NDA 22,307
Prasugrel
Clinical Reviewer Summary

Eli Lilly and Company submitted the new drug application (NDA) for prasugrel on December 26, 2007. I have reviewed this submission as well as 105 additional submissions ("sequences"), ranging in date from December 26, 2007 to June 23, 2009. I summarize my thoughts on this application below:

1. Based on the results of the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) study, I recommend approval of prasugrel for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention (PCI) as follows:

   - Patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI)
   - Patients with ST-segment elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI.

2. The TRITON-TIMI 38 study was a 13,608 patient, multicenter, international, randomized, double-blind, parallel-group trial comparing Effient to a regimen of clopidogrel, each added to aspirin and other standard therapy, in patients with acute coronary syndrome (ACS) (UA, NSTEMI, or STEMI) who were to be managed with PCI. Randomization was stratified for UA/NSTEMI and STEMI. In this trial, the primary outcome measure was the composite of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke in the UA/NSTEMI population. Success in this group allowed analysis of the same endpoint in the overall ACS and STEMI populations.

   a. In TRITON-TIMI 38, prasugrel significantly reduced total endpoint events compared to clopidogrel in the UA/NSTEMI, all ACS, and STEMI populations.

   b. Nonfatal MIs included both investigator-reported MIs as well as MIs detected through analysis of cardiac biomarker changes (creatine kinase muscle-brain (CK-MB) or troponin).

   c. The primary endpoint was driven primarily by a decrease in nonfatal myocardial infarctions. Approximately 40% of these myocardial infarctions were periprocedural MIs and were detected solely by changes in CK-MB.

   d. In the STEMI treatment group, all of the benefit with respect to the primary endpoint was seen within the first 30 days. However, in the UA/NSTEMI treatment group, approximately 50-60% of the benefit in the primary endpoint was seen within the first 30 days with the remainder of the benefit accruing over the course of the trial.

   e. Administration of the clopidogrel loading dose in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for ACS.

   f. Prasugrel caused higher rates of clinically significant bleeding than clopidogrel.

   g. In TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences. To further evaluate the safety of prasugrel, the Division has asked the sponsor to collect additional information with respect to cancer in their ongoing trial, H7T-MC-TABY ("A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) who are Medically Managed—The TRILOGY ACS Study").

3. **Stent Thrombosis**

In my initial review dated April 28, 2008, I did not recommend approval of prasugrel for the reduction of stent thrombosis because I did not think the sponsor met the scientific rigor required for such a claim and had selectively used the standardized definitions for stent thrombosis developed in 2007 by the Academic Research Consortium (ARC) and our colleagues at the Center for Devices and Radiological Health (CDRH). Furthermore, in TRITON-TIMI 38, there was no angiographic core laboratory review and there was limited pathological confirmation. The Clinical Endpoints Committee (CEC) adjudicated stent thrombosis clinically by review of cardiac catheterization and percutaneous coronary intervention reports, laboratory data, and 12-lead electrocardiograms.

During my review of some of the catheterization and PCI reports for patients who were adjudicated by the CEC as having definite or probable stent thrombosis, I realized some of these cases were not consistent with stent thrombosis at all.

As a result, the Division requested blinded angiographic core laboratory review of angiograms for 18 subjects, including 12 cases initially adjudicated by the TRITON CEC as definite stent thrombosis and 6 investigator reported cases of definite stent thrombosis that were never referred to the CEC for review. Of these 18 subjects, I thought the diagnosis of definite stent thrombosis was suspect in 9 subjects, including 6 out of the 12 subjects initially adjudicated by the TRITON CEC as definite stent thrombosis and 3 out of the 6 subjects who were thought by investigators to have definite stent thrombosis but who were not referred to the CEC for clinical adjudication. In addition, the sponsor was to submit angiograms to the core laboratory for 18 "control subjects," matched by age, sex, vessel (and if possible, lesion).

From the review of the 12 cases initially adjudicated by the TRITON CEC as definite stent thrombosis,

- the angiographic core laboratory (PERFUSE) adjudicated 7 cases as having angiographic evidence of stent thrombosis (3 prasugrel, 4 clopidogrel) and 5 cases as not having angiographic evidence of stent thrombosis (1 prasugrel, 4 clopidogrel).

- The Harvard Clinical Research Institute (HCRI) Clinical Endpoints Committee adjudicated 7 cases as definite (3 prasugrel, 4 clopidogrel), 1 case as probable (clopidogrel), and 4 cases as no stent thrombosis (3 clopidogrel, 1 prasugrel).

- In the case of Subject 01022421407, PERFUSE did not see angiographic evidence of thrombus or total occlusion involving the stent, but the clinical report documented the presence of thrombus likely involving the stent; therefore, HCRI adjudicated this case as probable stent thrombosis.

From the review of the 6 investigator reported cases of stent thrombosis (2 prasugrel, 4 clopidogrel) which were never referred to the TRITON CEC for adjudication,

- PERFUSE and HCRI downgraded these cases to 3 cases of definite stent thrombosis only (3 clopidogrel).

With respect to the 18 case-matched control subjects, PERFUSE and HCRI adjudicated all cases as no stent thrombosis.

Since most cases of definite stent thrombosis clinically adjudicated by the TRITON CEC appeared to be consistent with the results of angiographic core laboratory and HCRI adjudication, I recommended approval of prasugrel for the reduction of stent thrombosis. Please see my review dated February 2, 2009 and the ERRATUM dated May 13, 2009 for full details.

4. **Duration of Therapy**

In my review dated April 28, 2008, I recommended limiting therapy with prasugrel to short-term use (i.e., one week) so that patients could receive the benefits of this therapy while avoiding some of the possible risks (e.g., bleeding, possible increased rate of new malignancies). However, through the course of the review, I have modified my opinion on this matter.

Currently, I do not recommend short-term use of prasugrel or a switching strategy at a particular time point from prasugrel to clopidogrel because such a strategy has not been adequately studied to date with respect to clinical outcomes (CV death, nonfatal MI, nonfatal stroke, and stent thrombosis). Based on the stent thrombosis results from TRITON-TIMI 38, most cases of stent thrombosis in the clopidogrel treatment group occurred within the first 30 days of the index procedure, while most cases of stent thrombosis in the prasugrel treatment group occurred > 30 days to 1 year of the index procedure. Furthermore, most deaths associated with stent thrombosis occurred within the first 30 days for both treatment groups (8 prasugrel, 11 clopidogrel).

Therefore, I am especially concerned about a switch from prasugrel to clopidogrel that may take place within the first 30 days of stent placement, because any substantial change in inhibition of platelet aggregation may convey an increased risk of stent thrombosis. In my opinion, patients should be switched from prasugrel to clopidogrel only if they cannot tolerate prasugrel.

If a patient is tolerating prasugrel but a practitioner is considering a switch to clopidogrel, it may be helpful to determine if the patient is a clopidogrel responder first.

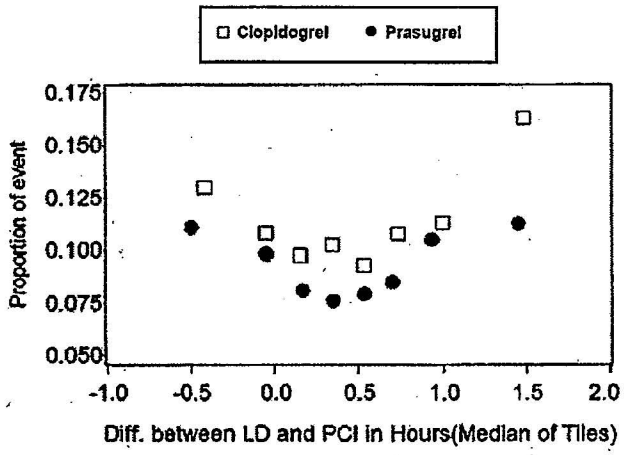
In my opinion, a randomized, prospective trial evaluating clinical outcomes after a switch from prasugrel to clopidogrel at different time points may enhance our understanding of the possible risks and allow us to provide better advice on the duration of therapy and switching strategy.

5. **Timing of Prasugrel Loading Dose Administration**

TRITON-TIMI 38 did not evaluate the optimal timing of the administration of the prasugrel loading dose. Most subjects received prasugrel or clopidogrel during PCI. The completion of the PCI procedure was defined as ≤ 1 hour of the subject leaving the cardiac catheterization laboratory.

When the loading dose of either prasugrel or clopidogrel was given within 30 minutes of the start of PCI, both treatments resulted in a decreased incidence of the primary endpoint over the course of the study, as shown in Figure 1.

Figure 1. Timing of Loading Dose and Effect on Primary Endpoint (TRITON-TIMI 38)



(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)

A separate analysis by Dr. Thomas A. Marciniak evaluated rates of patients with primary endpoint events in the first 10 days by timing of the loading dose. The number of patients included in this analysis is displayed in Table 1. The hours from symptom onset to loading dose administration by ACS type is shown in Table 2.

Table 1. Number of Patients by Hour from PCI Start in TRITON-TIMI 38

hour from PCI start	UA/NSTEMI		STEMI	
	clopidogrel	prasugrel	clopidogrel	prasugrel
-2	31	33	7	6
-1	81	75	81	86
0	2,353	2,378	768	770
1	2,024	2,026	707	709
2	234	247	98	81
3	22	11	3	5

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, NDA 22,307 Prasugrel Review dated May 6, 2009, page 47)

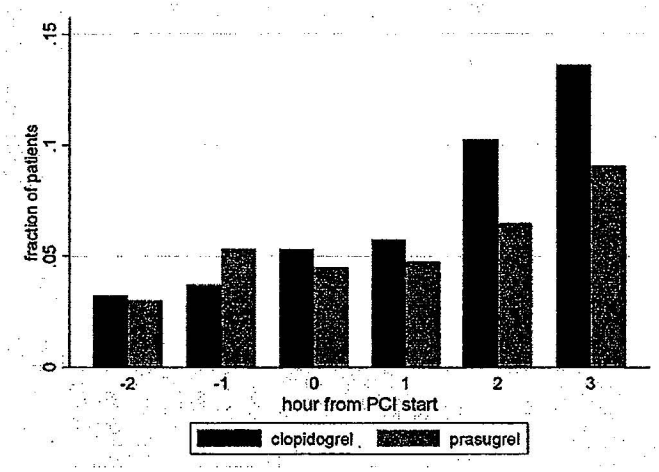
Table 2. Hours from Symptom Onset to Loading Dose Administration in TRITON-TIMI 38 by Acute Coronary Syndrome Type

	median	interquartile range
STEMI	7	3.7 - 28.5
UA/NSTEMI	29.7	17.4 - 49.8

(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, NDA 22,307 Prasugrel Review dated May 6, 2009, page 46)

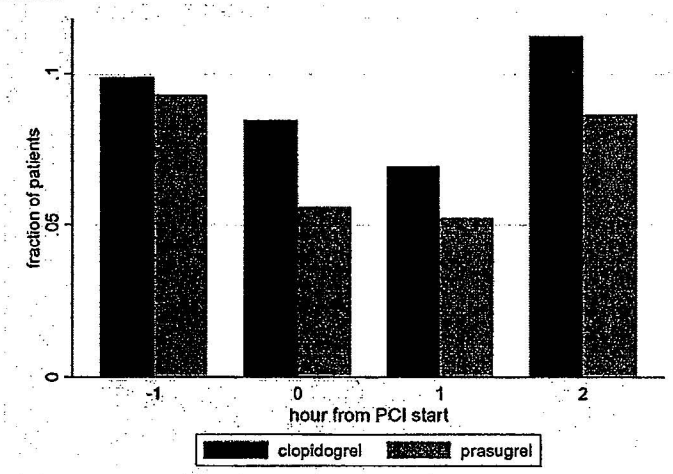
The rates of patients with primary endpoint events in the first 10 days by timing of loading dose are presented in Figure 2 and Figure 3. Although the results are not completely consistent for prasugrel, Figure 2 suggests that in the UA/NSTEMI population, the risk of a cardiovascular event within the first 10 days appears to increase continuously as the loading dose is delayed. However, for STEMI patients, the rates of CV events within the first 10 days show a U-shaped curve, similar to that seen in Figure 1. The reason for the discordance in results between the UA/NSTEMI and STEMI populations is unclear but may have to do with timing differences in undergoing PCI/receiving the loading dose.

Figure 2. Rates of UA/NSTEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TRITON-TIMI 38



(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, NDA 22,307 Prasugrel Review dated May 6, 2009, page 48)

Figure 3. Rates of STEMI Patients with Primary Endpoint Events in First 10 Days by Timing of Loading Dose in TRITON-TIMI 38



(Analysis by Thomas A. Marciniak, M.D., Division of Cardiovascular and Renal Products, NDA 22,307 Prasugrel Review dated May 6, 2009, page 48)

With respect to the management of acute coronary syndrome, the American College of Cardiology Guidelines for the treatment of UA/NSTEMI and STEMI generally recommend that antiplatelet therapy be administered promptly.

In TRITON-TIMI 38, 23% of the endpoint events occurred in the first hour, 45% of the endpoint events occurred in the first day, and 54% of the endpoint events occurred in the first week. With respect to bleeding, 1/3 of all bleeding events were reported on the first day and nearly half of all bleeds were reported within the initial 7 days. While it is plausible that giving prasugrel early could reduce endpoint events, the data above do

not necessarily support this practice. Patients who received the prasugrel loading dose during PCI had a low rate of primary endpoint events in both the UA/NSTEMI and STEMI groups. Unfortunately, there are too few patients who received prasugrel or clopidogrel outside of PCI to draw a meaningful conclusion. In my opinion, the optimal timing of the administration of the prasugrel loading dose is still to be determined and may require further study in a randomized, prospective manner. Changes in the timing of the administration of the prasugrel loading dose may also affect the benefit:risk ratio with respect to clinical outcomes and bleeding.

6. **Salt to Base Conversion**

Bioequivalence requires that Cmax and AUC meet the 90% confidence interval criteria of 80-125%.

Study TACR (no proton pump inhibitors) demonstrated that the low (5%), intermediate (58%), and high (70%) extent of conversion prasugrel lots were bioequivalent.

Study TACS demonstrated that in the setting of lansoprazole, the low (5%), intermediate (58%), and high (70%) extent of conversion prasugrel lots were bioinequivalent based on the Cmax failing to meet the 90% confidence interval criteria of 80-125. However, if based on area under the curve (AUC) only, these lots would have been found to be bioequivalent. The difference in plasma levels translated into significant differences in maximum platelet aggregation at 30 minutes and 1 hour. The LS mean difference in maximal platelet aggregation was 16.0% (90% CI: 11.3, 20.8) at 30 minutes between the high conversion and low conversion tablets. Theoretically, the more salt to base conversion, the less inhibition of platelet aggregation, and potentially the greater the risk of thrombotic events. Alternatively, the less salt to base conversion, the greater inhibition of platelet aggregation, and potentially the greater risk of bleeding. In TRITON-TIMI 38, we did not find any difference in efficacy between patients taking or not taking proton pump inhibitors.

With respect to bleeding, the incidence of bleeding in TRITON-TIMI 38 was higher in subjects in both treatment groups who received gastric pH-raising drugs than in those who did not. This finding was likely related to that fact that these agents were used per the discretion of the investigator. Overall, we found that prasugrel's bleeding risk, with or without proton pump inhibitors or H2 blockers, was consistent with the study as a whole.

In TRITON-TIMI 38, a retrospective analysis of the tablets indicated the range of salt to base conversion in the trial was 42-87%. Most of the lots used in the study had ≥ 50% base. Approximately 1/3 of the lots administered through Day 30 had ≥ 70% base. To date, bleeding has not been assessed in subjects receiving 5% base. The proposed marketed formulation is approximately [redacted] base. b(4)

Since bioequivalence covers a large range of values, anything that affects Cmax and AUC may affect safety or efficacy.

b(4)

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/s/

Karen Hicks
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