OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDAs	21-042/(SE5-026) & 21-052/(SE5-019)
Submission Dates	12/5/2003; 2/17/2004; 4/22/2004; 4/29/2004; 5/7/2004
Brand Name	VIOXX™ 12.5 mg and 25 mg Tablets VIOXX™ 12.5 mg/5 mL and 25 mg/5 mL Oral Suspension
Generic Name	Rofecoxib
Reviewer	Lei Zhang, Ph.D.
PM Reviewer	Jenny J. Zheng, Ph.D.
Team Leader	E. Dennis Bashaw, Pharm.D.
OCPB Division	DPE III (HFD-880)
OND Division	DAAODP (HFD-550)
Sponsor	Merck & Co., Inc.
Relevant IND	46,894
Submission Type	SE5 (Different/New Population)
	Labeling Changes with New Indications in Pediatric Populations
	Pediatric Exclusivity Determination Requested

1 EXECUTIVE SUMMARY

Vioxx (Rofecoxib), an orally active cyclooxygenase-2 (COX-2) inhibitor, was approved on May 20, 1999 for the relief of the signs and symptoms of osteoarthritis (OA), for the management of acute pain in adults, and for the treatment of primary dysmenorrhea. A supplement NDA was approved on April 11, 2002 for the relief of the signs and symptoms of rheumatoid arthritis (RA) in adults.

The Sponsor submitted this supplemental application (for both NDA 21-042 and NDA 21-052) to fulfill the requirements listed in FDA's Written Request (WR) issued on May 7, 2001, December 6, 2001 and May 14, 2003 amendments. The Sponsor is seeking pediatric exclusivity, and labeling changes that include a new indication in the treatment of signs and symptoms of juvenile rheumatoid arthritis (JRA) for Vioxx. Relatively few nonsteriodal anti-inflammatory drugs (NSAIDs), no COX-2 inhibitor, have been prospectively studied and approved for use in pediatric patients compared with adult arthritis patients. The addition of rofecoxib to the therapeutic armamentarium for JRA could represent a treatment advance.

This application consists of four PK studies (three in JRA patients aged 2-17 yrs and one in adult RA patients) and one clinical efficacy/safety study in JRA patients aged 2-17 yrs (with a 52-week open-label extension). The Sponsor has fulfilled the requirements listed in WR and FDA granted the pediatric exclusivity on February 18, 2004.

To guide dose selection for JRA patients, steady-state pharmacokinetics of rofecoxib was characterized in patients (aged 2-17 years old) with pauci (oligo)- or poly-articular course JRA. In addition, steady-state PK was characterized in adult RA patients for comparison. As part of the WR, changes in drug oral clearance (CL/F) were pre-defined as the parameter of interest. Body weight, body surface area (BSA) and age were found to be the most important covariates that affect clearance of rofecoxib.

The Pediatric Written Request (PWR) called for a statistical comparison of the PK parameters of rofecoxib between pediatric JRA patients and adult RA patients. The Sponsor proposed dose recommendations of 0.6 mg/kg (up to 25 mg) for JRA patients 2-11 years old and 25 mg for adolescent JRA patients based on comparison of clearance and exposure of rofecoxib in JRA patients and healthy adults. The assumptions used were: 1) similar exposure-response in pediatrics and adult patients; 2) similar exposure in healthy adults and adult RA patients; and 3) dose-proportional exposure in the effective dose ranges in JRA and RA patients. In fact, clearance data from adult RA patients was 32% lower than that in healthy adults (63 mL/min vs. 92 mL/min), thus contradicting one of the Sponsor's *a priori* assumptions. Therefore, exposure (AUC_{0-24}) of rofecoxib under the proposed dose recommendations in JRA patients was lower than that in adult RA patients dosed at 25 mg dose with a Geometric Mean Ratio (GMR) of 0.77 (90% CI, 0.64, 0.93) but was comparable to AUC_{0-24} in healthy adults dosed at 25 mg dose with a GMR of 1.12 (90% CI, 0.98, 1.29).

Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the safety and efficacy of the recommended doses in JRA patients aged 2-17 years have been demonstrated in the pivotal 12-week, double-blind active-controlled study. Naproxen (7.5 mg/kg BID) was used as the active control. The response rates based on the endpoint of JRA Definition of Improvement ≥ 30% (JRA DOI 30) were 54.5% and 55.1% for rofecoxib and naproxen, respectively. Rofecoxib at the proposed doses was statistically non-inferior to naproxen. Efficacy of a lower dose rofecoxib, half of the proposed dose, was also studied and found to have a lower response rate, 46.2%. The lower rofecoxib dose failed to demonstrate non-inferiority to naproxen. There is no chronic safety experience at doses greater than those studied in this study. Hence, the proposed doses are acceptable although resulting in lower exposure in JRA patients compared to RA patients. (Please refer to Dr. Carolyn Yancey's review for details.)

There are 3 types of JRA: pauciarticular, polyarticular, and systemic. Because systemic course JRA patients were not included in either PK or safety/efficacy studies, the indication will be limited to the treatment of signs and symptoms of pauciarticular and polyarticular course JRA in pediatric patients 2 years and older and who weigh more than 10 kg (22 lbs).

1.1 Recommendations

The Sponsor adequately characterized PK in JRA patients aged 2 to 17 years old and evaluated effect of age and body weight on PK of Vioxx. The Office of Clinical Pharmacology and Biopharmaceutics has found this sNDA to be acceptable provided that satisfactory agreement is reached between the Sponsor and the Division regarding the language in the package insert (PI) and patient prescription information (PPI).

1.2 Phase 4 Commitments

None. PK has been adequately characterized in both JRA patients (2-17 yrs) and adult RA patients, and no Phase 4 PK study is needed. However, population PK components may be added to additional clinical safety/efficacy trials to confirm exposure in patients either outside of the age/weight limits (e.g., < 10 kg) or to better refine dosage recommendations.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics (CPB) Findings

This application consists of four PK studies: three in JRA patients aged 2-17 yrs and one in adult RA patients.

To guide dose selection for JRA patients, steady-state pharmacokinetics of rofecoxib was characterized in patients (aged 2-17 years old) with pauci (oligo)- or poly-articular course JRA (Protocol 105 Part I, Protocol 109/110 Part I and Protocol 109/110 Part II). In addition, steady-state PK was characterized in adult RA patients (Protocol 228) for comparison. As part of the WR, changes in drug oral clearance (CL/F) were pre-defined as the parameter of interest as it is (ideally) dose independent and a fundamental parameter upon which both AUC and C_{max}, the more commonly used parameters, are dependent on.

Table 1.3.1. Rofecoxib Apparent Oral Clearance (CL/F, mean ± SD) in JRA Patients and Adults.

	JRA patients			Adults	
Group	2- to 5-year-old (N=21)	6- to 11-year-old (N=13)	12- to 17-year-old (N=11)	Adult RA (N=12)	Healthy Adults* (N=26)
CL/F (mL/min)	37 ± 15	52 ± 13	87 ± 21	65 ± 20	96 ± 30

*Historical data from P042 and P043.

From analysis of the data, body weight, body surface area (BSA) and age were the most important covariates that affect clearance of rofecoxib. In general, clearance of rofecoxib increases with body weight and BSA. Clearance also increases with age between 2-11years. In adolescents (12-17 years) and adults (<65 years) there is little age dependency on clearance. Clearance for adolescent JRA patients (12-17 yrs) is similar to clearance for healthy adults but higher than that for adult RA patients. Per the Vioxx labeling, clearance of rofecoxib declines with advancing age (>65 years). Examination of oral clearance by sex revealed no difference between genders, consistent with what have been found in adults. Differences in clearance by race were not explored because most subjects were classified as Caucasians or multiracial.

As noted earlier, in some respects the proper comparison to children with JRA would seem to be adults with RA. However, the available PK dataset for adult RA patients was limited (N=12) and does not fully reflect the demographics of the RA population in the pivotal clinical trials for Vioxx. Namely, patients weighed less in the PK trial than in the pivotal clinical trial (mean weight 62 kg vs. 73.1 kg) (Age and gender were similar between PK and clinical trials.). Because CL/F of rofecoxib increases with body weight, the oral clearance for these 12 PK patients may be somewhat lower than that in the RA population in the clinical trial and thus data

obtained may overestimate the PK exposures (AUC) in the general RA population. The data from the healthy adults (mean weight 77.7 kg) were also used for comparison to provide additional information on pharmacokinetic behavior of rofecoxib in adults.

The Sponsor proposed dose recommendations of 0.6 mg/kg (up to 25 mg) for JRA patients 2-11 years old and 25 mg for adolescent JRA patients based on comparison of clearance and exposure of rofecoxib in JRA patients and healthy adults because there was no PK data in adult RA patients available at that time. The assumptions used were: 1) similar exposure-response in pediatrics and adult patients; 2) similar exposure in healthy adults and adult RA patients; and 3) dose-proportional exposure in the dose effective dose ranges in JRA and RA patients. Later data from an adult RA patient PK trial suggested that clearance in RA patients was 32% lower than that in healthy adults (63 mL/min vs. 92 mL/min, geometric mean). Therefore, exposure (AUC_{0-24}) of rofecoxib under these dose recommendations in JRA patients was lower than that in adult RA patients dosed at 25 mg dose but was comparable to AUC_{0-24} in healthy adults dosed at 25 mg dose (Table 1.3.2).

Table 1.3.2. Comparison of Dose-adjusted AUC(0-24hr) [†] (ng·hr/mL) for Pediatric Patients to Adults.

Age Group	N	Geometric Mean (ng·hr/mL)	GMR (JRAPatients/ Adults)	90% CI
JRA Patients	45	5102.2		
Adult RA Patients	12	6642.4	0.77	(0.64, 0.93)
Healthy Adults	26	4543.4	1.12	(0.98, 1.29)

[†] Dosing regimen of 0.6 mg/kg (2 to 11 years; capped at 25 mg) with the adolescents receiving a fixed 25 mg dose.

Although the proposed doses in JRA patients seem less optimal based on AUC comparison to adult RA patients, the safety and efficacy of the recommended doses in JRA patients aged 2-17 years have been demonstrated in the pivotal 12-week, double-blind active-controlled study (Protocol 134/135) with a 52-week open-label extension. The response rates based on the endpoint of JRA Definition of Improvement ≥ 30% (JRA DOI 30) were 54.5% and 55.1% for rofecoxib and naproxen (active comparator), respectively. The efficacy of rofecoxib at the proposed doses was statistically non-inferior to that of naproxen. There is no chronic safety experience at doses greater than those studied in this study. Hence, the proposed doses are acceptable.

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Concurrence: _____

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Dennis Bashaw

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