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:	January 8, 2009
To:	Norman Stockbridge, M.D., Ph.D., Director Division of Cardiovascular and Renal Products (DCRP)
Through:	Henry Francis, MD, Deputy Director Office of Surveillance and Epidemiology (OSE)
From:	OSE EFFIENT Risk Management Review Team
Subject:	**Background Package for Advisory Committee** NDA 22-307 EFFIENT ™ (prasugrel hydrochloride) Tablets 5mg and 10 mg strengths
Sponsor:	Eli Lilly and Company

CONTENTS

EXECUTIVE SUMMARY

Prasugrel is an orally bioavailable thienopyridine adenosine diphosphate (ADP) receptor antagonist. The proposed indication is for the reduction of acute myocardial infarction in acute coronary syndrome (ACS) patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI) and patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

During the clinical trial prasugrel was shown to significantly reduce the rate of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke in the UA/NSTEMI, all ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Of note, overall mortality was not found to be significantly different between treatment groups. Although prasugrel has been shown to be more efficacious than the comparator, it is also associated with a significant increased risk of bleeding, including fatal bleeding. Additionally, during the review of this application, the Division became concerned regarding disproportionate numbers of malignancies in the prasugrel group compared to the clopidogrel group.

If approved, we believe that a boxed warning would be warranted to emphasize the increased risk of bleeding observed in patients treated with prasugrel, particularly in patients with a prior history of TIA or stroke and in patients older than ≥ 75 years. The boxed warning should emphasize the need to avoid the use of prasugrel in these two subgroups. We believe that the boxed warning should also convey an increased risk of bleeding in patients that are generally vulnerable including: 1) patients who are undergoing elective CABG or other surgical procedures and the need to discontinue use of prasugrel at least 7 days prior to surgical procedure and discourage using prasugrel when coronary anatomy is unknown and CABG is a possibility; 2) patients with body weight <60 kg (the sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily); and 3) emphasize the increased risk of bleeding in patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS. The need to initiate therapy in the inpatient setting should also be included in the boxed warning.

We believe the potential risk of tumor stimulation associated with prasugrel use should be addressed in the warnings/precautions section of the label. We agree with the Review Division that one way to minimize the risk of malignancy, as well as the risk of bleeding, would be to limit the duration of therapy. However, specific dose conversions would need to be explicitly stated in the labeling. An overdose could occur if patients receive another loading dose of clopidogrel resulting in increased risk of bleeding. Patients may also be at an increased risk of thrombosis if the switch results in underdosing or if therapy is delayed. This is especially concerning in patients at risk of stent thrombosis. Until a determination is made regarding number of days of therapy and a dose conversion strategy or algorithm from prasugrel to clopidogrel, DMEPA reserves their comments on other potential sources of error.

Lilly proposes a risk evaluation and mitigation strategy (REMS) which will consist of a patient package insert (PPI) and a schedule for the assessment for the REMS. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, and the potential effect of prasugrel on tumor stimulation, we have determined that a REMS would be necessary to ensure that the benefits of the drug outweigh the risks. The REMS should consist of a Medication Guide, a communication plan, a timetable for assessments, and assessments of the REMS.

Lilly also plans to conduct post-launch active surveillance activities using large administrative claims databases or hospital in-patient electronic medical records databases to estimate and monitor the incidence of bleeding events and to identify and monitor subpopulations at risk for bleeding events in ACS patients treated with prasugrel. Lilly's active surveillance plan is likely to experience logistical and scientific problems as this product is initiated in the hospital and

continued for an unknown period of time in an outpatient setting necessitating long-term follow-up of patients in different settings.

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Some members of the OSE prasugrel team recommend a public Advisory Committee meeting before general approval and marketing to discuss the benefit of prasugrel treatment over the current standard of care (clopidogrel) given the issues concerning the drug's reformulation, bleeding, and cancer.

1 INTRODUCTION AND BACKGROUND

This review follows the January 31, 2008 request from the Division of Cardiovascular and Renal Products (DCRP) for the Office of Surveillance and Epidemiology (OSE) to review Lilly's proposed risk management plan submitted on December 26, 2007.

Prasugrel, 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 ACS patients with unstable angina or NSTEMI who are managed with PCI and patients with STEMI who are managed with primary or delayed PCI. The recommended starting dose is a loading dose of 60 mg to be initiated in the hospital followed by 10 mg once daily dose. Prasugrel is available as 5 mg and 10 mg film coated unscored tablets. Currently, there are two thienopyridines approved for the treatment of ACS. These drugs are ticlopidine (Ticlid®) and clopidogrel (Plavix®). Similar to prasugrel, both are prodrugs requiring in vivo metabolism to form an active metabolite.

In the prasugrel NDA submission Lilly proposes a worldwide routine pharmacovigilance to manage the risks of this product. Additionally, for the U.S. the sponsor proposes a risk evaluation and mitigation strategy (REMS) which will consist of a patient package insert (PPI) and a schedule of assessment for the REMS.

1.1 REGULATORY HISTORY

Prasugrel is a new molecular entity (NME) that has not been approved for marketing in any country. During the clinical trial, prasugrel was shown to significantly reduce the rate of the combined endpoint of cardiovascular death, nonfatal myocardial infarction, or non-fatal stroke in the UA/NSTEMI, all ACS, and STEMI populations at a median follow-up of 12 months, compared to clopidogrel. Subjects appeared to receive much of the treatment benefit from prasugrel within the first several days of therapy. Based on the significant improvement demonstrated in the clinical trial with use of prasugrel over current standard of care (Plavix®, clopidogrel bisulfate), the application was granted priority review with a 6-month review clock.

The prasugrel NDA was included in the Quality by Design (QBD) pilot program.[1] The sponsor initiated the development program

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[1] Division of Cardiovascular and Renal Products. Importance of Prasugrel's Conversion from a Salt to the Base Form; dated September 12, 2008.

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The sponsor submitted a major amendment dated June 20, 2008 that included a draft proposal of post marketing commitments and a risk management proposal.[3] The document reiterated the commitments and timelines stated in the REMS document within the original application. The REMS submission was no different than the original proposal and included a PPI and a schedule for assessment. Inclusive of the risk management plan, the sponsor also stated there would be a pharmacovigilance plan with agreed upon surveillance terms, and surveillance of safety events relevant to special populations (such as, elderly, pregnant, patients of different racial or ethnic origin).

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

1) Proposed prasugrel "Risk Minimization Plan" submitted December 26, 2007 by Eli Lilly & Co.
2) Proposed prasugrel labeling submitted December 26, 2007 by Eli Lilly & Co.
3) Rahman MA, Lin K. Statistical Review and Evaluation – Carcinogenicity Studies, Division of Biometrics, FDA; dated February 19, 2008.
4) Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, FDA; dated April 22, 2008.
5) Hicks KA. Clinical Review of Prasugrel, Division of Cardiovascular and Renal Products, FDA; dated April 28, 2008.
6) Mann BS. Carcinogenic potential for prasugrel, Division of Drug Oncology Products, FDA; dated April 24, 2008.
7) Mishina EV, Mada S. Clinical Pharmacology Review. DPEI and Cardio-Renal Drug Products, FDA; dated May 23, 2008.
8) Turner T. Proprietary Name, Label, and Labeling Review, Division of Medication Error Prevention, FDA; dated May 29, 2008.
9) Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.
10) Brinker A. Team Leader covering Memorandum, Division of Epidemiology, FDA; dated June 13, 2008.

[2] Mishina EV, Mada S. Clinical Pharmacology Review. DPEI and Cardio-Renal Drug Products, FDA; dated May 23, 2008.

[3] Prasugrel: Submission of proposed post marketing requirements (NDA 22-307/Sequence: 0044) dated June 20, 2008.

11) Unger, EF. Division of Cardiovascular and Renal Products *Secondary Review*, FDA; dated July 10, 2008.

12) Division of Cardiovascular and Renal Products. Importance of Bleeding to Prasugrel's Risk Benefit Relation; draft dated September 23, 2008.

13) Division of Cardiovascular and Renal Products. Importance of Prasugrel's Conversion from a Salt to the Base Form; draft dated September 25, 2008.

2.2 ANALYSIS TECHNIQUES

The submission was assessed for risks associated with prasugrel use based primarily on the analysis of the pivotal Study TAAL (a study comparing prasugrel and clopidogrel in acute coronary syndrome subjects who are to undergo percutaneous coronary intervention). In Study TAAL (primary safety database), data were collected from 13,457 subjects (prasugrel: 6,741; clopidogrel 6,716) with ACS who were managed by PCI. Of the 6,741 subjects randomized to prasugrel, 4088 subjects were exposed to prasugrel for at least 1 year. The submission was reviewed for proposed risk mitigation strategies, as well as, conformance with the Food and Drug Administration Amendments Act of 2007.[4]

3 SAFETY CONCERNS

3.1 SPONSOR'S SAFETY CONCERNS

Prasugrel is an inhibitor of platelet aggregation and poses the risk of hemorrhagic events. The sponsor has identified important risks to include intracranial hemorrhage, gastrointestinal hemorrhage, intraocular hemorrhage, epistaxis, PCI-related hemorrhage, CABG-related hemorrhage, other procedure-related hemorrhage, and anemia. The sponsor has also identified important potential risks to include phototoxicity (ocular or skin), drug-induced hepatic injury, allergic reactions, thrombocytopenia, thrombotic thrombocytopenic purpura, and neutropenia. From the clinical trials three populations were identified by the sponsor as at risk population for hemorrhagic events when treated with prasugrel and are discussed below.

- Age ≥75 years was identified as a risk factor for hemorrhagic events among subjects on prasugrel. In Study TAAL, subjects age ≥75 years was associated with a higher incidence of Non-CABG-related Thrombolysis in Myocardial Infarction (TIMI) Major or Minor bleeding events in both treatment groups (8.98% prasugrel, 6.94% clopidogrel). Age ≥75 years was also associated with higher risk of Non-CABG-related TIMI Major Life-Threatening bleeding events (including fatal bleedings and symptomatic intracranial hemorrhage) for both treatment groups. Age ≥75 years was also associated with a higher risk of gastrointestinal hemorrhagic adverse events for both treatment groups. The sponsor concludes, though, that a statistically significant interaction between treatment and age ≥75 years was observed, which resulted in a statistically significant higher incidence of stroke in subjects aged ≥75 years treated with prasugrel compared to clopidogrel (2.89% versus 1.43%; p=0.024). The sponsor suggests, for patients ≥75 years of age, prasugrel should be given as a single 60 mg loading dose (LD) and consideration may be given to a 5 mg once daily dose as an alternative to 10 mg once daily dose.

- Body weight <60 kg was identified as a risk factor for hemorrhagic events for subjects on prasugrel. For patients with body weight < 60 Kg, the sponsor recommends dose adjustment of prasugrel maintenance dose to 5 mg once daily following the 60 mg loading dose.

[4] Food and Drug Administration Amendments Act of 2007. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public laws&docid=f:pub1085.110

- Prior history of TIA or stroke was associated with a higher risk of Non-CABG-related TIMI major or Minor Life-Threatening bleeding events (including fatal bleeding and symptomatic intracranial hemorrhage). The sponsor opines that the clinical findings support the proposed prescribing information stating that, in patients with a known history of TIA or stroke (ischemic or hemorrhagic) prasugrel should be used with caution.

Additionally, the concomitant use of prasugrel with warfarin, heparin, fibrinolytics, or chronic use of NSAIDS (non ASA) was considered to increase the risk of hemorrhage. Subjects at increased risk of bleeding due to use of concomitant medications (for example, fibrin-specific fibrinolytic therapy <24 hours or nonfibrin-specific fibrinolytic therapy <48 hours prior to randomization) or clinical conditions, in the judgment of the investigator, associated with increase risk of bleeding were excluded in Study TAAL.

3.2 DCRP SAFETY CONCERNS

The Review Division identified several safety concerns. Below are summary of the identified risks based on the primary and secondary medical reviews.[5,6]

3.2.1 Bleeding

TIMI major and TIMI minor or minor non-CABG related hemorrhages and CABG-related hemorrhage were statistically significantly higher in the ACS population for prasugrel subjects compared with clopidogrel subjects. According to the secondary review, prasugrel was associated with excess bleeding, irrespective of bleeding definition, seriousness, or location, and across most subgroups assessed. Many of the bleeding events occurred within the first 3 to 5 days of the index Procedure.

There were 21 and 5 fatal bleeding events in the prasugrel and clopidogrel non-CABG-related groups, respectively (RR = 4.19, 95% C.I.: 1.58, 11.1, p=0.002). For the clopidogrel group, all 5 fatal bleeding events were intracranial in location. For the prasugrel group, 9 bleeding events were intracranial, 5 were gastrointestinal (GI), 2 originated from puncture sites, 2 from surgical sites, 2 from retroperitoneal locations, and 1 from an intra-abdominal location. Dr. Ellis Unger stated in his review that none of the deaths in the clopidogrel group, but over half the deaths in the prasugrel group, were attributed to extra-cranial sites of hemorrhage.

The following subgroups were at particular risk of bleeding:

Patients with a prior history of a TIA or CVA

In all ACS subjects with a prior history of transient ischemic attack or stroke, there was a 38% increased risk of experiencing death, nonfatal myocardial infarction, or nonfatal stroke at a median of 12 months of follow-up on prasugrel, compared to clopidogrel.

Patients ≥ 75 years of age

For subjects ≥ 75 years of age, the RR of TIMI major or minor bleeding events was 1.35, which is similar to the RR in younger subsets. However, subjects ≥ 75 years of age had a higher frequency of fatal and life-threatening bleeding events, and the RR was very unfavorable for prasugrel, i.e., fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic intracranial hemorrhage: 0.79% prasugrel, 0.34% clopidogrel.

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[5] Hicks KA. Clinical Review of Prasugrel, Division of Cardiovascular and Renal Products, FDA; dated April 28, 2008.

[6] Unger, EF. Division of Cardiovascular and Renal Products Secondary Review, FDA; dated July 10, 2008.

Patients who undergo CABG

The frequency of CABG-related TIMI major bleeding was higher in subjects treated with prasugrel compared to clopidogrel, and there was higher risk even when prasugrel was discontinued more than 7 days in advance of CABG. In the prasugrel group, there were 24 TIMI major bleeding events (11.3%, RR=3.50), of which 2 were fatal (0.9%) compared to the clopidogrel group, where there were 8 TIMI major bleeds, and none were fatal. Based on the reviewer's analysis, prasugrel should not be the drug of choice for patients in whom CABG surgery is anticipated and prasugrel is not well-suited for pre-treatment of patients in whom coronary anatomy is unknown.

In summary, the Review Division concluded that risk of bleeding is higher and specific information is merited in labeling for:

- patients ≥ 75 years of age (here the greater risk is for fatal and life-threatening bleeding)
- patients with a prior history of a transient ischemic attack or cerebrovascular accident (contraindication)
- patients who undergo CABG, or by extension, probably any surgical procedure

3.2.2 Malignancy

During the review of this application, neoplasia was also identified as an important risk by the medical reviewers in DCRP. Two carcinogenicity studies in the rat and in the mouse were reviewed. In the rat studies, no statistically significant dose response relationship or difference in survival between prasugrel treatment group and clopidogrel were observed in either sex. However, the mouse study showed statistically significant positive dose response relationship in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma in both sexes.[7]

DCRP conducted analyses of neoplasms cases in the pivotal study, TAAL. In Study TAAL, 4088 subjects were exposed to prasugrel for at least 1 year. In this study an increased rate of neoplasms, particularly solid tumors, in the prasugrel treatment group compared to clopidogrel (p=0.006) was observed.[8] In the prasugrel treatment group, there were 104 nonskin, nonbrain cancers, compared to 69 in the clopidogrel group. A Kaplan-Meier plot for all new cancers (excluding skin and brain) after 7 days in TAAL showed a divergence between the drugs and higher rates beginning at four months for prasugrel. Cancer sites showing the largest difference between drugs included breast, colorectal, lung, and "unknown/other." Further analysis also suggested that cancers in women played an important role.

A consult was sent to the Division of Drug Oncology Products (DDOP) to assess the carcinogenic potential of prasugrel. DDOP agreed with DCRP that when the incidences of "all cancers" between the drugs were compared, a p value of < 0.05 was obtained. However, DDOP is not certain of the statistical or clinical significance of these findings given that the study was not designed to compare the cancer incidence between the study arms. Furthermore, based on the absence of well defined cancer screening at study entry and no specified follow up to detect specific cancer, DDOP concluded that the cancers diagnosed on study are more likely to be "incidental".[9]

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[7] Rahman MA, Lin K. Statistical Review and Evaluation – Carcinogenicity Studies, Division of Biometrics, FDA; dated February 19, 2008.

[8] Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, FDA; dated April 22, 2008.

[9] Mann BS. Carcinogenic potential for prasugrel, Division of Drug Oncology Products, FDA; dated April 24, 2008.