MEMORANDUM

To: **Meg Pease-Fye, MS**
Division of Cardiovascular and Renal Products

From: **Iris Masucci, PharmD, BCPS**
for Study Endpoints and Label Development (SEALD) Team, OND

Date: **August 28, 2008**

Re: **Comments on draft labeling for Effient (prasugrel)**
NDA 22-307

We have reviewed the proposed label for Effient (FDA version dated 8/14/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

13 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

X Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Iris Masucci
9/4/2008 09:56:08 AM
DDMAC REVIEWER

Laurie Burke
9/4/2008 12:18:06 PM
INTERDISCIPLINARY

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-307

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.

On June 20, 2008, we received your major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 26, 2008.

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}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Fortney
6/24/2008 10:06:00 AM
Signing for Edward Fromm

MEMORANDUM

To: Meg Pease-Fye, Regulatory Health Project Manager
Division of Cardiovascular and Renal Products

From: Lisa Hubbard, R.Ph.
Senior Regulatory Review Officer
DDMAC, HFD-42

Date: June 13, 2008

Re: Comments on draft labeling:
NDA 22-307
Effient (prasugrel) Tablets

DDMAC has reviewed the proposed package insert (PI) for NDA 22-307, Effient (prasugrel) Tablets and offers the following comments with regard to promotional considerations. This review is based on the proposed PI submitted to the EDR upon submission of the original application, and concerns only promotional considerations associated with the proposed PI.

Section 5.2 Risk of Bleeding

The proposed PI presents the following statement, "[redacted]." We note that this statement may offer a marketing advantage over another marketed thienopyridine. Please confirm that you consider this statement acceptable.

Section 8.8 Hepatic Impairment b(4)

This section of the proposed PI presents the statement, "No dosage adjustment is necessary in subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B)...[redacted] (emphasis added) Please consider presenting the emphasized risk first in this section in order to prevent minimization of these risks in a promotional context and the PI.

Section 11 DESCRIPTION

This section of the proposed PI presents the phrase, "EFFIENT...[redacted] inhibitor of platelet activation." (emphasis added) The emphasized term appears promotional in tone particularly in light of the language used in the PIs for other thienopyridines. Please confirm that the proposed term is essential or please consider eliminating the term. b(4)

Section 12.2 Pharmacodynamics

This section of the proposed PI presents the statement, '[redacted]' This statement appears promotional in tone. We note that no such description is included in the PIs for other thienopyridines. Please confirm that this statement is instructive to the healthcare provider and essential. Alternatively, please consider eliminating the statement as such language could be misleading within a promotional context. Similarly, this section of the proposed PI includes a discussion and figure, (Figure 1) describing '[redacted]' variability in terms of inhibition of platelet aggregation. Please confirm that this presentation is essential and instructive to the healthcare provider, as it may be used in a misleading manner within a promotional context. We note that the PIs for other thienopyridines do not contain such extensive presentations within the pharmacodynamics sections.

b(4)

DDMAC has no further comments at this time.

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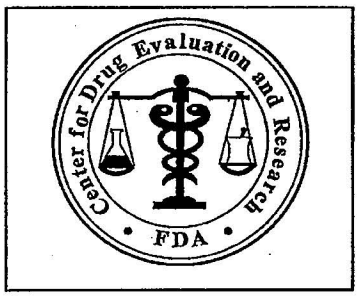
/s/

Lisa Hubbard
6/13/2008 10:38:50 AM
DDMAC REVIEWER



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Office of Surveillance and Epidemiology
Division of Drug Risk Evaluation

Date:	June 13, 2008
To:	Norman Stockbridge, M.D., Director, Division of Cardiovascular and Renal Products (DCRP)
Through:	Solomon Iyasu, M.D., M.P.H. Director, Division of Epidemiology Drug Risk Evaluation Office of Surveillance and Epidemiology (OSE)
From:	Allen Brinker, M.D., M.S., Epidemiology Team Leader
Subject:	Team Leader covering memorandum for Division of Epidemiology review of cancer and prasugrel by Diane Wysowski, Ph.D..
Drug Name(s):	prasugrel ("Effient")
Submission Number:	
Application Type/Number:	NDA 22-307
Applicant/sponsor:	Eli Lilly / Daiichi-Sankyo
OSE RCM #:	2008-750

This brief covering memorandum is written in association with and in support of a review of cancer with prasugrel by Diane Wysowski, Ph.D. and includes 4 discrete sections.

1. Regulatory Framework and Recommendations

Without advancing an opinion on absolute approvability, Dr. Wysowski recommends substantial more analysis and review of the TRITON clinical database "**before**" marketing. Because this recommendation appears to touch on the area of approvability, it is important to explicitly state that Dr. Wysowski's recommendation is fully supported by her team leader. To this end, I support Dr. Wysowski recommendations that outline specific analyses that should be performed by the sponsor and then submitted to the Agency for review (to include Dr. Wysowski or OSE representative) before general marketing.

2. Potential Presugrel Registry

With interest in Question 1 within the DCRP consult request, "In addition to the recommendations made by Oncology which include establishment of a registry by the sponsor…", Dr. Wysowski notes many limitations to a registry under Section 3.3 of her review. In addition to these, this reviewer would add *hierarchy of evidence*: an important safety signal that is identified in the setting of an RCT should not be tested in an observational setting like a registry but in a setting of equal or superior internal validity (e.g., another RCT).

3. Expected Major Clinical Outcomes

In addition to Dr. Wysowski's thoughtful review, which was almost solely focused on safety, her team leader believes it appropriate to further consider the potential population benefits afforded by prasugrel based on the large TRITON trial. With interest in the risk for incident cancer as noted in Dr. Marciniak's review, with up to 15 months of therapy on each arm, 104 incident cancers were recorded among 6,696 patients randomized to prasugrel verses 69 among 6,682 patients randomized to clopidogrel (1.56% versus 1.03%; $p = 0.007$). In contrast and based on the published results, 12.1% of patients with the trial randomized to clopidogrel experienced the primary composite endpoint of cardiovascular death versus 9.9% of patients randomized to prasugrel ($P < 0.001$).[1] However, the difference in deaths from any cause was not as impressive,

3.0% for patients randomized to plasurgrel versus 3.2% for patients randomized to clopidogrel (RR=0.95; 95% CI 0.78-1.16). The difference in these two metrics, a significant protective effect in a subset of deaths with a limited – and perhaps under-powered – effect in all deaths, should be a prime focus for the apparent effectiveness of this agent in any recipient population. In further calculations the latter metric, all-cause mortality, is advanced instead of cause-specific mortality based on the premise that death in the absolute is prioritized over the manner of death. Furthermore, although the difference in all cause mortality between prasugrel and clopidogrel was not statistically significant, for regulatory purposes the observed point estimates of 3.2% and 3.0%, respectively, represents the best estimate of that metric available at this time.

On their own, two of the metrics included above can be extrapolated as number needed to treat (NNT) and number needed to harm (NNH).[2] These epidemiological measures can be calculated from data that offer an option between two treatment / exposure regimens and indicate 1) how many people need to be treated with one agent in lieu of another in order to **prevent** one additional detrimental outcome (NNT) or 2) how many people need to be treated with one agent in lieu of another in order to **cause** one additional detrimental outcome (NNH). Both measures are based on the reciprocal of the absolute risk reduction. It should be stressed that, by their nature, NNT/NNH represent generalizations from trials into the population at large. If there are unique entry or exclusion criteria for a trial (e.g., TRITON), then the numbers generated in NNT/NNH calculations may not be generalizable to the general population.

In terms of effectiveness (NNT), the reciprocal of the absolute difference in all-cause mortality observed in TRITON (3.2% - 3.0% = 0.2%) of ~500 suggests that one additional life will be saved (or one additional death prevented) over 15 months of therapy with every 500 individuals assigned to treatment with prasugrel versus clopidogrel. However, in terms of safety (NNH), the reciprocal of the absolute difference in incident cancer observed in TRITON (1.56%-1.03% = 0.53%) of ~190 suggests that one additional incident cancer will be caused over 15 months of therapy with every 190 individuals assigned to treatment with prasugrel versus clopidogrel. These numbers can be compared as follows:

If the results of TRITON are generalizable to the population at large (including the point estimate for all cause mortality), then:

For every 500 patients exposed to prasugrel for up to 15 months, there is an expectation for one prevented death and 2.6 additional cancers to be observed over treatment with clopidogrel; or

For every 500 patients exposed to clopidogrel up to 15 months, there is an expectation for one additional death but 2.6 fewer cancers to be observed over treatment with prasugrel.

4. Recommendation for an Advisory Committee

In summary and in consideration of the points raised herein, this reviewer considers it prudent to present the body of current and pending FDA reviews (and analyses) to an FDA Advisory Committee prior to any regulatory action that would result in general marketing in the near term. As noted immediately above under point 3, presently available data suggest that there is a benefit and risk associated with prasugrel treatment over the current standard of care, clopidogrel. In consideration of the prasugrel NDA application, how much should the Agency weigh a risk for cancer against that of death? There are many other important questions with interest in any future prasugrel trials (i.e., TABY), including but not limited to the apparent risk of cancer (that will be part of an informed consent), that should be vetted and discussed before a public Advisory Committee before another prasugrel trial, let alone before general approval and marketing of prasugrel.

Allen Brinker, MD, MS,
Epidemiology Team Leader

References

1. Wiviott SD, Braunwald E, McCabe CH et al for the TRITON-TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001-15.
2. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997;126(9):712-20.

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/s/

Allen Brinker
6/13/2008 10:08:12 AM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
6/16/2008 06:15:21 PM
MEDICAL OFFICER