CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-647

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	21,647	Brand Name	Vioxx
OCPB Division (I, II, III)	I (HFD-860)	Generic Name	Rofecoxib
Medical Division	HFD-120	Drug Class	Cox-2 inhibitor
OCPB Reviewer	Wen-Hwei Chou, Pharm.D., Ph.D.	Indication(s)	Acute treatment of Migraine, with or without aura
OCPB Team Leader	Ramana, Uppoor, Ph.D.	Dosage Form	• Vioxx (Rofecoxib) tablets (12.5, 25 & 50 mg) • [redacted])
		Dosing Regimen	25mg, 50mg (max)
Date of Submission	05/23/2003	Route of Administration	P.O.
Estimated Due Date of OCPB Review		Sponsor	Merck & Co., Inc. West Point, PA 19486
Division Due Date	12/23/2003	Priority Classification	S (New indication)
PDUFA Due Date	02/23/2004		

Clin. Pharm. and Biopharm. Information

Background

- Rofecoxib is a selective cyclooxygenase (COX)- 2 inhibitor approved by FDA in 1999. It is currently indicated for the chronic treatment of osteoarthritis (12.5 to 25 mg daily) and rheumatoid arthritis (25 mg daily), as well as for the treatment of acute pain and primary dysmenorrhea (50 mg daily up to 5 days).

- The sponsor has conducted two clinical trials (protocols 161 & 162) to evaluate the efficacy and safety of rofecoxib in acute treatment of migraine where rofecoxib doses of 25 and 50 mg were tested

- The Vioxx for migraine development program focuses on Phase III studies evaluating the efficacy and safety in migraine patients using monotherapy treatment with rofecoxib at doses and dosage schedules for the acute treatment of migraine that are within the pre- existing FDA approved Vioxx label. Therefore, no additional PK/ BA studies were conducted in this program.

- The sponsor submitted the NDA in a CTD format with no new human PK and bioavailability documentation. The sponsor cross- referenced the approved NDA 21,042 for Vioxx.

- **CPB comments conveyed to the sponsor at Pre-NDA meeting versus current submission:**

1. Since this drug is to be used for treatment of migraine, it is important to know whether PK differs in patients during and between migraines. The sponsor should consider generating such information---------- No such information is submitted.
2. Electronic format:

- While the sponsor can cross- reference the approved NDA, it would facilitate the review if the following information is provided in the proposed NDA

a. Brief summary of PK of rofecoxib at the proposed dose and dosing regimen for treatment of migraine---- ----Sponsor did not provide such section in current submission Original NDA was cross-referenced.

b. Discussion of potential pharmacokinetic and pharmacodynamic interactions with concomitant drugs likely to be used in this indication----------Not provided. However, Vioxx label contains adequate information on potential metabolism-based DDIs. In addition, in a cross -study comparison (#161 & #162), the sponsor conducted treatment-by-covariates interactions for the primary efficacy endpoint . Covariates include gender, age, race, aura, concomitant migraine prophylactics, use of oral contraception, prior response to NSAIDs, dysmenorrhea(E-doc :2.7.3.3.3). Also, the adverse experiences in subgroups [age (>40 or <40yr) gender, race, drug-drug interactions] were evaluated (e-doc: 2.7.4.5.1-2.7.4.5.3). This section will be reviewed by the medical officer.

- Please provide dose response data from phase III trials as SAS transport files.---------- No PK measures. Dose-response relationship evaluation may not be useful since for the 50mg when compared to 25mg, odds ratio (95%CI) of the primary efficacy endpoint is 1.13 (0.75, 1.73)(study 161) & 1.1. (0.71, 1.68) (study 162); (see attachment).

3. Since this drug may be used in adolescents as well, a pediatric deferral may be more appropriate than a waiver (if the pediatric rule is even enforceable). When pediatric studies are conducted, we recommend a PK study in pediatric and adult patients with a history of migraine.----------Note: This NDA is for adult indication only at this time.

The sponsor proposed to use pre- existing FDA approved Vioxx label for tablet & suspension. The sponsor did not proposed any change in Clinical Pharmacology & Biopharmaceutics section. The results of covariate analyses were described under "Clinical studies".

	"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.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -	x	2		Subgroups analyses in clinical trials (161 &162) (age, gender, drug-interactions)
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -	x	2		Subgroups analyses in clinical trials (161 &162) [age(>40 or <40 yr), gender, drug-interactions]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	x	2		Clinical studies (161 & 162). No PK measures. Dose-response relationship evaluation may not be useful since for the 50mg when compared to 25mg, odds ratio (95%CI) of the primary efficacy endpoint is 1.13 (0.75, 1.73)(study 161) & 1.1. (0.71, 1.68) (study 162); (see attachment).
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				

replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	• This is an electronic submission. • No additional human PK data are submitted.
Comments sent to firm ?		No additional comments
QBR questions (key issues to be considered)		
Other comments or information not included above	The PK in patients during migraine would be good to know, however, not a requirement for filing. Since no new PK information is submitted, we will not review this NDA submission. If specific questions are raised by the Medical Officer during his review, we will look into this submission at that time.	
Primary reviewer Signature and Date	Wen-Hwei Chou, Pharm.D., Ph.D.	
Secondary reviewer Signature and Date	Ramana Uppoor, Ph.D.	

CC: NDA 21,647, HFD 860 (Mehta, Sahajwalla, Uppoor, Chou), HFD-850(Lee), HFD-120(CSO), CDR

Attachment

Table 2.7.3: 14

Number (%) of Migraine Patients Reporting Headache Relief at 2 Hours Postdose
(All-Patients-Treated Approach)
Individual Phase III Studies, and Combined Acute Phase Population

	Headache Relief		Odds Ratio (95% CI)		
	n	%	Compared to Placebo	Compared to Rofecoxib 25 mg	Compared to Rofecoxib 50 mg
Protocol 161					
Placebo (N=175)	60	34.3	N/A	--	--
Rofecoxib 25 mg (N=176)	95	54.0	2.21 (1.43,3.43)***	N/A	--
Rofecoxib 50 mg (N=187)	106	56.7	2.51 (1.63,3.86)***	1.13 (0.75,1.73)	N/A
Protocol 162 Acute					
Placebo (N=187)	57	30.5	N/A	--	--
Rofecoxib 25 mg (N=187)	111	59.4	3.67 (2.36,5.70)***	N/A	--
Rofecoxib 50 mg (N=188)	117	62.2	4.02 (2.58,6.26)***	1.10 (0.71,1.68)	N/A
Ibuprofen 400 mg (N=189)	109	57.7	3.37 (2.17,5.22)***	0.92 (0.60,1.40)	0.84 (0.55,1.28)
Combined Acute Phase Population (p=0.177)†					
Placebo (N=362)	117	32.3	N/A	--	--
Rofecoxib 25 mg (N=363)	206	56.7	2.79 (2.05,3.80)***	N/A	--
Rofecoxib 50 mg (N=375)	223	59.5	3.12 (2.30,4.25)***	1.12 (0.83,1.51)	N/A

*** p≤ 0.001 based on pairwise comparisons from logistic regression model.
† p-Value for treatment-by-protocol interaction.
An odds ratio >1 is in favor of the treatment group listed in the row of the pairwise comparison.
N = Number of patients with non-missing (or carried-forward) migraine headache severity at 2 hours.
n (%) = Number (percent) of patients with headache relief at 2 hours postdose.
N/A = Not applicable.
CI = Confidence interval.

[Ref. 5.3.5.1:P161; 5.3.5.1:P162]

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/s/

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7/8/03 12:00:16 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
7/8/03 12:03:45 PM
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