6 APPENDIX IV: OCP Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-307	Brand Name	**Effient**
OCPB Division (I, II, III)	DIV-1	Generic Name	Prasugrel
Medical Division	CARDIORENAL	Drug Class	ADP receptor antagonist of the thienopyridine class
OCPB Reviewer	ELENA MISHINA	Indication(s)	Reduction of atherothrombotic events and stent thrombosis in ACS patients with stable angina or NSTEMI
OCPB Team Leader	P. Marroum	Dosage Form	Tablets — 5, and 10 mg
		Dosing Regimen	Starting from [redacted]
Date of Submission	12/26/2007	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	Eli Lilly
PDUFA Due Date	6/26/2008	Priority Classification	P
Division Due Date	5/26/2008		

b(4)

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X	1		
Isozyme characterization:	X	5		
Blood/plasma ratio:	X	1		
Plasma protein binding:	X	1		
Pharmacokinetics (e.g., Phase I) -		[redacted]		
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	9		
Patients-				
single dose:				
multiple dose:	X	5		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:		1		
Drug-drug interaction studies -		[redacted]		
In-vivo effects on primary drug:	X	8		
In-vivo effects of primary drug:	X	6		
In-vitro:	X	7		
Subpopulation studies -				
ethnicity:		2		
gender:				
pediatrics:				
geriatrics:		1		
renal impairment:	X	2		
hepatic impairment:	X	3		
PD:				
Phase 2:				
Phase 3:	X	1		
PK/PD:				

Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:	X	1		
Population Analyses -	[redacted]	[redacted]		
Data rich:	X	2		
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	4		
Bioequivalence studies -				
traditional design; single / multi dose:	X	3		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:	X	1		
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Electrophysiololgy Study				
Pharmacodynamic studies	19			
Total Number of Studies Reviewed	36			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

7 APPENDIX V: Pharmacometrics Review

Pharmacometrics Review

NDA	22307
Submission Date(s)	12/27/2007
PDUFA Due Date	06/27/2008
Brand Name	Effient®
Generic Name	Prasugrel
Pharmacometrics Reviewer	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Reviewer	Elena Mishina Ph.D.
Clinical Pharmacology Review Team Leader	Patrick Marroum, Ph.D.
Sponsor	Eli Lilly
Submission Type	Original NDA (NME)
Formulation	Tablet
Proposed indication	Antithrombotic
Proposed Dosage and Administration	60 mg Loading Dose; 10 mg QD Maintenance

Executive Summary

In the present submission, the following key questions were addressed by the reviewer:

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

Prasugrel showed a concentration dependent inhibiton of the platelet aggregation. 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 out come (Composite of Cardiovascular death, non-fatal myocardial infarction and non-fata stroke) is not clearly understood. Further, in a double blind, randomized dose-ranging trial in patients undergoing percutaneous coronary intervention, 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 (N=200 for 40/7.5 and 60/10 groups and N=251 for 60/15 group).

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*?

A trend for increased bleeding-related adverse events with increase in exposure of the active metabolite of prasugrel was observed in the early clinical pharmacology studies. Similar trends were observed with increased bleeding with increased doses in patients with stable atherosclerosis. However, it should be noted that these events were predominantly driven by minimal bleeding.

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issues?

Dose selection for the pivotal trial was based primarily on the effect of prasugrel on the inhibition of platelet aggregation (IPA) and bleeding compared to clopidogrel in subjects with stable atherosclerosis.

The 60-mg prasugrel LD consistently achieved the highest level of platelet inhibition and was chosen as the Loading Dose to be studies in the pivotal trial. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD. However, the 15-mg MD of prasugrel was associated with higher bleeding adverse events (AEs) hence 10-mg prasugrel MD was selected. This effect of increased trend for bleeding with 15-mg prasugrel MD compared to 10-mg prasugrel MD was also observed in Study TAAH. Hence, a 10-mg once-daily maintenance dose (MD) was selected to be studied in the registration trial TAAL.

Since the relationship between the inhibition of platelet aggregation and the cardiovascular risk is not clearly understood, the effectiveness of lower dosing regimen is unknown.

Should the maintenance dose be reduced to 5 mg QD in patients with body weight below 60 Kg?

Dose adjustment to 5 mg QD in patients with bodyweight 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.

Should the maintenance dose be reduced to 5 mg QD in patients with age ≥75 years?

No. Age ≥75 y was an independent predictor for increased risk of primary composite efficacy endpoint (CVD/ Non-fatal MI/Non-fatal Stroke) and TIMI Major bleeding. The efficacy of prasugrel was better (numerically) than clopidogrel with a similar risk for bleeding in patients age>75 years. Further, after adjusting for bodyweight, the exposure of active metabolite of prasugrel did not increase with age. Hence dose reduction in elderly patients is not justified.

What is the impact of early loading dose (6 hours prior to the start of PCI) on the incidence of efficacy events?

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.

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 ≥ 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 should be administered at least within 30 minutes of the start of PCI.

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Introduction

EFFIENT® (prasugrel hydrochloride), an adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class, is a potent inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. 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).

Prasugrel is an orally administered pro-drug requiring in vivo metabolism to form the active metabolite (R-138727). This conversion occurs through rapid hydrolysis by carboxylesterases and then by multiple cytochrome P450 enzymes. 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). Study TAAL enrolled 13,608 subjects with ACS who were randomly assigned in a blinded fashion either to a 60-mg Loading Dose (LD) of prasugrel at the time of PCI, followed by a 10-mg daily Maintenance Dose (MD) of prasugrel, or to the approved clopidogrel 300-/75-mg LD/MD (all subjects concomitantly treated with aspirin). Subjects were treated (6 months minimum and 15 months maximum) for a median duration of 14.5 months. The primary objective of Study TAAL was to test the hypothesis that prasugrel co-administered with aspirin is superior to clopidogrel co-administered with aspirin in the treatment of subjects with ACS who are to undergo PCI, as measured by a reduction in the composite efficacy endpoint of CV death (CVD), nonfatal MI, or nonfatal stroke.

Three studies (TAAJ, TAAD, TABR) provide direct population PK/PD comparisons of prasugrel and clopidogrel in healthy subjects or subjects with stable atherosclerosis, whereas a population PK analysis of data from 1159 subjects in the Phase 3 Study TAAL characterizes the PK of prasugrel's active metabolite in the intended population of patients who are to undergo PCI for ACS management.