fatal bleeding: 1.01% prasugrel, 0.11% clopidogrel; symptomatic intracranial hemorrhage: 0.79% prasugrel, 0.34% clopidogrel.

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

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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.

specific cancer, DDOP concluded that the cancers diagnosed on study are more likely to be "incidental".[9]

The sponsor has related the excess cancers in the prasugrel group to ascertainment bias because prasugrel appears to cause earlier bleeding than clopidogrel, thus resulting in increased detection of cancer. Despite the sponsor's explanation, the Review Division remains concerned about the difference in cancer rates between the drugs. Based on the preliminary analysis as well as increased bleeding risk with prasugrel over time, the medical reviewer recommended limiting therapy with prasugrel to short-term use (i.e. 1 week) so that patients may receive the benefits of this therapy while avoiding some of the possible risks.

3.3 OSE SAFETY CONCERNS

Based on the identified and potential risks described by the sponsor, as well as the risks identified during the NDA review by DCRP, we note the following:

3.3.1 Bleeding

The risk identified by the sponsor of hemorrhagic events associated with prasugrel is a class effect of the thienopyridines, including clopidogrel and ticlopidine, and one that is well-known to prescribers. Typically, these risks are managed through routine pharmacovigilance plans and labeling consistent with the plan outlined by the sponsor. Clopidogrel and ticlopidine labeling consists of the package insert (PI) which addresses the risk of bleeding in the precautions and adverse reaction sections. However, prasugrel was associated with a significant increased risk of bleeding, including fatal bleeding compared to clopidogrel.

Based on the medical officer's review, there was a 36% increased risk of overall bleeding and a 46% increased risk of serious bleeding in the prasugrel treatment group compared to clopidogrel.[10] The sponsor has identified increased risk of hemorrhagic events in certain at-risk subpopulations to include patients age $\geq$ 75 years, patients with body weight <60 kg, patients with prior history of TIA or stroke, and patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS. Additionally, the review team in DCRP identified patients who underwent CABG at an increased risk of prasugrel-associated bleeding.

Because of the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we believe that a boxed warning is warranted. The above mentioned at-risk subpopulations should be included in the boxed warning. Patients with previous history of stroke and/or transient ischemic attacks should be contraindicated to receive prasugrel. We agree with the medical reviewer that in patients $\geq$ 75 years of age, prasugrel should not be the treatment of choice. Therefore, age $\geq$ 75 years old should be identified as a risk factor for hemorrhagic events and use should be discouraged. Lower body weight of <60kg should be included in the boxed warning as a risk factor. The sponsor should provide data to support their recommendation to reduce the maintenance dose of prasugrel from 10 mg to 5 mg daily. A significant pharmacodynamic drug-drug interaction, prolongation of the bleeding time, was observed when prasugrel was co-administered with aspirin, warfarin and heparin, and should be included in the boxed warning to emphasize the increased risk of bleeding. Finally, patients undergoing CABG or any surgical procedure are at increased risk of bleeding and should be included in the boxed warning.

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

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

The increased risk of both fatal and non-fatal bleeds associated with prasugrel might warrant additional communication such as a Medication Guide. A Medication Guide would advise patients about the risk of bleeding with prasugrel and ensure that patients in whom prasugrel is contraindicated are not receiving it. It would inform patients about the risk factors (e.g., age ≥75 years, body weight <60 kg) and the drug-drug interactions (e.g., NSAIDs, warfarin, heparin, and fibrinolytics). Additionally, a Medication Guide would inform patients of signs and symptoms of bleeding and the need to seek immediate medical attention as well as the need to discontinue prasugrel prior to elective surgery. Healthcare provider communication at product launch would also help familiarize prescribing physicians with important product information as described above to ensure appropriate patient selection and monitoring.

3.3.2 Malignancy

The risk of neoplasia has been raised and it remains questionable if this observed risk is "incidental" or real. Since the risk of malignancies cannot be ruled out, patients and prescribers need to be informed of this serious risk as it would directly affect the patients' decision as to whether or not to use or to continue to use prasugrel, and the information is necessary for the prescribers to provide adequate oversight in patient selection and follow up. The risk of malignancy is particularly concerning if the product is used long term. The sponsor identified several possible "off-label" uses in one section of their risk management proposal which includes uses that might result in long term therapy:

- primary prevention of cardiovascular events;
- treatment of subjects with clinical history of coronary artery disease with no symptoms of ACS;
- treatment of other clinical manifestations of atherosclerotic disease such as previous myocardial infarction;
- peripheral arterial disease and ischemic stroke treatment of subjects with ACS for whom PCI is not indicated;
- prescription of higher than the recommended dose, under the belief that higher doses may confer greater efficacy.

In some of these mentioned circumstances, "off-label" use can be minimized if the package insert labeling is consistent with the proposed risk management plan and explicitly states that the loading dose should be given in a hospital setting. Consistency between the labeling and the risk management plan will also avert dosing confusion.[11]

Some in DCRP have recommended limiting the duration of use of prasugrel as a strategy to minimize the potential risk of malignancy. Patients treated with prasugrel would be switched after an initial time frame to clopidogrel for the remainder of therapy. We agree 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.

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[11] Turner T. Proprietary Name, Label, and Labeling Review, Division of Medication Error Prevention, FDA; dated May 29, 2008.

The Division of Epidemiology (DEPI) was consulted to comment on the usefulness of registries and to provide recommendations on the design of a study planned by the sponsor called TRILOGY ACS Study (previously called TABY) with respect to assessing prasugrel's risk of neoplasia. Dr. Wysowski, Ph.D., DEPI, stated in her review that the question of cancer etiology in prasugrel users cannot be adequately answered using a registry.

The review also outlined suggested analyses that should be performed by the sponsor on the available data from TAAL to resolve the question of carcinogenicity before the drug is approved for marketing.[12] Dr. Wysowski suggested that Lilly proceed with its proposed second randomized clinical trial, TRILOGY ACS Study. The study would need to be performed with enough power to detect prasugrel's effect on lung, breast, colon, and prostate cancers, and with careful collection of data on risk factors for lung, breast, colon, and prostate cancers. Collection of complete histories of cancer, symptoms of cancer, alcohol use, cigarette smoking, and medication use (including aspirin), and weight and body mass index, would be required.

3.3.3 Formulation (Salt to Base Conversion)

The clinical pharmacology analysis showed that concomitant use of 30 mg lansoprazole (proton pump inhibitor) reduced the C_{max} of prasugrel's active metabolite by nearly 30% and that the low, intermediate, and high rate of conversion tablets were not bioequivalent to each other since the C_{max} failed to meet the 90% confidence interval criteria of 80-125. The concern is that the differing amounts of conversion from lot to lot, in the presence of proton pump inhibitors (PPIs), leads to differences in the peak plasma concentrations which could be clinically significant. The review team in DCRP has assessed efficacy as a function of the age of the prasugrel lots in the presence and absence of PPI use and has determined that prasugrel's efficacy was at least comparable to clopidogrel for all lots, and efficacy was not importantly affected by pill age. The frequency of bleeding in prasugrel-treated subjects was also found to be very similar in subjects who did and did not receive a PPI, 2.5% and 1.7%, respectively.[13]

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4 SPONSOR'S RISK MANAGEMENT PROPOSAL

The sponsor proposes labeling, routine pharmacovigilance, and continued safety assessment of the following specific adverse events of interest: general bleeding, epistaxis, intraocular bleeding, anemia, photosensitivity, hepatic abnormalities, allergic reactions, thrombotic thrombocytopenic purpura, thrombocytopenia, and neutropenia. Targeted surveillance activities with specific follow-up forms for general bleeding, epistaxis, intraocular bleeding, procedure related bleeding; evaluation of type, severity, seriousness, localizations, concomitant medication, and indication of use will be implemented. Of note, the aforementioned follow-up forms have not been submitted for review.

[12] Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.

[13] Division of Cardiovascular and Renal Products. Importance of Bleeding to Prasugrel's Risk Benefit Relation; dated September 15, 2008.

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. The details of these post-marketing surveillance activities have not been submitted.

Additionally, the sponsor proposes, in the U.S., to distribute a patient package insert (PPI) for prasugrel and states that this will constitute a Risk Evaluation and Mitigation Strategy (REMS) and will be implemented in accordance with the REMS requirements. The assessment of the REMS will be submitted to the agency according to the following schedule:

- No later than 18 months after the REMS submission is approved;
- No later than 3 years after the REMS submission is approved;
- No later than 7 years after the REMS submission is approved, unless FDA waives this requirement after determination that serious risks of the drug have been adequately identified and assessed and are being adequately managed;
- When a supplemental application for a new indication for use is submitted to the agency;
- At other times, if requested by FDA;
- At other times, at the discretion of Lilly.

5 OSE'S ASSESSMENT OF THE ACTIVE SURVEILLANCE PLAN

Lily submitted a brief section, 2.1.4, "Active (Additional) Surveillance Activities" and this was reviewed. The company stated that it plans to conduct additional surveillance of relevant special populations (e.g., pediatric, elderly, pregnant or lactating women, patients of different racial or ethnic origin) or particular conditions of use (e.g., outside a drug's current approved indications). If Lilly identifies a serious safety signal in a special population or condition of use, Lilly will conduct "further targeted assessments." No detail was provided about the nature of the targeted assessments.

Lilly also plans to conduct periodic data mining of its surveillance system and publically available versions of FDA's Adverse Event Reporting System database to evaluate patterns of disproportionate reporting of adverse events following exposure to prasugrel. In addition, the company plans to "conduct active surveillance activities using appropriate large administrative claims databases or hospital in-patient electronic medical records databases." They state that, "The estimation of background mortality incidence of and ascertainment of possible risk factors for bleeding events in ACS patients who are managed by PCI and in relevant subgroups within this population will be established." The company does not explain how it will estimate "background mortality incidence" and ascertain possible risk factors for bleeding events from spontaneously submitted reports. If prasugrel is approved by the FDA, the company should be asked to explain these statements and provide more detail and rationale.

Although prasugrel has been compared with clopidogrel in the TRITON-TIMI 38 (also called TAAL) randomized clinical trial and the reformulated prasugrel will be compared with clopidogrel in the randomized clinical trials called the TRIOLGY ACS study, active surveillance will identify adverse events in real world situations. However, the active surveillance that Lilly plans is likely to experience numerous logistical and scientific hurdles. The first administration of prasugrel in most, if not all, patients will be in a hospital. The drug will then be continued for an indefinite period of time on an outpatient basis. The onset of prasugrel's antiplatelet effect to reduce risk for myocardial infarction is rapid--within the first few days of treatment. Active surveillance of adverse events would have to begin in inpatient hospital settings, and to obtain representative data and incidence rates, a sample of hospitals would need to be drawn from hospitals that administer the drug. Patients administered prasugrel identified in the hospital setting would need to be followed for adverse events in the outpatient setting. Many of the serious adverse events of

interest such as major bleeding would require assessment of data from emergency room treatment or hospital readmissions.

Aside from the Premier in-hospital database, administrative claims databases do not capture drugs administered in the hospital and would not include adverse events that occur during hospitalization if they are not entered as a discharge diagnosis. Consequently, a study using administrative claims data from most hospital systems would not capture in-patient prasugrel use.

To identify adverse events of low frequency associated with prasugrel use in the clinical trials setting, the sponsor should be asked to release these data from its TRITON-TIMI 38 clinical trial in which 6,813 patients were randomized to prasugrel and followed for 6 to 15 months. Incidence rates should be calculated for both prasugrel and clopidogrel and relative risks and 95% confidence intervals estimated.

To identify low frequency adverse events associated with prasugrel use in the postmarketing setting, a large representative sample of patients administered prasugrel would need to be followed from hospital administration through discharge and outpatient use. The study should document appropriate or inappropriate indication and use, deaths due or associated with bleeding, serious bleeding events and other adverse events. A sample of hospital medical records and discharge data would need to be obtained and there would need to be continued follow-up of patients outside of the hospital. Deaths and causes of death in patients lost to follow-up would need to be identified through the National Death Index of the National Center for Health Statistics. This study would be a postmarketing requirement.

The TRILOGY ACS Study, which will utilize a new formulation of prasugrel, will provide data on prasugrel and risk of cancer. It would be desirable to perform TRILOGY with enough statistical power to detect prasugrel's initiation or promotion effect on lung, breast, colon, and prostate cancers, and with careful collection of data on risk factors for these cancers. Collection of complete medical histories including histories of cancer, symptoms of cancer, social and reproductive history, family history, alcohol use, cigarette smoking, medication use (including aspirin), and weight and body mass index, would be required.

6 DISCUSSION

Available data suggest that there is a benefit and risk associated with prasugrel over the current standard of care, clopidogrel. In patients with acute coronary syndrome with scheduled percutaneous coronary intervention, prasugrel therapy was associated with reduced rates of ischemic events, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality was not shown to differ significantly between treatment groups.

If approved, the increased risk of both fatal and non-fatal bleeds associated with prasugrel use warrants a boxed warning. The contraindicated conditions and risk factors that increase the risk of bleeding should be provided and use of prasugrel in patients with these risk factors should be discouraged. The identified at-risk subpopulations include patients with prior history of TIA or stroke, patients age $\geq$ 75 years, patients with body weight <60 kg, patients who are undergoing CABG or other surgical procedure, and patients on concomitant medications such as warfarin, heparin, fibrinolytics or chronic use of NSAIDS.

During the review of this application, the review team in DCRP also identified neoplasia as an important risk. DEPI was consulted on the issue of neoplasia and they do not believe that the etiology of carcinogenicity associated with the use of prasugrel can be adequately answered using a registry[14], one possible strategy being considered by DCRP. DEPI also provided recommendations that outline specific analyses that should be performed on available data for

[14] Wysowski D. Cancer in Clinical Trials of Prasugrel, Division of Epidemiology, FDA; dated June 12, 2008.

TAAL and the proposed TRILOGY trial prior to approval of prasugrel to resolve the question of prasugrel's carcinogenicity.

Because the risk of malignancies cannot be ruled out at this point, we recommend that information specific to the risk of malignancy observed in patients treated with prasugrel be included in the warnings/precautions section of the labeling. Given that most of the treatment benefit from prasugrel was observed within the first several days of therapy, some in DCRP have proposed to limit the duration of treatment. We agree 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 has proposed a REMS which will consist of a patient package insert (PPI) and a schedule for assessment. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we have determined that a REMS to include a Medication Guide and a communication plan would be necessary to ensure that the benefits of the drug outweigh the risks. Therefore, instead of a voluntary PPI, as currently proposed by the sponsor, we recommend that Lilly be required to develop and submit for review and approval, a Medication Guide that will be required to be provided to patients with each dispensed prescription.

A Medication Guide would advise patients about the risk of bleeding associated with prasugrel and ensure that patients in whom prasugrel is contraindicated are not receiving it. It would inform patients about the risk factors (e.g., age ≥75 years, body weight <60 kg) and the drug-drug interactions (e.g., NSAIDs, warfarin, heparin, and fibrinolytics). Additionally, a Medication Guide would inform patients of signs and symptoms of bleeding and the need to seek immediate medical attention, as well as, the need to discontinue prasugrel prior to elective surgery. Healthcare provider communication at product launch would help familiarize physicians with the important product information as described above to ensure appropriate patient selection and monitoring.

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. Active surveillance of prasugrel's appropriate use, including indications and dose, specific bleeding events, other adverse events should be a postmarketing requirement.

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7 CONCLUSION

If prasugrel is approved, we believe that a boxed warning is warranted to emphasize the increased risk of bleeding observed in patients treated with prasugrel, particularly in certain subgroup of patients. Given the four-fold increased risk of fatal bleeding events with prasugrel compared with clopidogrel, we have determined that in addition to appropriate labeling a REMS would also be