FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC, AND OPHTHALMOLOGIC DRUG PRODUCTS
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DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVABLE ACTION

DATE: June 4, 2004

DRUG: Vioxx (rofecoxib)

NDA: 21-042 (SE5-026)
21-052 (SE5-019)

SPONSOR: Merck & Co., Inc.

INDICATION: The treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis in patients 2 years and older and who weigh over 10 kg

Merck & Co., Inc. has submitted efficacy supplements for Vioxx (rofecoxib) for the indication of the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) to NDAs 21-042 (Tablets 12.5 mg and 25 mg) and 21-052 (Oral Suspension 12.5 mg/mL and 25 mg/mL). One 12-week double-blind, active-control efficacy study with a 52 week open-label extension and four pharmacokinetic studies, including one adult PK study to provide comparative data, have been submitted to support this indication and to fulfill the requirements of the Pediatric Written Request (PWR) issued December 6, 2001. A clinical review has been completed by Carolyn Yancey, M.D. Review of the clinical pharmacology and biopharmaceutics data was completed by Lei Zhang, Ph.D. and Jenny J. Zheng, Ph.D. A statistical review and evaluation was completed by M. Atiar Rahman, Ph.D. No new CMC nor nonclinical pharmacology data was submitted with this application. The studies submitted were considered adequate to fulfill the requirements of the PWR.

Rofecoxib is a COX-2 selective nonsteroidal anti-inflammatory drug which has been approved for relief of the signs and symptoms of osteoarthritis, the relief of the signs and symptoms of rheumatoid arthritis in adults, the management of acute pain in adults, the treatment of primary dysmenorrhea, and most recently, for the acute treatment of migraine attacks with or without aura in adults. The most common adverse events reported in adults taking rofecoxib include abdominal pain, nausea, and heartburn, as well as upper respiratory infection, headache, and back pain. An additional concern is a risk of cardiovascular thrombosis identified during a gastrointestinal safety trial in adults with rheumatoid arthritis.

JRA can present in any of three predominant forms, systemic, polyarticular, and pauciarticular. Patients enrolled in the one study submitted in support of efficacy had predominantly polyarticular and pauciarticular JRA. The treatment of JRA centers on the use of disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, to slow the progression of the diseases, and nonsteroidal anti-inflammatory drugs (NSAIDs) for treatment of joint inflammation and pain. It is considered inappropriate to require patients with JRA to go without NSAID therapy, even with use of a DMARD. As a result, an active-control, non-inferiority design was accepted to support a finding of efficacy of rofecoxib for this indication.

Efficacy

Study 134/135 was a multi-center, 12-week, double-blind, active-control, noninferiority study comparing lower-dose rofecoxib (0.3 mg/kg/day up to 12.5 mg), higher-dose rofecoxib (0.6 mg/kg/day up to 25 mg), and naproxen 15 mg/kg/day in patients with pauciarticular and polyarticular JRA, stratified by form of JRA and age. Patients ages 2 through 11 were dosed with rofecoxib based on weight using the suspension formulation. Patients ages 12 through 17 were dosed at the 12.5 mg/day and 25 mg/day doses, using the tablet formulation, for the lower and higher-dose rofecoxib groups, respectively. Patients were washed out from prior NSAID therapy for 3 days, but were permitted to continue stable prior DMARD therapy. Acetaminophen was the prespecified rescue medication, but not permitted within 24 hours of an assessment. Subjects were eligible to enter a 52-week open-label extension on either higher-dose rofecoxib or naproxen.

The primary outcome measure was the JRA Definition of Improvement (DOI) 30, a composite score requiring at least 30% improvement in any three of the six core measures, provided there was no more than one of the variables worsening by >30%. These six measures are physician's global assessment of disease severity (10 cm VAS), patient's or parent's global assessment of overall well-being (10cm VAS), physical

function, as measured by Child Health Assessment Questionnaire Disability Index, number of joints with active arthritis, as defined by the American College of Rheumatology (ACR) criteria (a joint with swelling not due to deformity or a joint with limited range of motion plus pain and/or tenderness), number of joints with limited range of motion plus pain and/or tenderness, and erythrocyte sedimentation rate (ESR).

All of the 310 randomized patients received at least one dose of study medication. Two hundred eighty five patients completed the 12-week double-blind period. Discontinuations due to lack of efficacy were few, three patients from the lower-dose rofecoxib group, and four from both the higher-dose rofecoxib and naproxen groups. There were also few discontinuations due to adverse events (AEs), three from the lower-dose rofecoxib group and two from the naproxen group. The JRA DOI 30 responder rates were (b) (4) 55%, and 55% from the (b) (4) higher-dose rofecoxib, and naproxen groups, respectively. (b) (4) The 95% confidence interval for comparison of the higher-dose rofecoxib group and naproxen was 0.76 to 1.26. (b) (4) For this analysis, the Division set the lower bound for noninferiority at 0.75 (b) (4)

The individual components of the JRA DOI 30 were evaluated as secondary endpoints. Parent/patient assessment of overall well-being, physician global assessment of disease activity, CHAQDI, and ESR were similar across treatment groups. The number joints with active arthritis and number of joints with limited range of motion plus pain and/or tenderness trended better in the naproxen group, but the difference did not reach statistical significance.

The efficacy results for subgroups of patients ages 2 to 11 and 12 to 17 were examined and were qualitatively similar to the overall group of ages 2 to 17. The small number of patients overall preclude confident quantitative comparisons across subgroups.

Patients who elected to continue in the 52-week open-label extension received either higher-dose rofecoxib or naproxen based upon allocations made at the time of the initial randomization for the 12-week study. Although the efficacy endpoints from the 12-week study were measured, as the study was open-label, no conclusions about efficacy during the 52-week period can be made. The overall efficacy appeared durable during this time period.

Safety

Study 134/135 was the primary source for safety data with additional information obtained from the pharmacokinetic studies. A total of 357 patients were studied, 297 of whom received rofecoxib, 183 were 2 to 11 years of age and 114 were 12 to 17 years of age. The Sponsor did not provide any overall integrated accounting of AEs.

There were no deaths during any of the clinical trials submitted to the supplements under review. There were 21 serious adverse events (SAEs) according to the Sponsor. Dr. Yancey's review of the safety data yielded one additional SAE during the 12-week double-blind period of Study 134/135. This patient experienced worsening of JRA requiring hospitalization. Of the remaining 4 SAEs during the 12-week double-blind study, one patient was in the lower-dose rofecoxib group, one patient was in the naproxen group, and two patients were in the higher-dose rofecoxib group. All of these SAEs were worsening of JRA requiring hospitalization with additional symptoms including uveitis in one patient and gastroenteritis, fever, lymphadenopathy and anemia in one patient. There does not appear to be a causal relationship between these events and study drug.

During the 52-week extension, 10 patients in the rofecoxib group and seven in the naproxen group experienced SAEs. In the rofecoxib group, the SAEs were: two cases of worsening uveitis (including one patient with head trauma as well), and one case each of pneumonia, acute bronchitis, acute appendicitis, angina tonsillaris, hepatitis A, head injury sustained in an accident, accidental overdose of one additional dose of study drug, and *helicobacter pylori* infection with chronic gastritis. In the naproxen group, the SAEs were one case each of GI infection requiring IV hydration, varicella with mouth ulcers, gastroenteritis, inpatient reevaluation of JRA, abdominal pain with emotional distress, abdominal pain, and a patient with convulsions with sepsis, bone marrow depression and worsening JRA. There is no apparent relationship between the SAEs, other than abdominal pain, and study drug.

The adverse events resulting in discontinuation were few in number. These are presented in detail in Dr. Yancey's review. Abdominal pain and worsening JRA were the most common AEs leading to discontinuation. LFT abnormalities were defined in this study as AST or ALT greater than 3 X the upper limit of normal or 2X baseline if above the upper limit of normal and were present in 2% to 4% of patients across treatment groups, during the 12-week study. Three patients discontinued from the lower-dose rofecoxib group, one from the higher-dose rofecoxib group and none from the naproxen group due to LFT elevations during the 12-week study, and all elevations returned to normal following discontinuation of study drug. Two patients treated with rofecoxib discontinued the 52-

week open-label extension due to LFT elevations including one patient reported with the SAE of hepatitis A and one with the SAE of bronchitis also found to have hepatomegaly.

Adverse events occurred in 63% of all patients in the 12-week double-blind study, and 75% of patients during the 52-week extension. There were none reported during the pharmacokinetic studies. The AE profile during the 12-week study and 52-week extension was generally not unexpected in patients with JRA receiving NSAIDs and DMARDs and was similar across treatment groups. The most common AEs were abdominal pain, nausea, diarrhea, headache, upper respiratory infections, fever. In addition to the LFT abnormalities noted previously, there were a few additional LFT abnormalities noted in each treatment group. No elevations of creatinine were reported. There was no clear dose-response for the adverse events reported across the lower and higher-dose rofecoxib treatment groups.

Clinical Pharmacology and Biopharmaceutics

Four studies were submitted to provide pharmacokinetic information. Steady-state pharmacokinetic parameters of rofecoxib were characterized in patients ages 2 through 17 and compared to the steady-state PK in adult patients with rheumatoid arthritis (RA). Enrollment criteria in the three pediatric PK studies included patients with JRA ranging from 10 kg to 42 kg, with pauciarticular and polyarticular JRA. Dosing for the clinical efficacy trial was based on assumptions that the exposure-response relationship in pediatric patients was similar to healthy adults, in healthy adults was similar to adults with RA, and the exposure was dose-proportional across the effective dose range in patients with JRA and RA. Findings from the PK studies revealed that the clearance from adult RA patients was lower than normal adults by as much as 32% so that had dosing in the JRA efficacy trial would have been higher had this information been known earlier. Apparent oral clearance of rofecoxib increases with body weight and body surface area for all in JRA patients, and with increasing age for patients 2 years through 11 years old. Furthermore, clearance in JRA patients 12 to 17 years of age was comparable to healthy adults and so, higher than adults with JRA. The pharmacokinetic study results have been reviewed in detail by Dr. Lei Zhang.

Dosing and Administration

The higher-dose of rofecoxib during the clinical trial has sufficient evidence of efficacy based on non-inferiority to naproxen, without any notable difference in adverse event profile compared to the lower-dose rofecoxib and so, is recommended for use. The maximum dose of rofecoxib for treating the signs and symptoms of JRA is 25 mg/day. The dosing recommendation for patients between 2 years and 11 years of age weighing

between 10 kg and 42 kg is 0.6 mg/kg/day. For patients between 2 years and 11 years of age over 42 kg, and patients between 12 years and 17 years of age the dose is 25 mg/day.

Product Labeling

There were limitations in this pediatric development program. The efficacy trial was a non-inferiority design, just one clinical efficacy trial was performed, and the overall the number of patients studied was small. While sufficient evidence of efficacy was demonstrated for the purpose of establishing a pediatric indication for the treatment of the signs and symptoms of pauciarticular and polyarticular JRA in patients 2 years and older and who weigh over 10 kg, no comparative claim against naproxen can be supported. It is important to provide sufficient information in the package insert to describe the basis for the indication, but the specific identification of naproxen in the package insert would provide the basis for an implied claim of equivalence. Therefore, it is most prudent to describe the study and use the term 'active comparator' (b) (4)

The patient package insert should be updated to reflect the new indication. Risk communication should be prioritized such that safety information is presented first. The Medication Guide format is recommended as the format for the patient package insert.

Discussion

The Sponsor has submitted four pharmacokinetic studies and one clinical efficacy study with an open-label extension in support of the efficacy and safety of rofecoxib for the treatment of juvenile rheumatoid arthritis. These studies fulfilled the requirements of the Pediatric Written Request. Adequate evidence of efficacy was demonstrated as non-inferiority of rofecoxib 0.6 mg/kg/day up to a maximum of 25 mg/day, to the active comparator, naproxen 15 mg/day. The non-inferiority study design was deemed acceptable for the clinical setting of JRA. The safety profile was similar across treatment groups and without unexpected findings in the JRA population relative to the adult RA population.

Negotiations took place between the Division and the Sponsor over the language of package insert and patient package insert. (b) (4)

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[redacted] (b) (4)

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