Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

NDA#:	22-307
Products:	Effient (prasugrel) 10 mg Tablet
SPONSOR:	Eli Lilly and Daiichi Sankyo
FROM:	Robert Temple, M.D. Director, Office of Drug Evaluation I
DATE:	June 8, 2009

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments 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)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Effient (prasugrel) to ensure that the benefits of the drug outweigh the risks of major bleeding. In reaching this determination, we have considered the following:

A. Over 1.4 million hospitalizations for Acute Coronary Syndrome (ACS) occur in the United States each year.[1] Patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) comprise approximately 70% of the population presenting with ACS.[2]

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[1] Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. 2008. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation117(4):e25-146.

[2] Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Dabbous O, Fox KA, Gore JM. 2004. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). Am J Cardiol 93(3):288-293.

B. ACS is associated with cardiac ischemia and infarction which can lead to death or serious morbidity including heart failure.

C. Effient (prasugrel) significantly reduced the rate of the combined primary endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the UA/NSTEMI, all ACS, and STEMI clinical trial populations, at a median follow-up of 12 months, compared to clopidogrel. Subjects appeared to receive most of the treatment benefit from Effient (prasugrel) over clopidogrel within the first thirty days of therapy and most of the effect was on the non-fatal myocardial infarction component of the combined primary endpoint.

D. ACS is an acute condition, but there is no limitation on duration of use in the labeling because Effient (prasugrel) may be used chronically for the prevention of future events in patients who have had an ACS and patients who have had a coronary stent.

E. The primary risks associated with Effient (prasugrel) use relate to bleeding. These risks may be mitigated by avoiding prescribing it to certain patient populations (e.g., patients with a history of previous stroke or transient ischemic attack (TIA)) and by informing patients to contact their physician if they experience bleeding.

F. Effient (prasugrel) is a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Effient (prasugrel). FDA has determined that Effient (prasugrel) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Effient (prasugrel). FDA has determined that Effient (prasugrel) is a product for which patient labeling could help prevent serious adverse events; that it has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Effient (prasugrel); that the Medication Guide is important to health; and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be Medication Guide, a Communication Plan, and a timetable for submission of assessments of the REMS.

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/s/

Margaret Pease-Fye
6/8/2009 01:28:49 PM
CSO

REMS memo for prasugrel

Robert Temple
6/8/2009 07:04:57 PM
MEDICAL OFFICER

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:	October 7, 2008
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Through:	Henry Francis, MD, Deputy Director Office of Surveillance and Epidemiology (OSE)
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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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EXECUTIVE SUMMARY

Prasugrel is an orally bioavailable thienopyridine adenosine diphosphate (ADP) receptor antagonist indicated 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 a promotional effect of prasugrel on carcinogenesis 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 carcinogenesis, 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. However, active postmarketing surveillance of appropriate prasugrel use (including indications and dose), deaths associated with or due to bleeding, other specific serious bleeding events, and other adverse events, should be a postmarketing requirement. This surveillance could be accomplished through a postmarketing cohort study of representative prasugrel users followed long term.

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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. Prasugrel is indicated 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 most 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 using

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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.

b(4)

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.

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[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.

10) Brinker A. Team Leader covering Memorandum, Division of Epidemiology, FDA; dated June 13, 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

[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

adjustment of prasugrel maintenance dose to 5 mg once daily following the 60 mg loading dose.

- 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 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.,

[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.