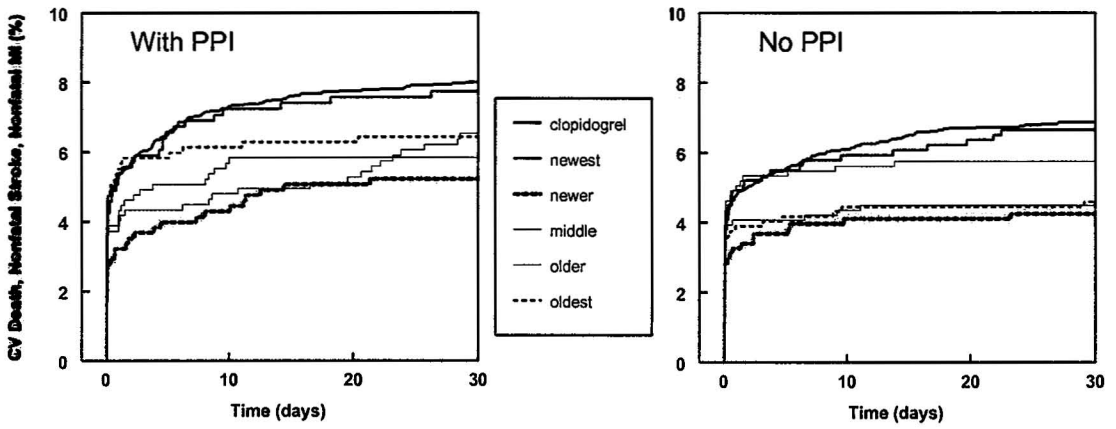
Figure 6: 1° Efficacy Endpoint by Age of Prasugrel Lot Administered Through Day 30



Because the sponsor asserts that there was at least some conversion of salt to base during storage, the review team also assessed efficacy as a function of the age of the prasugrel lot used to supply each subject with their initial 30 day supply, in the presence and absence of PPI use (age = date administered minus date of manufacture). Of note, use of PPIs was transient or intermittent in some subjects; subjects with recorded PPI use at any time were considered PPI users for the purpose of this analysis. In both the presence and absence of PPIs, there was no relation between age of lot administered during the initial 30 days and efficacy (Figure 6, from secondary review).

These analyses suggest that prasugrel's efficacy was at least similar to clopidogrel for the vast majority of lots, and efficacy was not importantly affected by pill age. (The lot with the highest event rate included only 36 subjects.)

Association between Use of Proton Pump Inhibitors and Efficacy

If PPI had importantly diminished prasugrel's pharmacodynamic effects in the setting of salt-to-base conversion, one would expect diminished efficacy in subjects who were receiving PPI. Approximately 40% of the subjects in each treatment group reported use of PPI as a concomitant medication. The Cox proportional hazard ratio favored prasugrel over clopidogrel in subsets of subjects who received and did not receive PPI, and was virtually the same in both subsets. Hazard ratios were 0.82 and 0.80 in subjects who reported and did not report use of PPI, respectively.

Impact of Salt-to-Base Conversion on Safety

The principal risk of prasugrel is bleeding. In essence, salt-to-base conversion has the potential to lead to lower bioavailability in the presence of PPI or H2 antagonists, which would tend to cause less bleeding. Thus, potentially lower bioavailability does not pose a safety risk, per se.

Table 4: Non-CABG-Related TIMI Major or Minor Bleeding Events Through 3 Days by PPI Medication Use and H2 Receptor Blocker Use

Study Population	Prasugrel			Clopidogrel			Cox Proportional HR (95% C.I.)
	N	n	%	N	n	%	
Overall	6741	138	4.5	6716	113	3.4	
PPI Yes	2760	70	2.5	2719	62	2.3	1.11 (0.79, 1.56)
PPI No	3981	68	1.7	3997	51	1.3	1.35 (0.94, 1.94)
H2 Antagonist Yes	1027	30	2.9	1017	25	2.5	1.19 (0.70, 2.02)
H2 Antagonist No	5714	108	1.9	5699	88	1.5	1.23 (0.93, 1.63)

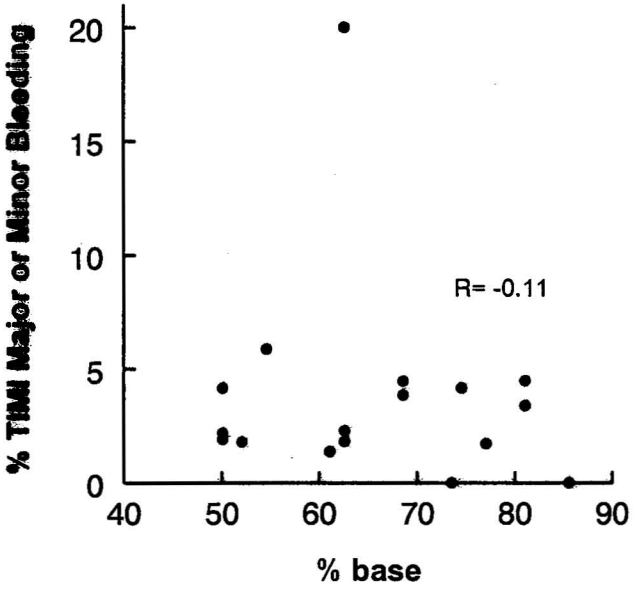
Table 4 shows the incidence of TIMI Major and Minor bleeding events through 3 days, dichotomized by PPI use or non-use (top) or H2 receptor antagonists use or non-use (bottom) through 3 days. If higher gastric pH decreased the bioavailability of prasugrel, one would expect to observe fewer bleeding events in patients who received PPI or H2 antagonists in the prasugrel group, relative to the clopidogrel group.

For both treatment groups, the incidence of bleeding was higher in subjects who received gastric pH-raising drugs than in those who did not. This may be related, in part, to the fact that PPI and H2 antagonists were discretionary, and physicians may have been more willing to prescribe them for patients perceived to be at higher risk of bleeding events.

Given to the limited numbers of bleeding events, due in part to considering events through only Day 3, the analysis is not robust. Whereas the data do not suggest a bioavailability issue, neither do they provide much reassurance to refute one. They do suggest that prasugrel's bleeding risk, with or without PPIs or H2 receptor antagonists, is consistent with the study as a whole.

When the review team analyzed TIMI Major or Minor bleeding rates by lot administered during the first 30 days, there was no relation between salt-to-base conversion and bleeding (Figure 7).

Figure 7: TIMI Major or Minor Bleeding Versus Base Content of Lot Administered Through Day 30



Importance of Dose to Safety and Efficacy:

Finally, when considering the potential influence of salt-to-base conversion on safety and efficacy, it is useful to place the potential differences in bioavailability into perspective. If we assume a worst-case scenario, that is, that salt-to-base conversion cannot be controlled, that this phenomenon results in a 38% difference in C_{max} between the low- and high-conversion lots at the 30 minute time point, and that the impact on platelet aggregation, although transient, is important, it should be recognized that the variability is only moderate when compared to the variability in weight-adjusted dose between patients of higher and lower weight (all patients receive the same dose of prasugrel). Of course the critical issue is whether higher weight patients taking gastric pH raising medications could receive lots with higher salt-to-base conversion and experience reduced efficacy. Fortunately, the clinical data provide a fair measure of reassurance in this regard.

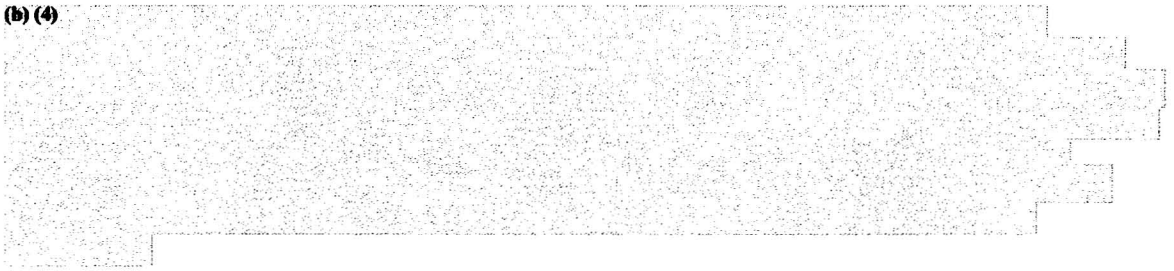
Conclusions:

The conversion of the drug product from salt to base is a heretofore-unknown phenomenon that could have been discovered as a result of following the Quality by Design paradigm of drug development. Conversion affects the pharmacokinetics of the product when it is co-administered with a PPI or H2 receptor antagonist; the high-conversion drug substance is technically bio-inequivalent to the low- and medium-conversion lots. The difference in bioavailability is evident in C_{max}, but not AUC, and translates into less biological activity than the low- and medium-conversion products at the 0.5- and 1-hour time points. However, at 2 hours and beyond, the difference disappears. This can be conceptualized as a delay of approximately 20 minutes in achieving maximal inhibition of platelet aggregation. On the other hand, inhibition

of platelet aggregation resulting from prasugrel greatly exceeds that of clopidogrel at all time points. Thus, even when conditions are most unfavorable for prasugrel (high salt-to-base conversion with high gastric pH), its pharmacodynamic effect is greater than that of clopidogrel.

The clinical data are also reassuring with regard to salt-to-base conversion. In terms of efficacy, the results for essentially all prasugrel lots administered during the first 30 days trended favorably relative to clopidogrel (Figure 5). Moreover, the use of PPI had no discernable effect on the efficacy of prasugrel in relation to clopidogrel. From the standpoint of safety, the importance of salt-to-base conversion is more difficult to assess, because the analyses are based on bleeding events, which were relatively uncommon. In any case, a product with high salt-to-base conversion administered in the presence of a PPI or H2 receptor antagonist has reduced bioavailability, which would lead to *less* bleeding. In actual use, the relation between PPI use and bleeding for subjects who received prasugrel was similar to that of clopidogrel, and there was no apparent relation between the salt/base content of the lots used during the first 30 days and bleeding events.

(b) (4)



In conclusion, although the conversion of the product from the salt to base form is counter to product purity, it could have been detected as a result of the QbD initiative. Such conversion may be an issue for marketed products, although this is purely conjecture. More importantly, approval of a product with significant conversion sets a poor precedent. On the other hand, the biological activity of prasugrel on inhibition of platelet aggregation exceeds clopidogrel at all time points, and the clinical data argue strongly that the salt-to-base conversion has no clinically important effect on the performance of prasugrel. Its performance exceeds that of clopidogrel, and therefore salt-to-base conversion should not be a reason to deny approval of this NDA.

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS
Secondary Review

Date: July 10, 2008

NDA: 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets
Eli Lilly and Company

Status: priority

Submitted: 26 December 2007

Goal Date: 26 June 2008

Reviewer: Ellis F. Unger, M.D.
Deputy Director
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products

To: The File

This secondary review is based, in part, on the primary reviews of:

- Chemistry (Sharmista Chatterjee, Zhengfang Ge, and Kasturi Srinivasachar), May 14, 2008
- Preclinical Pharmacology and Toxicology (Belay Tesfamariam and Albert DeFelice), April 26, 2008
- Clinical Pharmacology and Biopharmaceutics, (Elena V. Mishina, Sripal Mada, Patrick Marroum, Raj Madabushi, Yaning Wang), May 23, 2008
- QT (Suchitra Balakrishnan, Yeh-Fong Chen, Joanne Zhang, Nitin Mehrotra, and Christine Garnett), April 9, 2008
- Clinical (Karen A. Hicks), April 28, 2008
- Clinical Team Leader (Thomas A. Marciniak)
- Biostatistics (Ququan Liu), April 29, 2008

The legal basis for submission is 505(b)(1).

1. Background and Introduction

Background:
Prasugrel is a thienopyridine adenosine diphosphate (ADP) receptor antagonist that irreversibly inhibits the platelet P2Y12 receptor, inhibiting platelet activation and aggregation. Prasugrel is a pro-drug that undergoes deacetylation by esterases to form an inactive thiolactone, that is then converted to the active moiety, R-138727, through the cytochrome P450 system. The active metabolites of prasugrel irreversibly inhibit the P2Y12 ADP receptor for the entire lifespan of the platelet (approximately 10 days).

Indication Sought by Sponsor:
"Acute Coronary Syndromes

[Trade Name] (prasugrel hydrochloride) is indicated for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS) as follows:

- patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) who are managed with percutaneous coronary intervention (PCI).
- patients with ST-segment elevation myocardial infarction (STEMI) who are managed with primary or delayed PCI.

[Trade Name] has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke."

Currently Available Related Drugs for Indication:
Clopidogrel bisulfate (PLAVIX and generic) and ticlopidine hydrochloride (TICLID and generic) are ADP receptor antagonists of the thienopyridine class that inhibit platelet activation and aggregation and carry cardiovascular claims:

1. Clopidogrel is indicated for the reduction of atherothrombotic events as follows:

Recent MI, Recent Stroke or Established Peripheral Arterial Disease
For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease...to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

Acute Coronary Syndrome
For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG...to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.

For patients with ST-segment elevation acute myocardial infarction, PLAVIX has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke. This benefit is not known to pertain to patients who receive primary angioplasty.

2. Ticlopidine is indicated:

- To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke.
- As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation

Ticlopidine carries black box warnings for thrombotic thrombocytopenic purpura (TTP), neutropenia/agranulocytosis, and aplastic anemia, and the indication states that the drug "...should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy."

2. Regulatory History and Status

The data submitted in support of the safety and efficacy of prasugrel were developed from studies conducted under IND 63,449, held by Eli Lilly and Company.

The original application was filed December 26, 2007. The important regulatory history has been summarized by others.

3. Chemistry Manufacturing and Controls

3.1 Conversion from Salt to Base Form

The CMC review team opined that the application is "approvable" from the CMC perspective, due to variability in end product quality. Their primary concern is the observed conversion of the prasugrel salt to free base.

The sponsor initiated the prasugrel development program using the free base of the drug substance, but switched to a hydrochloride (HCl) salt with the expressed intent of increasing bioavailability at higher gastric pH. Gastric pH is an important issue in patients who use anti-platelet medications, because a substantial fraction of these patients take proton pump inhibitors (PPI) to reduce gastric acidity, with the goal of reducing gastric bleeding.

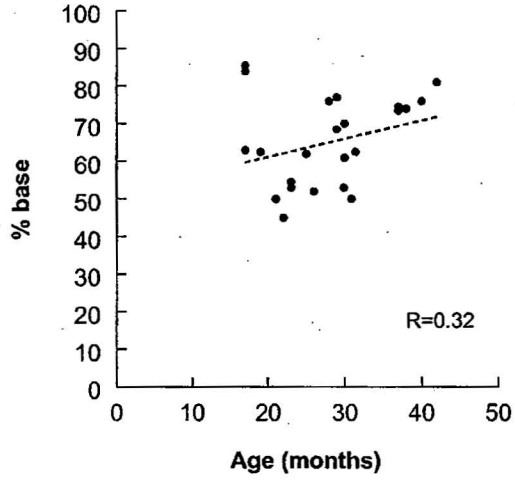
Late in development, near the time that the pivotal efficacy study (TAAL) was completed, the sponsor discovered that an acid-base reaction [redacted], was converting up to 70% of the salt to the free base. The sponsor conducted two bioequivalence studies wherein they compared lots with low (5%), intermediate (58%), and high (70%) degrees of conversion, with and without co-administration of a PPI (lansoprazole) to raise gastric pH. The sponsor concluded that up to 70% conversion from salt to free base was clinically acceptable in patients, both with and without concomitant PPI use; however, the agency's clinical pharmacology reviewer did not concur. When prasugrel was administered alone, the reviewer agreed that lots with low, intermediate, and high salt to base conversion were bioequivalent. However, when coadministered with lansoprazole, the clinical pharmacology reviewer opined that the three lots were bioinequivalent with respect to C_{max}. (They were bioequavalent with respect to area under the curve [AUC].) The mean difference in C_{max} between the low and the high conversion lots was 29%, with a 10% difference between the intermediate and high conversion lots. These differences translated to disparities in mean inhibition of the platelet aggregation (IPA) of greater than 10% at 0.5 and 1 hour post-dose.

b(4)

The sponsor determined that conversion from salt to base begins at the initial [redacted] Conversion continues during storage, reaching a plateau after approximately [redacted] Relative humidity and storage temperature affect conversion, which may explain why the extent of conversion is not linear with time (Figure 1, R=0.32).

b(4)

Figure 1: Base Content of Prasugrel as a Function of Time



b(4)

b(4)

3.2 Compliance

The 3 clinical sites selected for inspection were the largest sites in their respective countries/ continents, and showed the most favorable results for prasugrel. According to the Division of Scientific Investigations' overall assessment, "Based on preliminary review, the data are considered reliable in support of the proposed indication. Follow-up action: An inspection summary addendum will be generated if conclusions changes significantly upon receipt and review of the EIRs and evidence exhibits from the international sites."

Inspection of manufacturing facilities was not complete as of May 14, 2008, and an overall recommendation from the Office of Compliance is still pending at the time of this writing.

3.3 Degradation Products

b(4)

Several of the degradation products of the drug substance, e.g., , have structural alerts for genotoxicity. In a Discipline Review Letter dated April 9, 2008, the CMC Team asked the sponsor: 1) to provide comprehensive analysis of these substances; 2) to determine the levels of these impurities

detected under normal storage conditions; 3) to assess safety based on the Threshold of Toxicological Concern (EMEA Guidance) under recommended storage conditions; and 4) to provide justification for not monitoring these compounds in release and stability testing.

The sponsor provided a comprehensive analysis of specified and unspecified degradation products in the drug substance and drug product. All specified degradation products were found to have been products of metabolism or were determined to have been appropriately qualified. A number of unspecified degradation products were further evaluated for potential genotoxicity using quantitative structure-activity relationship (QSAR) methodology. None of the compounds were predicted to be genotoxic. Consequently, the sponsor's approach is to treat these according to ICH guidelines, and not the EMEA guideline for genotoxic impurities.

The Pharm/Tox team was consulted regarding the sponsor's QSAR approach regarding determination of genotoxic potential, and their opinion is pending at this time.

4. Nonclinical Pharmacology/Toxicology

4.1. Pharmacokinetics and Metabolism

Prasugrel's metabolic pathways are similar in mice, rats, dogs, and humans. Following oral administration, the drug is rapidly absorbed, hydrolysed by esterases, and metabolized by cytochrome P450 enzymes to form the active metabolite. Protein binding of metabolites was high (>80%) in rats and dogs, and binding of the active metabolite, R-138727, was estimated to be 98% in human serum albumin (HSA) solution *in vitro*. Biliary excretion was the major route for elimination of prasugrel and its metabolites in rats and dogs; in mice, elimination was primarily in the urine.

Prasugrel causes induction of cytochrome P450 of phase I and phase II drug metabolizing enzymes, which is consistent with observed decreases in exposure to prasugrel metabolites after multiple dosing. No specific animal studies were conducted on the effects of induction of drug metabolizing enzymes and interaction with other drugs metabolized via CYP2B and CYP3A.

4.2 Safety Pharmacology

Prasugrel is a prodrug whose active metabolite irreversibly inhibits the platelet P2Y12 receptor, inhibiting ADP-mediated platelet activation and aggregation. Prasugrel is approximately 10- and 100-fold more potent than clopidogrel or ticlopidine, respectively, in inhibiting platelet aggregation, inhibiting thrombus formation, and prolonging bleeding times. The antiplatelet effects of the active metabolites of prasugrel and clopidogrel are approximately equipotent *in vitro*, implying that prasugrel's greater pharmacodynamic effect is related to more extensive formation of its active metabolite, compared to clopidogrel.

Compared with the free base form, oral administration of the prasugrel HCl salt form is associated with approximately 20-30% higher exposure to active metabolites.

Gastric pH is an important determinant of prasugrel absorption after oral administration, and this is particularly true for the free base form. Concomitant administration of PPIs (which increase gastric pH) reduced plasma concentrations of metabolites following oral administration of both forms. Concomitant administration of ranitidine, a histamine H2 receptor blocker, reduced plasma concentrations of prasugrel metabolites by 30% and 65%, respectively, for the HCl salt and free base forms. Because the gastric pH effects were less pronounced for the HCl salt