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6 APPENDIX IV: OCP Filing Review Form

Office of Clinical Pharmac	ology	and Biopharn	naceutics			
New Drug Application Filin	ng an	d Review Forn	n			
General Information About the Submissi	on					
	Infor	mation			Info	mation
NDA Number	22-307		Brand Name		Effient	
OCPB Division (I, II, III)	DIV-1		Generic Name		Prasugrel	
Medical Division	CAR	DIORENAL	Drug Class		ADF	receptor antagonist of the
					thier	opyridine class
OCPB Reviewer	ELE	NA MISHINA	Indication(s)		Redu	action of atherothrombotic events and
					stent	infombosis in ACS patients with
OCPP Team Loader	P. Marroum		Dosage Form		Tablets 5 and 10 mg	
OCPB Team Leader	ader P. Marioum		Dosing Regimen		Stor	ing from
Date of Submission	12/26/2007		Route of Administration		oral	
Estimated Due Date of OCPB Review	12/20	12001	Sponsor	aration	FliI	illy
PDUFA Due Date	PDUEA Due Date 6/26/20		Priority Classification		P	
Division Due Date	bivision Due Date 5/26/2008		Thority classification		-	
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		A If included	Number of	number	OI	Critical Comments if any
		at ming	submitted	reviewed		
STUDY TYPE			oublinded	101101100		
Table of Contents present and sufficient	ent to	X				
locate reports, tables, data, etc.						
Tabular Listing of All Human Studies		Х				
HPK Summary		X				
Labeling		X				
Reference Bioanalytical and Analytic	al	X				
Methods						
I. Clinical Pharmacology				·		
Mass balance:		X	1			
Isozyme characterization:		X	5			· · · · · · · · · · · · · · · · · · ·
Blood/plasma ratio:		×				·
Plasma protein binding.		^				
Healthy Volunteers						
single dose:		x	1	-		·
multiple dose:		x	9	<u> </u>	·	
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 -			- iti			
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:						
genatrics:			1			
henetia impairment:		÷	2 .			
pp.		^	3			
Phase 2						
Phase 3		X	1			
PK/PD:			·			

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Clinical Pharmacology Review NDA 22-307, Prasugrel

5/23/2008

Phase 1 and/or 2 proof of concent:	I Y	3	1	
Phase 3 clinical trial:	X	1		
Population Applycoc			<u></u>	
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Data non.	÷	4		
Data sparse.	^			
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Relative bloavallability -				
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			
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7 APPENDIX V: Pharmacometrics Review

Prasugrel (Effient®)

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

5/22/2008

Raj Madabushi

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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 10mg 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.

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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 \geq 75 years?

No. Age \geq 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.
- The proposed dose adjustment of prasugrel maintenance dose in patients with age ≥ 75 y is not acceptable.
- 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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Prasugrel (Effient[®])

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 P2Y₁₂ 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).

Prasuarel 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.

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