Clinical Team Leader's Memorandum:

Reviewer: James Witter MD, PhD (HFD-550)

Date: June 3, 2004

NDA: 21-042/S-026 and NDA 21-052/S-019

Sponsor: Merck Research Laboratories
Vioxx® (rofecoxib) tablets-12.5, 25 mg and suspension-12.5 mg/5 mL and 25 mg/5 mL

Summary:
NDA 21-042/ S-026 (tablets) and NDA 21-052/S-019 (suspension) is a pediatric efficacy supplement for the treatment of the signs and symptoms of pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years to 17 years of age. It was submitted December 5, 2003 in response to a pediatric Written Request (WR) issued by HFD-550 on May 7, 2001. The submission consisted of four PK studies (protocol 105, 109, 110 and 228) along with one 12-week, double-blind, active control, phase 3 clinical efficacy and safety study which was followed by a 52-week, open-label extension (see below, protocol 134/135).

PK studies
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.

Clinical Efficacy and Safety
Protocol 134/135 was a multi-center study that involved sites in Australia, Europe, Mexico, Israel, South America and United States. These protocols were identical and were assigned different numbers to differentiate the U.S. site (protocol 134) from the other multi-national sites (protocol 135). These studies consisted of a 12-week, double-blind, double-dummy, active-controlled study in 2 to 17 year old pauciarticular and polyarticular JRA patients. In this portion of the study, both a low-dose (0.3 mg/kg/d to a maximum of 12.5 mg/d) and high-dose (0.6 mg/kg/d to a maximum of 25 mg/d) rofecoxib suspension was compared to the active control (naproxen, 7.5 mg/kg BID). For children whose weight was greater than 40 kg, the corresponding rofecoxib tablet (12.5 or 25 mg) was employed rather than the suspension. Patients were then allowed to enter

the 52-week extension study which included only the higher-dose rofecoxib suspension or tablet compared to naproxen. The extension was intended to address the durability of the efficacy response and to continue to study safety. A total of 209 JRA patients were enrolled and exposed to rofecoxib (109 patients to lower dose, 100 patients to higher dose) during the 12-week portion of the study while 160 patients were enrolled into the extension portion of the study and exposed to high-dose rofecoxib.

Efficacy was assessed in this trial using the JRA-DOI (definition of improvement) ≥ 30% which is a valid metric in this JRA population (*Giannini, et.al. Arth. Rheum. 1997; 40: 1202-1209*). This study was designed as a non-inferiority trial with the lower margin of the point estimate of the 95% confidence interval pre-specified at (b) (4) This margin was noted to be unacceptable to HFD-550 in the WR letter (b) (4) Consequently, the lower margin for the 95% confidence interval of the point estimate of ≥ 0.75 was employed for the determination of efficacy for these two pediatric NDA supplements.

For the primary endpoint of JRA DOI 30, the point estimates and 95% CI for comparison to naproxen were as follows in a modified ITT during the 12-week portion of the study:

- **higher dose** (0.6 mg/kg rofecoxib)
  - regardless of completion status **(0.98: 0.76-1.26)**
  - completers **(1.00: 0.78-1.29)**

(b) (4)

The proportion of patients who achieved the JRA DOI 30 criterion in the modified ITT population regardless of completion status, over the 12-week study was (b) (4) **54.5% and 55.1%** for the (b) (4) higher-dose rofecoxib and naproxen treatment groups, respectively. At the end of the 52-week extension, the JRA DOI 30 (regardless of completion status) was 66.7% (rofecoxib) and 60.3% (naproxen); for completers the rates were 57.9% (rofecoxib) and 42.4% (naproxen) supporting the conclusion that the higher-dose rofecoxib offer long-term efficacy.

The safety of rofecoxib was established from this combined protocol. No deaths occurred and the adverse event profile obtained with rofecoxib did not reveal any new or unexpected findings with regards to short-or long-term safety other than the adverse event of pseudoporphyria in one child treated with higher-dose rofecoxib in the extension study.

Regulatory Action:
As noted above, the sponsor is interested in the INDICATION for treatment of JRA. Proposed revisions to the VIOXX labeling include additions to the **CLINICAL PHARMACOLOGY (Pediatric), Special Studies (Pediatric Patients), INDICATIONS and USAGE, Precautions (Pediatric Use),** and the **Adverse Reactions-(Pauciarticular and Polyarticular Course JRA)** section.
Following several teleconferences with the sponsor (including participation by DDMAC), the proposed changes to the label are not acceptable. (b) (4)

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Appendix

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/s/

James Witter
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MEDICAL OFFICER
Team Leader Memorandum