies on tumor cell progression



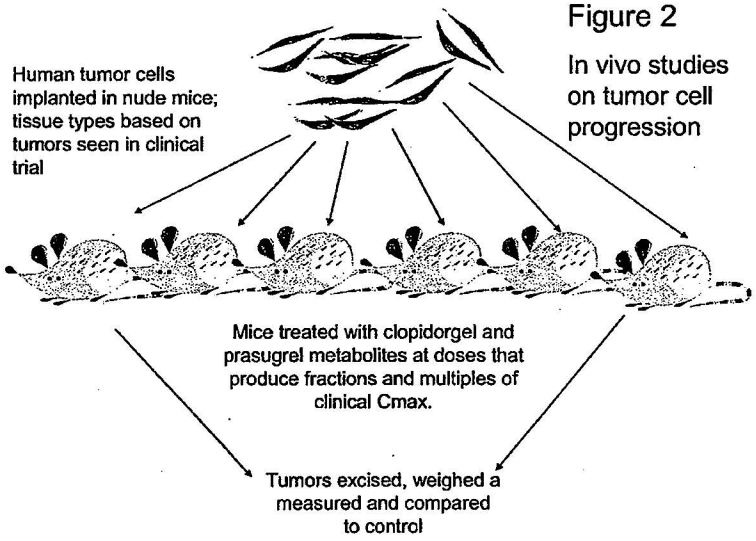


Figure 2

In vivo studies on tumor cell progression

The second reference (Zhang et al.) may identify a possible positive control for use in these studies.

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

Reference:

[1]Huff, J.E. (1994) Chemicals causally associated with cancers in humans and in laboratory animals: A perfect concordance. In *Carcinogenesis* (M.P. Waalkes and J.M. Ward, Eds.) pp. 25-37 Raven Press, New York.

[2]Zhang, H., et. al., J Biol Chem. 2007 May 25;282(21):15541-9. Epub 2007 Apr 12. Lysophosphatidic acid facilitates proliferation of colon cancer cells via induction of Krüppel-like factor 5.

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/s/

Norman Stockbridge
10/17/2008 03:48:52 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: August 25, 2008 **Date Consulted:** August 21, 2008

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Cardiovascular and Renal Products (DCRP)

Drug: Effient (prasugrel) Tablets; NDA 22-307

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Effient labeling.

Consult Question: Please review the Pregnancy and Nursing Mothers subsections of labeling.

INTRODUCTION

On December 26, 2007, Eli Lilly and Company submitted a new drug application (NDA 22-307) to the Division of Cardiovascular and Renal Products (DCRP) for Effient (prasugrel hydrochloride). The sponsors proposed indication for Effient is for the reduction of cardiovascular events in patients with Acute Coronary Syndromes including unstable angina or non ST segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI), or ST segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

On August 21, 2008, the Safety Endpoints and Labeling Development (SEALD) Team requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of Effient labeling. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Effient labeling.

BACKGROUND

The Maternal Health Team (MHT) and the Safety Endpoints and Labeling Development (SEALD) Team have been working together to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Effient labeling.

SUMBMITTED MATERIAL

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

8.1 Pregnancy

b(4)

b(4)

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

8.1 Pregnancy
Pregnancy Category B

b(4)

b(5)

8.3 Nursing Mothers

b(4)

b(5)

b(4)

b(5)

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Effient is provided on pages 3-4 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A –
Track Changes Version of Labeling

14 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Chardae Araojo
9/8/2008 10:38:46 AM
CSO

Karen Feibus
9/16/2008 05:03:13 PM
MEDICAL OFFICER

Lisa Mathis
9/18/2008 09:08:57 PM
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