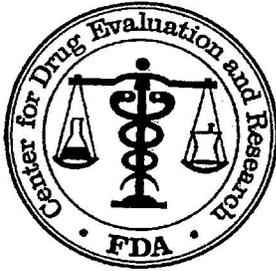


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**22-307**

**SUMMARY REVIEW**



**DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS**  
**Revised Secondary CDTL Review**

Date: January 9, 2009

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.  
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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, and August 29, 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), December 31, 2008
- Biostatistics (Ququan Liu), April 29, 2008

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

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## 1. Background and Introduction

### 1.1. 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).

## **1.2. 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.”

## **1.3. 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 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

From the CMC perspective, the review team recommended the application for "approval." Their primary concern is the observed conversion of the prasugrel salt to free base, but pursuant to an Information Request and additional requests in a Discipline Review Letter, they opined that the sponsor has addressed this issue adequately.

The sponsor initiated the development program using the free base of the drug substance, but became aware that the hydrochloride (HCl) salt had better bioavailability at higher gastric pH. Gastric pH is an important issue in patients who use anti-platelet medications in the ACS setting, because a substantial fraction of these patients take proton pump inhibitors [PPI] or H2 receptor antagonists to reduce gastric acidity, with the goal of reducing gastrointestinal bleeding. Thus, with the concurrence of the Division, the sponsor decided to switch the manufacturing process to the HCl salt form of the drug substance, to enhance bioavailability at higher gastric pH.

Late in development, near the time that the pivotal efficacy study (TAAL) was completed, the sponsor discovered that an acid-base reaction (b) (4) was converting up to 86% of the salt form to the free base form. Using x-ray powder diffraction, the sponsor determined that conversion from salt to base was beginning at the initial (b) (4). Conversion continued during storage to some extent, reaching a plateau after approximately (b) (4). Relative humidity and storage temperature were key factors affecting conversion. Originally, the sponsor proposed to limit the form conversion in the finished product to Not More Than (NMT) (b) (4).

The Division issued a **Discipline Review Letter** on April 9, 2008, summarizing concerns related to form conversion. The sponsor then added several in-process controls as well as a desiccant to packaging, in order to limit form conversion of the to-be-marketed product to Not More Than (NMT) (b) (4).

The CMC team opined that the current specification would allow the sponsor to market a product with wide variability (i.e. NMT (b) (4)) that is inelegant from a quality viewpoint. However, given the analyses of safety and efficacy of form conversion by other disciplines, (b) (4)

. The main basis was:

- There have been extensive discussions with the Clinical Pharmacology and Clinical reviewers of this NDA, as well as with the Cross Discipline Team Leader, Division Director, and Office Director concerning the clinical implications of form conversion. The consensus

is that, although sub-optimal from a quality viewpoint, the presence of a mixture of salt and free base in prasugrel does not appear to have any bearing on safety or efficacy.

- The Clinical Pharmacology reviewer noted in her May 23, 2008, review that the 30% difference in  $C_{max}$  for the active metabolite in patients on PPI who received high-conversion tablets did not change the pharmacodynamic response and consequently may not have clinical significance.

- (b) (4) [REDACTED]

### 3.2. Compliance

The three 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, the data were considered reliable in support of the proposed indication. The manufacturing facility was inspected by the Office of Compliance on September 6, 2008, and the Current Good Manufacturing Practice status was found to be acceptable.

### 3.3. Degradation Products

Several of the degradation products of the drug substance, e.g. (b) (4), (b) (4), 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 (EMA 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 EMA guideline for genotoxic impurities.

## 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, hydrolyzed by esterases, and metabolized by cytochrome P450 enzymes to form the active metabolite, R-138727. Protein binding of metabolites was high (>80%) in rats and dogs, and binding of the active metabolite 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 P2Y<sub>12</sub> 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 H<sub>2</sub> 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 form, it was selected for further development. The review teams opined that the data suggest that dose adjustment may be warranted during treatment with PPI or H<sub>2</sub> receptor blockers.

Additive or synergistic platelet inhibitory effects that result from co-administration of prasugrel and aspirin were demonstrated in several studies of platelet aggregation (*ex vivo*), thrombus formation (*in vivo*), and bleeding times.

#### **4.3. Genetic Toxicity**

No evidence of prasugrel-induced genetic toxicity was observed in standard tests for mutagenicity or clastogenicity that included an *in vitro* bacterial mutation (Ames) test, Chinese hamster lung chromosomal aberration assay, and an *in vivo* mouse micronucleus assay for clastogenicity.

#### **4.4. Carcinogenicity**

Carcinogenicity studies in the rat and in the mouse were reviewed by the Pharmacology/ Toxicology Review team, the Executive Carcinogenicity Advisory Committee, and the Medical Team Leader.

##### **4.4.1. Rat**

In a 24-month carcinogenicity study in rats, doses as high as 100 mg/kg were administered, and associated with systemic R-138727 and R-106583 exposure up to 1000- and 50-fold higher than the anticipated human exposures, respectively. The highest dose was associated with decreases in body weight, and was considered the maximally tolerated dose (MTD). There was no overall difference in survival between prasugrel and controls in either sex, and no apparent dose-response in terms of excess tumors. Diffuse hepatocyte hypertrophy was observed in both sexes at the high dose (100 mg/kg), as well as increased severity of hepatic eosinophilic foci (in males). These foci were thought to be secondary to induction of drug-metabolizing enzymes. Although such foci are considered to be progenitor lesions from which hepatocellular

neoplasia might arise, there was no evidence of malignant tumors in the 2-year lifetime rat studies. The primary pharmacology/toxicology reviewer, Carcinogenicity Assessment Committee (CAC), and Medical Team Leader agreed with this interpretation.

#### 4.4.2. Mouse

Prasugrel doses up to 300 mg/kg were administered in the 24-month carcinogenicity study in mice, yielding systemic exposures of R-138727 and R-106583 about 500-fold greater than the anticipated human exposures. The highest dose was associated with body weight decreases, and considered the MTD. An increased incidence of hepatocellular adenoma was observed in males in the high-dose group (300 mg/kg) and in females in the mid- and high-dose groups (100 and 300 mg/kg), exposures approximately 190-fold greater than the anticipated human exposure levels. The dose-response relationship for the incidence of hepatocellular adenoma was statistically significant, as was the dose-response relationship for the combined incidences of hepatocellular adenoma and hepatocellular carcinoma. Pairwise comparisons showed statistically significant increases in the incidence of hepatocellular adenoma and combined incidences of hepatocellular adenoma and hepatocellular carcinoma for the high-dose group in males, as well as the mid- and high-dose groups in females, compared to respective controls. Combining male and female groups, the numbers of hepatic adenomas (per 110 animals in each group) were 25 in the control group, versus 16, 46, and 83 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively. The numbers of hepatocellular carcinomas were 12 in the control group, versus 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively. The Executive Carcinogenicity Advisory Committee concluded that the mouse study was adequate, and positive for hepatocellular adenomas in both sexes. In their minutes, the Committee did not comment on the trend for increased hepatocellular carcinomas in the high-dose group. The Medical Team Leader also noted weak associations between prasugrel exposure and both intestinal and lung cancers in the mouse study.

#### 4.5. **Reproductive Toxicology**

There was no significant effect of prasugrel on male or female fertility or on early embryonic development at oral doses up to 100 mg/kg (30 times human exposure). At doses  $\geq$ 100 mg/kg, decreases in adrenal gland, seminal vesicle/prostate gland, and epididymal weights were observed, as well as a reduction in mean fetal weight. Dose-associated maternal toxicity and decreases in fetal weight were observed; however, there were no adverse effects on *in utero* survival or morphological development of the conceptus at 100 mg/kg dose. There was no evidence of teratogenicity, based on the absence of changes in the frequency of external, visceral, and skeletal anomalies (100 times human exposure). Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. However,  $^{14}\text{C}$ -prasugrel was excreted in the milk of lactating rats.

#### 4.6. **Summary of Major Pharmacology-Toxicology Issues**

Toxicology studies identified the liver as a target organ, with increases in liver mass, hepatocellular hypertrophy, elevations of alkaline phosphatase, and proliferation of smooth endoplasmic reticulum. There were tendencies for increased incidence of eosinophilic altered cell foci in the higher dose groups, thought to be consequence of induction of hepatic drug-metabolizing enzymes. Such altered cell foci are progenitor lesions that are thought to have the potential to lead to hepatocellular neoplasia. In the mouse, at exposures approximately 190 times higher than those anticipated in humans, there was, in fact, a statistically significant dose-response relationship for hepatocellular adenoma. Though not statistically significant, there was a trend in favor of increased hepatocellular carcinomas at the highest dose, with 12 in the

control group, and 16, 15, and 21 in the prasugrel 50, 100, and 300 mg/kg/day groups, respectively (per 110 animals in each group).

The Pharmacology/Toxicology Team and the Executive Carcinogenicity Advisory Committee concluded that the 2-year rat and mouse studies were reassuring, and found no evidence of a prasugrel-associated increase in malignant tumors in either species. Overall, although inconclusive, they regarded the hepatic findings to be consistent with induction of hepatic drug metabolizing enzymes.

No genetic toxicity was observed for prasugrel in standard tests that included an *in vitro* bacterial mutation test, Chinese hamster lung chromosomal aberration assay, and *in vivo* mouse micronucleus test.

Prasugrel did not cause any significant effects on fertility, early embryonic development, embryo-fetal development, or pre-/postnatal development in the rat or rabbit (approximately 30 times human exposure). At doses high enough to cause effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight relative to controls. Placental transfer of prasugrel metabolites to the fetus of pregnant rats was low. <sup>14</sup>C-prasugrel was excreted in the milk of lactating rats.

#### **4.7. Pharmacology Toxicology Reviewer's Recommendations**

"The extent and scope of the pharmacological and toxicological documentation provided are appropriate to support the clinical use of prasugrel at daily oral dose of 10 mg.

Adequate exposure was obtained in the toxicology studies, and all circulating metabolites in humans occurred in the circulation of species used in the non-clinical toxicity studies. The non-clinical studies adequately address the safety of prasugrel.

The proposed prescribing information includes an appropriate description of the genotoxicity, animal carcinogenicity studies, developmental and reproductive studies, and appropriate advice on breast feeding."

### **5. Clinical Pharmacology/Biopharmaceutics**

#### **5.1. Absorption, Distribution, Metabolism, Excretion**

More than 79% of an oral dose of prasugrel is absorbed. The pro-drug is rapidly hydrolyzed by intestinal hydroxysterases to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. The parent drug cannot be detected in plasma. Absorption and metabolism are both rapid; peak plasma concentrations of the active metabolite are reached approximately 30 minutes after administration. Exposure to the active metabolites increases slightly more than proportionally over the therapeutic dose range. The administration of repeated doses of 10 mg does not lead to the accumulation of the active metabolite.

In subjects with stable atherosclerosis, estimates of the apparent volume of distribution of prasugrel's active metabolite ranged from 30-84 L, and estimates of apparent clearance ranged from 73-266 L/hr.

Binding of the active metabolite to plasma proteins was not determined *in vivo*, but was highly bound *in vitro*. The inactive metabolites are also highly bound to human plasma proteins.