1 EXECUTIVE SUMMARY

Eli Lilly Inc. submitted NDA 22-307 - EFFIENT (Prasugrel Hydrochloride tablets) on December 26, 2007. Prasugrel is proposed for the reduction of atherothrombotic events and the reduction of stent thrombosis in acute coronary syndromes (ACS).

EFFIENT is a novel adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class and an inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. EFFIENT was developed in collaboration with Daiichi Sankyo Inc.
EFFIENT will be marketed as an oral 5 and 10 mg film coated tablets.

The recommended administration: an initial single oral 60 mg loading dose and then continued at a 10 mg once daily dose. All patients taking prasugrel should also take aspirin (75 mg to 325 mg) daily. Prasugrel may be taken with or without food. Patients weighing less than 60 kg should be given a single 60 mg loading dose and then continued at a 5 mg once daily dose.

The submission included 48 clinical pharmacology studies where the pharmacokinetics and pharmacodynamics of prasugrel were assessed. The sponsor conducted several in vitro studies to assess the metabolism by CYP450, binding to plasma protein and drug-drug interaction studies with drugs that could be possibly co-administered in the clinic. A total of 36 studies were reviewed.

1.1 RECOMMENDATIONS:

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics (CPB) information submitted to NDA 22-307. The CPB information provided in NDA 22-307 is acceptable.

SPECIFIC RECOMMENDATIONS:

1. The proposed dose adjustment of prasugrel maintenance dose to 5 mg QD for patients with body weight less than 60 Kg is acceptable.
2. The proposed dose adjustment of prasugrel maintenance dose in patients with age $\geq$ 75 y is not acceptable.
3. Pre-treatment of at least 6 hrs for prasugrel or clopidogrel is not necessary to achieve maximum effectiveness. The loading dose for either prasugrel or clopidogrel should be administered at least within 30 minutes of the start of PCI.

The following comments should be properly addressed by the sponsor.

COMMENTS:

1. The sponsor should consider lowering the 60/10 dosing regimen of prasugrel in order to decrease the incidence of bleeding.

2. The sponsor should investigate the effects of a CYP2B6 inhibitor on the PK of prasugrel.

3. Not enough information is provided in the study reports in patients with ESRD. The sponsor is requested to provide additional information in order to better evaluate the study results and be able to provide labeling recommendations in this patient population.

4. [redacted] b(4)

5. The labeling comments should be addressed by the sponsor.

1.2 PHASE IV COMMINMENTS:

The sponsor should : [redacted] b(4)

Date_____

Elena Mishina, Ph. D.
Senior Clinical Pharmacologist

Sripal Mada, Ph.D
Clinical Pharmacologist

Raj Madabushi, Ph.D
Pharmacometrics Reviewer

Yaning Wang, Ph.D
Pharmacometrics Team Leader

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

CPB Briefing was held on May 21, 2008

Attendees: Menon D, Younis I, Burkhart G, Mehta M, Unger E, Rahman A, Huang SM, Uppoor R, Zhang L, Chen TO, Orlof D, Yun X, Iyer G, Dorantes A, Ququan L, Hicks K, Marroum P, Mada S, Mishina E, Madabushi R.

cc list: NDA 22-307, MehulM, MarroumP, MishinaE, UppoorR, HFD 110 BIOPHARM

1.3 Summary of OCPB Findings

1.3.1 Background

Eli Lilly and Co is seeking the approval of prasugrel for the reduction of atherothrombotic events and the reduction of the stent thrombosis in acute coronary syndromes (ACS).

1.3.2 Current Submission

The investigation of prasugrel was performed under the IND 63449. The clinical pharmacology program for the NDA 22-307 includes 48 clinical pharmacology and biopharmaceutics studies.
The assessment of the prasugrel PK and PD in healthy subjects included a single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect, and 10 drug-drug interaction PK and PD studies.. The influence of race, age, hepatic and renal impairment on prasugrel PK and PD were evaluated in 13 studies. The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies. The efficacy of prasugrel as an anti-thrombotic therapy in the treatment of patients with ACS managed by Percutaneous Coronary Intervention (PCI) was supported by one large Phase 3 clinical study (TAAL).
Also, protein binding, metabolism, and formation of the isomer sets (RS/RR and SR/SS) of R-138727, the active metabolites were studied in 7 in vitro studies. A population PK/PD data analysis was performed for the pivotal study TAAL. A thorough QT study was also done.
In total, 36 studies submitted under the NDA 22-307 were reviewed.

Pharmacokinetics

Absorption, Distribution, Metabolism, Excretion

Following oral administration, more than 79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (Cmax) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases slightly higher 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.
The parent drug is not detected in plasma following oral administration. It is rapidly hydrolyzed by hydroxyesterases in the intestine 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 estimates of apparent volume of distribution of prasugrel's active metabolite ranged from 30 L to 84 L and the estimates of apparent clearance ranged from 73 L/hr to 266 L/hr in subjects with stable atherosclerosis.
The binding of the active metabolite to plasma proteins was not determined in vivo, and in vitro, it was 98% in a 4% human serum albumin solution in phosphate buffer, pH 7.4. All the inactive metabolites are highly bound to human plasma proteins.
Although the plasma-to-whole blood ratio measured by total radioactivity was generally greater than one, it does not prove that the penetration into red blood cell was limited to a specific molecular entity.
The active metabolite R-138727 contains 2 chiral centers, and thus is comprised of 4 enantiomers which possess different activities towards the platelet P2Y12 ADP receptor, with the (R,R)/(R,S) pair being the most potent. In humans, the (R,R)/(R,S) pair comprised about 84% of the total active metabolite in plasma. The ratios of R-138727 enantiomers were consistent among all subjects.

Prasugrel is cleared both by the liver and the kidney: about 68% of the prasugrel dose is excreted in the urine and 27% in the feces, as inactive metabolites. The active metabolite has an elimination half life of about 7.4 hours (range 2 to 15 hours).

Pediatric Patients
The pharmacokinetics of prasugrel in children has not been studied in this NDA.

Intrinsic Factors
Body Weight
Dose adjustment to 5 mg QD in patients with body weight below 60 kg is acceptable. Trends of increased bleeding related adverse events were associated with increased exposures of R-138727. Exposure of R-138727 increased with decreasing body weight and the Thrombolysis in Myocardial Infarction (TIMI) Major bleeding risk was 2 fold higher in patients with body weight less than 60 Kg. Efficacy was similar across the body weight groups. Reducing the maintenance dose of prasugrel to 5 mg shifts more than 50% of patients with body weight less than 60 Kg to lower quartiles of exposure seen with 10 mg in patients with body weight greater than 60 kg.
Gender
No dose adjustment based on gender is recommended
Age
There is no need for the dose adjustment for the patients older than 75 years of age. Age ≥75 y was an independent predictor for increased risk of primary composite efficacy endpoint (Cardiovascular death, non-fatal myocardial infarction and non-fatal stroke CVD/ Non-fatal MI/Non-fatal Stroke) and TIMI Major bleeding. Even with 10 mg QD regimen, the risk of observing efficacy endpoint was ~2 fold higher in patients with age ≥75 y compared to patients below 75 y. Further the relative risk for TIMI major bleeding was 65% higher. However, prasugrel is shown to be better than clopidogrel in patients above 75 years age group. The impact of further dose reduction on the efficacy is not known. Hence dose reduction is not justified.
Race
The exposure to the prasugrel active metabolite in African, Hispanic, and Caucasian subjects were similar; however, the exposure were about 40-45% higher in Asian compared to Caucasian subjects. After adjusting for the population body weight and the effect of other covariates, Cmax and AUC0-tlast were still 20% higher in Asians than in Caucasians. The IPA response in the Asian subjects was stronger than in Caucasians. The highest incidence of bleeding-related adverse events was reported for Korean subjects.
The administration of prasugrel to subjects of Asian origin should be performed with caution.
Renal Impairment
After 60 and 10 mg doses of prasugrel, the exposure to R-138727 (both Cmax and AUC(0-tlast)) decreased by half in subjects with ESRD compared to that in healthy controls and subjects with moderate renal impairment. A conclusion about the MPA response in patients with ESRD is difficult to make due to the small sample size. The bleeding events were not assessed in these studies. The label should contraindicate prasugrel administration to ESRD patients.
Hepatic Impairment
The PK parameters estimated for the active metabolite R-138727 in healthy subjects and in subjects with moderate hepatic impairment were similar. The PD response measured as MPA to

20 mcM ADP was similar in the groups of healthy subjects, and subjects with mild and moderate hepatic impairment.
A dose adjustment is not required for the patients with mild and moderate hepatic impairment. Prasugrel should be contraindicated in patients with severe hepatic impairment due to the potential risk of bleeding.

Extrinsic Factors
Food Effect
In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but Cmax was decreased by 49% and the time to reach Cmax (Tmax) was increased from 0.5 to 1.5 hours. Prasugrel can be administered without regard to food.
Drug-drug interaction information

The in vivo DDI studies with a CYP3A4 inhibitor (ketoconazole), a CYP3A4 inducer (rifampicin), and a CYP2B6 substrate (bupropion) did not reveal any clinically important interactions. A clinically significant pharmacodynamic drug-drug interaction: prolongation of the bleeding time was observed when prasugrel was co-administered with aspirin, warfarin and heparin. Caution should be exercised when these drugs are coadministered with prasugrel. Due to an increased incidence of liver enzyme elevation observed following coadministration of prasugrel and atorvastatin, this combination should be prescribed under close physician monitoring.
The potential role of prasugrel as a Pgp substrate was not evaluated in this NDA. Co-administration of prasugrel with digoxin reveals that prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration.

Exposure-Response Relationships
Effectiveness
Prasugrel showed a concentration dependent inhibition of the platelet aggregation (IPA). The exposures achieved with the proposed loading dose of prasugrel result in maximum inhibition of the platelet aggregation. However, the relationship between the inhibition of platelet aggregation and the clinical outcome (CVD/Non-fatal MI/Non-fatal Stroke) is not clearly understood. Further, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention (PCI), no consistent relationship between the dose of prasugrel and the endpoint (major adverse cardiovascular event [MACE] at 30-day visit) was observed. However, it should be noted that this study was not designed to characterize dose-response and the sample size was small.
Lowest incidence of the primary efficacy endpoint was seen when the loading dose was administered within 30 minutes of the start of Percutaneous Coronary Intervention (PCI). The increased incidence of the primary efficacy endpoint when the loading dose was administered at least 6 hrs prior to the start of PCI was confounded with Prior Coronary Bypass Graft Surgery. The effect of timing of loading dose on the efficacy was seen independently for prasugrel and clopidogrel, suggesting that pre-treatment 6 hrs before the start of PCI may not be necessary.
Safety
A meta analysis of the pharmacokinetic data from 6 clinical pharmacology studies found that among subjects treated with prasugrel 10-mg MD, a trend towards a higher rate of bleeding-related adverse events in the highest quartile of exposure to the active metabolites. Further in a

phase 1b study TAAD, the rate of epistaxis was higher in subjects treated with 15 mg prasugrel. Similar results indicating increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding rates were observed in the phase II study TAAH indicating exposure bleeding relationship. In the phase II study TAAH in ACS patients, increasing doses of prasugrel resulted in increased Thrombolysis in Myocardial Infarction (TIMI)/Major/Minor/Minimal bleeding (5.2% with 60/15-mg MD versus 3.5% with 40/7.5-mg and 60/10-mg doses respectively). However, this difference was primarily in TIMI minimal bleeding. All these studies indicate towards a relationship between the exposure of R-138727 and bleeding.

Prasugrel was found not to prolong the QT interval.

Biopharmaceutics

Prasugrel particle size does not seem to affect the bioavailability of the active metabolite after coadminisrtation with 30 mg lansoprazole.

Lots with differing amounts of prasugrel salt (78, 50 and 5%) were found to be bioequivalent. However, when these lots were coadminestered with 30 mg lansoprazole,. These lots were bioequivalent in terms of AUC but not CMAX. (30 % differences in means between the high and low conversion lots). This difference in CMAX translated into a greater than 10% difference in IPA at 0.5 and 1 hour postdose.

2 QUESTION BASED REVIEW

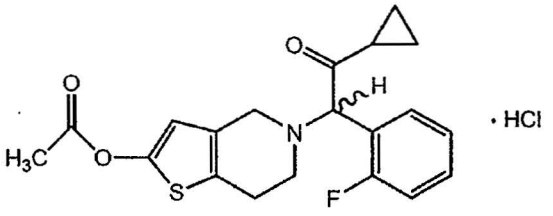
2.1 General Attributes

History of Regulatory Development

EFFIENT® (prasugrel hydrochloride), an adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class, is an inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. Prasugrel (also known as CS-747 and LY640315) was discovered by Sankyo Company, Ltd. (now Daiichi Sankyo), which sponsored the initial preclinical and clinical studies. Prasugrel is currently a co-development project between Daiichi Sankyo and Eli Lilly and Company.
In the present submission, the sponsor is seeking the approval of prasugrel for the reduction of atherothrombotic events and the reduction of the stent thrombosis in acute coronary syndromes (ACS).

Highlights of chemistry and physical-chemical properties of the drug substance and product
Prasugrel is available as a hydrochloride salt. The Chemical Name (USAN): (±)-2-[2-Acetyloxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]-1-cyclopropyl-2-(2-fluorophenyl)ethanone hydrochloride. Other Chemical Name: 2-Acetoxy-5-(a-cyclopropyl carbonyl-2-fluorobenzyl)-4,5,6,7- tetrahydrothieno[3,2-c]pyridine hydrochloride.

Molecular Formula: $C_{20}H_{20}FNO_3S \cdot HCl$
Molecular Weight: 409.90
Structural Formula:



Prasugrel is administered as a racemic prodrug that is metabolized in vivo to the active moiety, R-138727 which contains 2 asymmetric centers, therefore, has 4 diastereomers.
Prasugrel hydrochloride is a white to light brown solid.
Solubility: It was not feasible to conduct equilibrium solubility determination of this molecule due to the rapid solution hydrolysis of prasugrel hydrochloride prodrug.

What are the proposed mechanisms of action and therapeutic indication?

Prasugrel's pharmacological action results from a covalent and irreversible binding of R-138727 to the P2Y12 platelet adenosine diphosphate (ADP) receptor. Once bound, a platelet is rendered ineffective for its remaining lifespan. After prasugrel dosing is stopped, return to baseline platelet aggregation occurs only as new platelets are formed.

What are the proposed dosages and route of administration?

The sponsor recommends that prasugrel be initiated with a single oral 60 mg loading dose and then continued at a 10 mg once daily dose. All patients taking prasugrel should also take aspirin (75 mg to 325 mg) daily. Prasugrel may be taken with or without food. Patients weighing less than 60 kg should be given a single 60 mg loading dose and then continued at a 5 mg once daily dose. Patients 75 years of age and older should be given a single 60 mg loading dose and consideration may be given to a 5 mg once daily dose as an alternative to 10 mg once daily dose.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The investigation of prasugrel was performed under IND 63449. The clinical pharmacology program for NDA 22-307 includes 48 studies.
An assessment of prasugrel PK and PD in healthy subjects was performed in 8 clinical studies. The early studies investigated the base-formulation of the drug. A single and a multiple dose PK, a dose ascending, a mass-balance and a food-effect study were also performed. The influence of race, age, hepatic and renal impairment on prasugrel PK and PD were evaluated in 13 studies.
The PK and PD in subjects with atherosclerotic vascular disease were evaluated in 4 studies including the pivotal trial TAAL.
Drug-drug interaction PK and PD studies of prasugrel and aspirin, proton pump inhibitors, ketoconazole, rifampicin, atorvastatin, warfarin, bupropion, heparin, and digoxin were performed.
Also, protein binding, metabolism, and formation of the isomer sets (RS/RR and SR/SS) of R-138727, the active metabolites were studied in 7 in vitro studies.
Several studies describing the base formulation and also studies performed under the other investigation program in Japan were not reviewed.
In total, 36 studies submitted under the NDA 22-307 were reviewed.

Were the correct moieties identified and properly measured to assess clinical pharmacology?

Yes. The sponsor measured the concentrations of prasugrel metabolites since prasugrel is a prodrug and cannot be measured in plasma. In the majority of the clinical pharmacology studies, the active metabolite of prasugrel R138727 was measured as well as the inactive metabolites R-95913, R119251, and R106583. In the early studies, the other inactive metabolite R100932 was measured (instead of R119251). In order to measure the plasma concentrations of the active metabolite R-138787 of prasugrel, the sample should be derivatized immediately after the sample is taken. Due to the difficulties with the handling of blood samples, in the pivotal clinical study only inactive metabolites were measured in plasma, and the active metabolite characteristics were estimated based on the proposed population PK model.
For the assessment of pharmacodynamics, the inhibition of platelet aggregation (IPA) by 5 and 20 mcM of ADP was measured. Also, a few other methods were used, as VASP phosphorylation (flow cytometry), platelet reactivity index (PRI), bleeding time.
All assay methods were properly validated and are acceptable, chromatograms were shown.