Application Type	NDA 21-042/S-026 NDA 21-052/S-019
Submission Code	SE5
Letter Date	December 5, 2003
Stamp Date	December 5, 2003
Received	January 6, 2004
Reviewer Name	Carolyn L. Yancey, MD, Medical Officer
Completion Date	May 28, 2004
Established Name	Rofecoxib
Trade Name	VIOXX
Therapeutic Class	NSAID (COX-1/COX-2-Inhibitor)
Applicant	Merck Research Laboratories
Priority Designation	P Pediatric Exclusivity
Formulation	Tablet and Suspension
Dosing Regimen	Oral tablets: 12.5, 25 mg Oral suspension: 12.5mg/5 ml; 25 mg/5 ml
Proposed Indications	Signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)
Intended Population	Poly- and pauciarticular JRA
Related Reviews	Clinical Pharmacology, Lei Zhang, PhD and Jenny J. Zheng, PhD; Statistics, Atiar M. Rhaman, PHD; NDA 21-042 (capsules) and NDA 21-052 (oral solution) S007 Gastrointestinal Safety
Project Manager	Barbara Gould

EXECUTIVE SUMMARY

This Executive Summary is restricted to the evaluation of NDA 21-042, Supplement 026 (tablets), and the NDA 21-052, Supplement 019 (suspension), for the efficacy and safety of VIOXX (rofecoxib) for the proposed indication of treatment of the signs and symptoms of pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years to 17 years of age. VIOXX was approved for adult treatment May 20, 1999. The Division of Analgesic, Anti-inflammatory and Ophthalmic Drug Products (DAAODP), HFD-550, issued a pediatric Written Request (WR) on May 7, 2001 pursuant to Section 505A of the Federal Food, Drug and Cosmetic Act, to Merck Research Laboratories (MRL) to obtain needed pediatric information about VIOXX (rofecoxib) tablets and suspension. MRL responded to the pediatric WR on December 5, 2003 with submissions, NDA 21-042/S-026 and NDA 21-052/S-019, consisting of six studies, including the tablet and suspension formulations: four pharmacokinetic (PK) studies, one Phase 3 clinical efficacy and safety study and one open-label extension study in JRA patients. The Food and Drug Administration (FDA) granted MRL six months of marketing exclusivity for VIOXX (rofecoxib) on February 18, 2004 based on the submitted pediatric supplements cited above, study of tablet and oral suspension, performed to investigate the use of VIOXX for treatment of JRA.

RECOMMENDATION ON APPROVABILITY

Approval is recommended for rofecoxib, oral suspension and tablets, at the higher of two study doses, 0.6mg/kg/day to a maximum dose of 25mg once per day, indicated for relief of the signs and symptoms of pauciarticular and polyarticular course JRA in patients ≥ 2 years to ≤ 17 years of age. The effect size and the adverse event profile of the higher of the two rofecoxib study doses demonstrate statistical non-inferiority to naproxen with an acceptable adverse event profile. The lower-dose rofecoxib failed to demonstrate non-inferiority to naproxen.

The Division recommends label changes in the following sections of the current approved VIOXX (Rofecoxib) label: See separate document for text in the following sections. CLINICAL PHARMACOLOGY, CLINICAL STUDIES, PRECAUTIONS, INDICATIONS and ADVERSE REACTIONS

RECOMMENDATION ON POST-MARKETING ACTIONS

RISK MANAGEMENT ACTIVITY

The sponsor should continue to report post-marketing data collected in the Worldwide Product Safety Report Generation System to the DAAODP, HFD-550. There is no additional recommended JRA patient risk management activity.

REQUIRED PHASE 4 COMMITMENTS

There are no required Phase 4 commitments.

OTHER PHASE 4 REQUESTS

There were no clinical or PK studies of rofecoxib oral suspension in JRA patients weighing less than 10 kg submitted in these pediatric supplements. In consideration of

the small number of JRA patients, recruitment for Phase 4 studies with rofecoxib suspension to further define PK exposure, dosage and safety for JRA patients with body weight less than 10 kg will be difficult.

SUMMARY OF CLINICAL FINDINGS

Within the non-inferiority study design of these two clinical trials, utilizing an active comparator arm, the primary endpoint for evaluating efficacy was the proportion of patients meeting the JRA Definition of Improvement ≥ 30% (JRA DOI 30), a composite score of 6 core variables. The proportion of patients meeting the JRA DOI 30 criterion, regardless of completion status, over the 12-week study was 46.2%, 54.5% and 55.1% in lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. From the 12-week study, rofecoxib, as 0.6 mg/kg per day to a maximum of 25mg per day, is an acceptable dose for treatment of pauciarticular or polyarticular JRA in patients ≥ 2 years and ≤ 17 years of age. Higher-dose of rofecoxib appears to offer acceptable durability, using the JRA DOI 30 criterion.

The overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of rofecoxib and naproxen. Caution should be used when administering rofecoxib to JRA patients taking concomitant mediations with similar adverse event profiles as rofecoxib.

BRIEF OVERVIEW OF CLINICAL PROGRAM

VIOXX (Rofecoxib) tablet (12.5mg; 25mg) and suspension (12.5mg/5ml; 25mg/5ml) [both formulations are bioequivalent] is a selective cyclogenase-2 (COX-2) inhibitor which inhibits prostaglandin synthesis. Rofecoxib is indicated for the treatment of osteoarthritis, rheumatoid arthritis, chronic low back pain, acute pain, and dysmenorrhea in the United States and, additionally, indicated for acute gouty arthritis and ankylosing spondylitis in Europe. In these two pediatric supplements, rofecoxib was studied for the indication of relief of signs and symptoms of pauciarticular and polyarticular course JRA in patients ≥ 2 years to ≤ 17 years old.

Overall number of patients enrolled and exposed:

Note the word "patients" in the below protocol descriptions of enrollment and exposure refers to "patients with pauciarticular and polyarticular course JRA". The words "adults with RA" in Protocol 228 description below refers to "adult patients with Rheumatoid Arthritis" (RA). See Section 4.1 Data Sources, Review Strategy and Data Integrity, Sub-Section 4.2 Tables of Clinical Studies for additional study details.

Protocol 134/135 Clinical Efficacy, Safety

Enrolled 310 patients: 285 patients completed the study, 99 patients were treated with rofecoxib 0.3mg/kg/day, 95 patients were treated with rofecoxib 0.6mg/kg/day and 91 patients were treated with naproxen 15mg/kg/day.

Protocol 134/135 Open-Label Extension

Enrolled 227 patients: 181 patients completed the study, 134 patients were treated with rofecoxib 0.6mg/kg/day and 47 patients were treated with naproxen 15mg/kg/day.

Protocol 105

Enrolled 11 patients: 7 patients were treated with rofecoxib 12.5mg/day and 4 patients were treated with rofecoxib 25mg/day.

Protocol 109

Enrolled 26 patients: 25 patients received study medication, 10 patients were treated with rofecoxib 5mg/day, 8 patients were treated with rofecoxib 7.5mg/day and 7 patients were treated with rofecoxib 10mg/day.

Protocol 110

Enrolled 12 patients: 10 patients completed this study and all 10 were treated with rofecoxib 0.7mg/kg/day.

Protocol 228

Enrolled 14 adults with RA: 12 completed the study with rofecoxib 25mg/day.

One Phase 3, 12-week study of efficacy and safety with an open-label extension, **Protocol 134/135***, was designed to assess both the short-term and long-term efficacy and safety of the treatment effect of rofecoxib in patients with JRA. The 12-week portion was a double-blinded, double-dummy, active-controlled trial to evaluate the efficacy and safety of rofecoxib for treatment of JRA was designed to investigate whether the proportion of patients that demonstrate improvement, defined by the JRA DOI 30 criterion, was similar between the rofecoxib and naproxen treatment groups. The 52-week, open-label, active-controlled extension to the 12-week trial of rofecoxib in JRA patients was designed to investigate the durability and effect, tolerability and safety of chronic administration of rofecoxib. Ethical considerations precluded performing a placebo-controlled study in a JRA population with a chronic, painful inflammatory disease. Naproxen, approved for treatment of JRA, was used as the active comparator.

In the 12-week study, the mean duration of exposure in 2 year to 11 year old patients was 81.6, 82.3 and 80.6 days for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. The mean duration of exposure in 12 year to 17 year old patients was 82.2, 84.7 and 79.2 days for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen groups, respectively.

Four PK studies were completed. **Protocol 105** was an open-label study to evaluate the steady-state plasma concentration profile of rofecoxib in late-stage and post-pubertal adolescents, 12 to 17 years of age with JRA. This study was followed by a 12-week, double-blind, active-controlled extension. The PK portion of this study was designed to investigate area under the curve (AUC) of rofecoxib at steady state in adolescent JRA patients compared to rofecoxib 25mg daily adult historical controls. Similarly, **Protocol 109 and Protocol 110,** investigated the same PK parameters and adult comparisons as in Protocol 105 except the JRA patients were 2 years to 11 years and 2 years to 5 years, respectively. **Protocol 228** was a single-period, multiple-dose PK study in adult RA patients to investigate the steady-state plasma concentration profile of rofecoxib.
Safety and efficacy data were assessed in the 6 completed trials, though the four PK trials included small numbers of JRA patients and did ***not*** include either an active comparator or placebo. Therefore, the safety database includes 310 patients from the 12-week base

study, Protocol 134/135, and 227 patients from the 52-week open-label extension portion of this study.

Data sources used for this review include the sponsor's electronic files and hard copy volumes submitted to the FDA, Center for Drug Evaluation and Research (CDER), HFD-550. Electronic post-marketing data submitted by the sponsor was reviewed but was not summarized in this review.

***** *Note:* ***Protocol 134/135*** *was a multicenter (41) study: Australia, Europe, Mexico, Israel, South America, United States;* ***Protocols 134 and 135*** *were* ***identical****. The protocols were assigned different numbers to differentiate the* ***domestic study****,* ***Protocol 134*** *from the* ***multinational study****,* ***Protocol 135****. This was a 12-week, double-blind, double-dummy, active comparator-controlled study in 2 to 17 year old pauciarticular and polyarticular JRA patients. The use of 2 protocol numbers was administrative to allow compliance with regulatory requirements in different regions. The study was designed as a single study. Throughout this review, Protocol 134/135 numbers will be used together and the specific trial under review will be clearly explained. Only higher-dose rofecoxib was used in the open-label extension study.*

EFFICACY

12-Week Study, Protocol 134/135: There were 310 JRA patients in this double-blind, non-inferiority trial. Two study doses of rofecoxib were compared to naproxen. Rofecoxib was administered as a lower-dose of 0.3mg/kg per day to a maximum of 12.5mg per day and as a higher-dose of 0.6mg/kg per day to a maximum of 25 mg per day. The active comparator, naproxen, was administered as approximately 7.5mg/kg per day, twice daily.

The prespecified criterion for the non-inferiority trial design was the lower limit margin of the point estimate, of the 95 % confidence interval (CI) for the ratio of the JRA Definition of Improvement (JRA DOI 30) responder rate (rofecoxib/ naproxen) ≥ 0.50. Patients are classified as improved if they experience ≥ 30% improvement in at least three of 6 of the JRA DOI core set variables, with no more than one of the 6 variables worsening by more than 30%.

The Division specified in the pediatric WR, that a lower limit margin of the point estimate ≥ 0.50 (95% CI), was too low to support a finding of efficacy based on a non-inferiority trial design. This review was conducted using a lower limit margin of ≥ 0.75, employing this margin, as discussed below, only the higher-dose of rofecoxib achieved non-inferiority to naproxen.

The point estimate was 0.98 (95% CI, **0.76*** to 1.26), in a modified intent-to-treat analysis (MITT), using the JRA DOI 30 responder index, *regardless of completion status* and the point estimate was 1.00 (95% CI, **0.78*** to 1.29), MITT, by the JRA DOI 30 *responder and completer status.* The lower-dose of rofecoxib achieved a point estimate of 0.81 (95% CI **0.61*** to 1.07, in a modified-intent-to-treat analysis, *regardless of completion status*, and achieved a point estimate of 0.81 (95% CI, **0.61*** to 1.09), modified intent to treat, *responder and completer.* Therefore, since the lower limit of the point estimate (***bold font**) was less than 0.75 in the lower-dose rofecoxib group, this dose was considered inferior to naproxen.

The proportion of patients who achieved the JRA DOI 30 criterion, MITT, *regardless of completion status*, over the 12-week study was 46.2%, 54.5% and 55.1% for the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively.

Secondary endpoints: The proportion of patients with improvement from baseline in the parent/patient's assessment of overall well-being, parent/patient assessment of pain and discontinuation the study dose due to lack of efficacy was similar across the three treatment groups with no statistically significant differences between the treatment groups. In the assessment of the individual components of the JRA DOI 30, naproxen demonstrated statistically significant improvement in the number of joints with limited range of motion, compared to both higher-dose and lower-dose rofecoxib. No other component of the JRA DOI 30 had a statistically significant difference across the three treatment groups.

52-Week Open-Label Extension, Protocol 134/135: The proportion of patients achieving the JRA DOI 30 criteria, *regardless of completion status,* was 66.7% and 60.3%; and, for *responders and completing,* was 57.9% and 42.4%, for rofecoxib and naproxen, respectively.

In conclusion from the 12-week study, rofecoxib, as 0.6 mg/kg per day to a maximum of 25mg per day, is an effective dose for treatment of pauciarticular or polyarticular JRA in patients ≥ 2 years and ≤ 17 years of age. The higher-dose of rofecoxib appears to offer durability over the 52-week extension study period.

SAFETY

During the **12-week, double-blind portion of this study, Protocol 134/135,** safety data was collected from 310 JRA patients, 109 and 100 patients, treated with lower-dose rofecoxib and higher-dose rofecoxib, respectively. One-hundred-and-one JRA patients were treated with the active comparator, naproxen. The **52-week open-label extension** collected **s**afety data from 160 and 67 JRA patients, rofecoxib and naproxen, respectively. In this open-label extension, only the higher-dose rofecoxib was studied.

Deaths
There were no deaths, malignancies, significant overdoses or pregnancies in the 12-week study or in the 52-week open-label extension.

Serious Adverse Events
In the 12-week study, there were four **serious clinical adverse events** (SAE) reported as JRA flare. Of these four patients, one was treated with lower-dose rofecoxib, two were treated with higher-dose rofecoxib and one was treated with naproxen. In the 52-week extension, there were SAEs reported in 10 and 7 patients, for rofecoxib and naproxen, respectively. Two of these 17 SAE resulted in discontinuation of study medication, one patient developed hepatitis A (rofecoxib group) and one patient suffered worsening of their JRA (naproxen group).

Discontinuations Due to Clinical Adverse Events
In the 12-week study, 5 patients withdrew due to clinical adverse events. Of these five patients, two patients treated with lower-dose rofecoxib suffered abdominal pain; 1 patient treated with lower dose rofecoxib suffered worsening JRA; 1 patient, treated with naproxen, suffered headaches and 1 patient, treated with naproxen, suffered hematochezia.

In the 52-week extension, 12 patients discontinued study medication due to the following clinical adverse events:

- 4 patients discontinued rofecoxib treatment secondary to GI disorders, upper abdominal pain (1 patient) and gastritis (1 patient), alopecia (one patient) and hepatitis A (1 patient).
- 8 patients discontinued naproxen treatment secondary to GI disorders, GI upset, upper abdominal pain, abdominal pain and constipation (5 patients), worsening JRA (2 patients) and hepatitis A (1 patient).

Non-Serious Clinical Adverse Events
In the 12-week study, there were 196 non-serious clinical adverse events observed in the three treatment groups. In the 52-week open label extension, there were 171 non-serious clinical adverse events among 227 JRA patients.

In the 12-week double-blind study, **gastrointestinal disorders** as abdominal pain, upper abdominal pain, diarrhea and nausea, **upper respiratory tract infections** and **headache** were the three most commonly reported **clinical adverse events**. There were 29(26.6%), 32(32%) and 40 (39.6%) patients with GI adverse events, the lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. A higher incidence of **abdominal pain** was noted in the naproxen treated group, 13 patients (12.9%), compared to the 7 patients (6.4%), lower-dose of rofecoxib, and 6 patients (6.0%) higher-dose of rofecoxib. **Upper abdominal pain** occurred in 7(6.4%), 12(12.0%) and 7 (6.9%) patients treated with lower-dose rofecoxib, higher-dose rofecoxib, and naproxen. **Upper respiratory tract infections** were the second most common clinical adverse event. Upper respiratory tract infection was noted in 6 (5.5%), 6 6.0%) and 7(6.9%) patients treated with lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. Nasopharyngitis was noted in 11 (10.1%), 1(10.0%) and 1(1.0%) patients and pharyngitis was noted in 7(6.4%), 3(3.0%) and 3(3.0%) patients treated with lower-dose rofecoxib, higher-dose rofecoxib and naproxen, respectively. **Headache** was the third most commonly reported clinical adverse event occurring in 6(5.5%), 5(5.0%) and 13(12.9%) of patients in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. Headache is a well-known adverse event with naproxen, other NSAIDs and selective COX-2 inhibitors.

Pyrexia occurred in each treatment group with increased incidence in the naproxen treatment group. Insomnia occurred in each treatment group with increased incidence in the higher-dose rofecoxib group. Two cardiorenal system adverse events were reported, one patient treated with higher-dose rofecoxib suffered edema of the feet and ankles and

one patient treated with naproxen reported swelling on the dorsum of the foot. Allergic skin/hypersensitivity reactions were noted in each three treatment groups as 9, 11 and 10 patients for lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment, respectively. There was one case of pseudoporphyria reported with higher-dose rofecoxib treatment.

In the 52-week extension, the most common adverse events were **upper respiratory tract infections**; **gastro-intestinal events,** as upper abdominal pain, abdominal pain and diarrhea, **headache** and **pyrexia**.

Laboratory Adverse Events
In the 12-week study, the most common laboratory adverse event was **elevated hepatic enzymes**. Hepatic enzymes were reported as abnormal if consecutive values 3 x upper limit of normal (ULN). Abnormal hepatic enzymes were reported in five, four and two patients in the lower-dose rofecoxib, higher-dose rofecoxib and naproxen treatment groups, respectively. Four patients discontinued study drug due to elevated hepatic enzymes, three patients in the lower-dose rofecoxib group and one patient in the higher-dose rofecoxib group. There were no abnormal bilirubin values. Less common laboratory adverse events of note were abnormal urinalysis, two patients on naproxen treatment, and urinalysis with protein, two patients treated with low-dose rofecoxib and two patients treated with naproxen.

In the 52-week extension, the incidence of adverse laboratory tests, **elevated hepatic enzymes**, ALT and/or AST, was numerically larger in the rofecoxib treatment group than in the active comparator group. One patient treated with rofecoxib was discontinued from study therapy.

In conclusion, the overall safety profile of adverse events was consistent with the underlying disease and the known adverse events of rofecoxib and naproxen. However, caution should be used when administering rofecoxib to JRA patients taking concomitant mediations with similar adverse event profiles as rofecoxib due to the potential for synergistic toxicity. Safety monitoring for clinical signs and symptoms of adverse events is important, particularly, for the risk of hepatotoxicity. Concomitant medication, specifically DMARD therapy, appears to increase the risk of elevation of hepatic enzymes.

DOSING REGIMEN AND ADMINISTRATION

The rofecoxib dose in the 12-week study and the 52-week open-label extension, Protocol 134/135, was based on results of PK studies with JRA patients. The recommended dose, based upon the review of the two NDA pediatric supplement data, is 0.6mg/kg per day up to a maximum dose of 25 mg per day in JRA patients ≥ 2 years and ≤ 17 years of age. This dose is supported by the non-inferiority trial design findings from the efficacy measurements and supported by the safety profile in both the 12-week study and the 52-week extension.

DRUG-DRUG INTERACTIONS

Pediatric patients with hypersensitivity (e.g., angioedmea and/or bronchoconstriction) to aspirin and/or nonsteroidal anti-inflammatory drugs were excluded from these rofecoxib clinical trials. Similarly, caution should be used with concomitant medications such as gold, methotrexate, sulfasalzine, anti-malarials and steroids because the adverse event profiles are similar and concomitant medication may precipitate adverse experiences.

SPECIAL POPULATIONS

The COX-2 inhibitor, rofecoxib, has been studied in the adult special populations previously. Clinical studies demonstrate safety risks because renal clearance may be decreased from normal; similarly, hepatic insufficiency may be worsened because of the drug's hepatic metabolism and decreased plasma protein binding in liver disease.

There are three subtypes of JRA characterized by course of onset: pauciarticular, polyarticular and systemic JRA with approximately 60%, 30 % and 10% frequency of cases, respectively. JRA is one of the most common rheumatic disease of childhood and the leading cause of childhood disability, affecting approximately 1.3 to 22.6 per 100,000 pediatric patients in North America. This pediatric program enrolled 144 pauciarticular and 166 polyarticular JRA patients. These supplements did not study pauciarticular *versus* polyarticular JRA differences in response to rofecoxib. Systemic JRA was not included in this review due to known risks and the more common need to adjust doses of concomitant medications in this course JRA.

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/s/

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5/28/04 04:07:42 PM
MEDICAL OFFICER

executive summary vioxx ped rheumatology

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For clarity, the last paragraph, first line on page 5 should read "The point estimate of the higher dose rofecoxib was ...."